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European Regulations for Labeling Requirements for Food Allergens and Substances Causing Intolerances: History and Future

Popping, Bert; Diaz-Amigo, Carmen

ABSTRACT
Food allergens and intolerances have been diagnosed by doctors for decades, but have received heightened attention in the last two decades because diagnosis and awareness have increased. Consequently, regulators in many jurisdictions have addressed this topic by introducing labeling requirements for substances causing allergies and intolerance reactions in affected individuals. Mandatory labeling of food allergens allows persons suffering from these to make informed choices. However, regulations in some geographic areas have resulted in significant problems for manufacturers as well as consumers. This has been mainly due to frequent changes and amendments, and it has been difficult for all stakeholders to follow and understand the status quo of legislation. The present paper describes the development of European directives and regulations for the labeling of food allergens and intolerances to substances like gluten over the past decades and provides an outlook of what can reasonably be expected to change in the coming years. It also identifies existing gaps, like a lack of threshold levels for adventitious contamination and consequently a proliferation of precautionary allergen labeling, which neither benefits the consumer nor the food industry in its current form.

Pharmacological Approach to the Management of Crohn’s Disease Patients with Perianal Disease

Fernando Bermejo, Iván GuerraAlicia AlgabaAntonio López-Sanromán

ABSTRACT
Perianal localization of Crohn’s disease involves significant morbidity, affects quality of life and results in an increased use of healthcare resources. Medical and surgical therapies contribute to its management. The objective of this review is to address the current understanding in the management of perianal Crohn’s disease, with the main focus in reviewing pharmacological therapies, including stem cells. In complex fistulas, once local sepsis has been controlled by surgical drainage and/or antibiotics, anti-TNF drugs (infliximab, adalimumab) are the first-line therapy, with or without associated immunomodulators. Combining surgery and anti-TNF therapy has additional benefits for healing. However, response is inadequate in up to half of cases. A possible role of new biological drugs in this context (vedolizumab, ustekinumab) is an area of ongoing investigation, as is the local application of autologous or allogeneic mesenchymal stem cells. These are non-hematopoietic multipotent cells with anti-inflammatory and immunomodulatory properties, the use of which may successfully treat refractory patients, and seem to be a promising and safe alternative to achieving fistula healing in Crohn’s disease, without known systemic effects.
Current and New Therapeutic Strategies for Relapsed and Refractory Multiple Myeloma: An Update
Inger S. Nijhof, Niels W. C. J. van de DonkSonja ZweegmanHenk M. Lokhorst

ABSTRACT

Although survival of multiple myeloma patients has at least doubled during recent years, most patients eventually relapse, and treatment at this stage may be particularly complex. At the time of relapse, the use of alternative drugs to those given upfront is current practice. However, many new options are currently available for the treatment of relapsed multiple myeloma, including recently approved drugs, such as the second- and third-generation proteasome inhibitors carfilzomib and ixazomib, the immunomodulatory agent pomalidomide, the monoclonal antibodies daratumumab and elotuzumab and the histone deacetylase inhibitor panobinostat, but also new targeted agents are under active investigation (e.g. signal transduction modulators, kinesin spindle protein inhibitors, and inhibitors of NF-kB, MAPK, AKT). We here describe a new paradigm for the treatment of relapsed multiple myeloma. The final goal should be finding a balance among efficacy, toxicity, and cost and, at the end of the road, achieving long-lasting control of the disease and eventually even cure in a subset of patients.

Gábor Holló, Andreas KatsanosKostas G. BoboridisMurat IrkecAnastasios G. P. Konstas

ABSTRACT

Glaucoma therapy-related ocular surface disease (OSD) is a serious pathology with a broad spectrum of insidious clinical presentations and complex pathogenesis that undermines long-term glaucoma care. Preservatives, especially benzalkonium chloride (BAK), contained in topical intraocular pressure-lowering medications frequently cause or aggravate OSD in glaucoma. Management of these patients is challenging, and to date often empirical due to the scarcity of controlled long-term clinical trials. Most of the available data are extracted from case series and retrospective analysis. Preservative-free prostaglandins and prostaglandin/timolol fixed combinations are novel options developed to remove the harmful impact of preservatives, especially BAK, upon ocular tissues. Based on what is currently known on the value of preservative-free antiglaucoma therapies it is tempting to speculate how these new therapies may affect the future medical management of all glaucoma patients. This article provides a comprehensive and critical review of the current literature on preservative-free prostaglandins and preservative-free prostaglandin/timolol fixed combinations.
Effects of Allopurinol on Endothelial Function: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

Arrigo F. G. Cicero Matteo Pirro Gerald F. Watts Dimitri P. Mikhailidis Maciej Banach Amirhossein Sahebkar

ABSTRACT

Introduction: Uric acid (UA), the final product of purine catabolism, may be associated with an increased risk of cardiovascular disease.

Aim: The aim of this meta-analysis of randomized placebo-controlled trials was to evaluate whether lowering serum UA (SUA) levels with allopurinol is associated with improved flow-mediated dilation (FMD), a validated marker of early vascular damage.

Methods: A literature search was carried out from inception until 20 June 2017. Meta-analysis was performed using an inverse variance-weighted, random-effects model with standardized mean difference (SMD) as the effect size estimate.

Results: Meta-analysis of data from the ten eligible randomized controlled trials (RCTs), with 670 subjects, suggested a significant increase in FMD following allopurinol treatment (weighted mean difference [WMD] 1.79%, 95% confidence interval [CI] 1.01–2.56, p < 0.001; I²: 86.77%). The effect size was robust and remained significant after omission of each single study. Subgroup analyses of RCTs based on the administered dose or duration of treatment did not reveal any significant impact of these variables on FMD change. Nor was a significant association found between allopurinol-induced changes in SUA levels and FMD (slope 0.46, p = 0.253), whereas baseline FMD significantly influenced the degree of FMD improvement following allopurinol treatment (slope 0.52, p = 0.022). Nitroglycerin-mediated dilation was not altered by allopurinol treatment (WMD 0.88%, 95% CI – 1.15–2.91, p = 0.395; I²: 80.88%).

Conclusion: This meta-analysis of available RCTs suggests a significant benefit from allopurinol intake in increasing FMD in humans, independent of its effect on SUA levels.
Correlation of Opioid Mortality with Prescriptions and Social Determinants: A Cross-sectional Study of Medicare Enrollees


ABSTRACT

Background: The opioid epidemic is an escalating health crisis. We evaluated the impact of opioid prescription rates and socioeconomic determinants on opioid mortality rates, and identified potential differences in prescription patterns by categories of practitioners.

Methods: We combined the 2013 and 2014 Medicare Part D data and quantified the opioid prescription rate in a county level cross-sectional study with data from 2710 counties, 468,614 unique prescribers and 46,665,037 beneficiaries. We used the CDC WONDER database to obtain opioid-related mortality data. Socioeconomic characteristics for each county were acquired from the US Census Bureau.

Results: The average national opioid prescription rate was 3.86 claims per beneficiary that received a prescription for opioids (95% CI 3.86–3.86). At a county level, overall opioid prescription rates (p < 0.001, Coeff = 0.27) and especially those provided by emergency medicine (p < 0.001, Coeff = 0.21), family medicine physicians (p = 0.11, Coeff = 0.008), internal medicine (p = 0.018, Coeff = 0.1) and physician assistants (p = 0.021, Coeff = 0.08) were associated with opioid-related mortality. Demographic factors, such as proportion of white (p white < 0.001, Coeff = 0.22), black (p black < 0.001, Coeff = −0.19) and male population (p male < 0.001, Coeff = 0.13) were associated with opioid prescription rates, while poverty (p < 0.001, Coeff = 0.41) and proportion of white population (p white < 0.001, Coeff = 0.27) were risk factors for opioid-related mortality (p model < 0.001, R^2 = 0.35). Notably, the impact of prescribers in the upper quartile was associated with opioid mortality (p < 0.001, Coeff = 0.14) and was twice that of the remaining 75% of prescribers together (p < 0.001, Coeff = 0.07) (p model = 0.03, R^2 = 0.03).

Conclusions: The prescription opioid rate, and especially that by certain categories of prescribers, correlated with opioid-related mortality. Interventions should prioritize providers that have a disproportionate impact and those that care for populations with socioeconomic factors that place them at higher risk.
Dimethyl Fumarate: A Review in Moderate to Severe Plaque Psoriasis

Hannah A. Blair

ABSTRACT

Fumaric acid esters (FAEs) have been used in the treatment of psoriasis in some European countries for over 20 years, and are recommended in the European guidelines for the management of moderate to severe plaque psoriasis. Dimethyl fumarate (Skilarence®; hereafter referred to as DMF) is an orally administered FAE indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy; unlike other available FAEs, it is not formulated in combination with monoethyl fumarate salts. EU approval was based on results of the phase III BRIDGE trial, and supported by previous publications of FAE preparations, including a combination of FAEs containing dimethyl fumarate and monoethyl fumarate salts (DMF/MEF; Fumaderm®). In the BRIDGE trial, DMF was superior to placebo in terms of the proportion of patients achieving a ≥ 75% improvement from baseline in the Psoriasis Area and Severity Index (PASI 75) and a Physician Global Assessment score of 0 (clear) or 1 (almost clear) at week 16. DMF was also noninferior to DMF/MEF for PASI 75 at week 16. Patients receiving DMF also reported clinically meaningful improvements in body surface area involvement and health-related quality of life. The safety profile of DMF was similar to that of DMF/MEF, and no major or unexpected safety concerns were identified. The most common adverse events (flushing and gastrointestinal disorders) occurred mainly during the first few weeks of treatment. Currently available data indicate that DMF is an effective oral systemic treatment option for patients with moderate to severe plaque psoriasis.

Fulvestrant: A Review in Advanced Breast Cancer Not Previously Treated with Endocrine Therapy

Emma D. Deeks

ABSTRACT

Fulvestrant (Faslodex®), a selective estrogen receptor (ER) degrader, is now indicated for the treatment of ER+ or hormone-receptor positive (HR+)/HER2− advanced breast cancer in postmenopausal women previously untreated with endocrine therapy. In the phase 3 FALCON trial conducted in this setting, intramuscular fulvestrant 500 mg/month (plus an additional dose at 2 weeks) was significantly more effective in prolonging progression-free survival (PFS) than oral anastrozole 1 mg/day (particularly in patients with non-visceral disease), with this benefit seemingly driven by fulvestrant recipients responding significantly longer to treatment. Other efficacy measures, including objective response rate, did not significantly or markedly differ between the two regimens and median overall survival was not yet calculable. Fulvestrant was generally well tolerated in this trial, displaying an overall tolerability profile consistent with its known tolerability in other breast cancer settings. Thus, monotherapy with intramuscular fulvestrant is a generally well tolerated and more effective treatment option than standard-of-care anastrozole for ER+ or HR+/HER2− advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
Acalabrutinib: First Global Approval
Anthony Markham Sohita Dhillon

ABSTRACT
Acerta Pharma is developing the Bruton’s tyrosine kinase inhibitor acalabrutinib (Calquence®) for the treatment of various haematological and solid malignancies. The drug has received accelerated approval from the US FDA for the treatment of mantle cell lymphoma based on the results of a phase II study, and phase III trials in mantle cell lymphoma and chronic lymphocytic leukaemia are currently underway. This article summarizes the milestones in the development of acalabrutinib leading to this first approval for mantle cell lymphoma.

Letermovir: First Global Approval
Esther S. Kim

ABSTRACT
Letermovir (Prevymis™) is an orally or intravenously administered cytomegalovirus (CMV) DNA terminase complex inhibitor being developed by Merck & Co., Inc., under a global license from AiCuris Anti-infective Cures GmbH. Letermovir has been approved in Canada and the USA for the prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant (HSCT). In addition, letermovir has received a positive opinion from the European Medicines Agency’s Committee for Medicinal Products for Human Use, and is under review in several countries, including Japan. This article summarizes the milestones in the development of letermovir leading to its first global approval in Canada as well as the USA for the prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic HSCT.
Hypermutated Tumors and Immune Checkpoint Inhibition
Kristen K. CiomborRichard M. Goldberg

ABSTRACT
Microsatellite instability-high/DNA mismatch repair deficient tumors are found across the cancer spectrum and often harbor markedly increased numbers of mutations when compared to microsatellite stable/DNA mismatch repair proficient tumors. As a result of this high mutational load, tumor-infiltrating lymphocyte density is increased and more immunogenic neoepitopes are expressed, leading to upregulation of immune checkpoints in these tumors. Checkpoint inhibitors such as pembrolizumab and nivolumab, both immunoglobulin G4 (IgG4) monoclonal antibodies that block interactions between the programmed cell death receptor-1 and its ligands, have significant activity in this tumor class. This review will focus on hypermutated tumors and immuno-oncology drug development for this biologically unique tumor type, with an emphasis on FDA-approved immunotherapies for these cancers, as well as a short discussion of the many therapeutic and scientific challenges ahead in order to optimize the uses of this new class of drug.

Drug-Induced Kidney Stones and Crystalline Nephropathy: Pathophysiology, Prevention and Treatment
Michel Daudon, Vincent FrochotDominique BazinPaul Jungers

ABSTRACT
Drug-induced calculi represent 1–2% of all renal calculi. The drugs reported to produce calculi may be divided into two groups. The first one includes poorly soluble drugs with high urine excretion that favour crystallisation in the urine. Among them, drugs used for the treatment of patients with human immunodeficiency, namely atazanavir and other protease inhibitors, and sulphadiazine used for the treatment of cerebral toxoplasmosis, are the most frequent causes. Besides these drugs, about 20 other molecules may induce nephrolithiasis, such as ceftriaxone or ephedrine-containing preparations in subjects receiving high doses or long-term treatment. Calculi analysis by physical methods including infrared spectroscopy or X-ray diffraction is needed to demonstrate the presence of the drug or its metabolites within the calculi. Some drugs may also provoke heavy intra-tubular crystal precipitation causing acute renal failure. Here, the identification of crystalluria or crystals within the kidney tissue in the case of renal biopsy is of major diagnostic value. The second group includes drugs that provoke the formation of urinary calculi as a consequence of their metabolic effects on urinary pH and/or the excretion of calcium, phosphate, oxalate, citrate, uric acid or other purines. Among such metabolically induced calculi are those formed in patients taking uncontrolled calcium/vitamin D supplements, or being treated with carbonic anhydrase inhibitors such as acetazolamide or topiramate. Here, diagnosis relies on a careful clinical inquiry to differentiate between common calculi and metabolically induced calculi, of which the incidence is probably underestimated. Specific patient-dependent risk factors also exist in relation to urine pH, volume of diuresis and other factors, thus providing a basis for preventive or curative measures against stone formation.
Pharmacological Prevention of Cardiovascular Outcomes in Diabetes Mellitus: Established and Emerging Agents
David R. Saxon, Neda RasouliRobert H. Eckel

ABSTRACT
Cardiovascular disease is a major cause of morbidity and mortality in patients with type 2 diabetes. For this reason, there is a great deal of interest in determining how therapies commonly used to treat patients with diabetes impact cardiovascular outcomes. Results from recently completed cardiovascular outcomes trials of diabetes agents from several medication classes are leading to a sea change in how we think about diabetes treatment. The primary focus of this paper is to review recently completed and ongoing diabetes medication cardiovascular outcomes trials. We also review cardiovascular outcome evidence for other classes of medications commonly used in patients with diabetes (i.e., aspirin, anti-hypertensive agents, lipid-lowering agents, and weight loss medications).

Lipid Management in Chronic Kidney Disease: Systematic Review of PCSK9 Targeting
BinBin Zheng-LinAlberto Ortiz

ABSTRACT
Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) and CKD is considered a coronary artery disease risk equivalent. So far, statins have been the mainstay of primary and secondary prevention of cardiovascular disease in the general population. However, their benefit on outcomes is limited and controversial in CKD patients and new therapeutic approaches to reduce cardiovascular risk are needed. Monoclonal antibodies targeting proprotein convertase subtilisin/kexin 9 (PCSK9) reduce low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) in high-risk populations and cardiovascular events in secondary prevention. We now review the limitations of the current approach to lipid management in CKD and information on CKD patients from clinical trials of anti-PCSK9 monoclonal antibodies alirocumab and evolocumab. In CKD subgroup analysis, ODYSSEY COMBO I and ODYSSEY COMBO II studies demonstrated significant superiority of alirocumab on LDL-cholesterol lowering in comparison to placebo and ezetimibe, respectively, when added to statins, and case reports have shown efficacy in nephrotic syndrome. A detailed analysis of CKD subgroups in general population trials of anti-PCSK9 strategies addressing events is needed, given the limited efficacy of statins in CKD both in terms of lipid lowering and events, the high rate of statin non-compliance in these patients, and the high lipoprotein(a) levels. This information should guide the design of trials addressing the safety profile and efficacy on cardiovascular outcomes of PCSK9-targeted therapies in CKD patients.

Paola PansaYingfen HsiaJulia BielickIrja LutsarA. Sarah WalkerMike SharlandLaura Folgori

ABSTRACT

Background: There are very few options to treat multidrug-resistant bacterial infections in children. A major barrier is the duration and complexity of regulatory trials of new antibiotics. Extrapolation of safety data from adult trials could facilitate drug development for children.

Objective: We performed a systematic review on the safety of antibiotic clinical trials (CTs) in children (0–18 years) to evaluate the overall quality of safety trials conducted in children and to determine if age-specific adverse events (AEs) could be identified for specific antibiotic classes.

Data Sources: We searched the MEDLINE, Cochrane CENTRAL, and ClinicalTrials.gov electronic databases for trials conducted between 2000 and 2016.

Study Selection: All trials in which safety was declared a primary or secondary endpoint were included. Exclusion criteria were (1) topical or inhalational route of administration; (2) non-infectious conditions; (3) administration for prophylaxis rather than treatment; (4) selected population (i.e. cystic fibrosis, malignancies, HIV and tuberculosis); and (5) design other than randomized controlled trials. Trials reporting data on both adults and children were included only if paediatric results were reported separately.

Data Extraction and Synthesis: Two authors independently extracted the data. To assess the quality of published trials, the Extension for harms for Consolidated Standards of Reporting Trials (CONSORT) Statement 2004 was used.

Main Outcome and Measure: In order to quantitatively assess the rate of developing AEs by drug class, the numbers of overall and body-system-specific AEs were collected for each study arm, and then calculated per single drug class as median and interquartile range (IQR) of the proportions across CTs. The AEs most frequently reported were compared in the meta-analysis by selecting the CTs on the most represented drug classes.

Results: Eighty-three CTs were included, accounting for 27,693 children. Overall, 69.7% of CONSORT items were fully reported. The median proportion of children with any AE was 22.5%, but did not exceed 8% in any single body system. Serious drug-related AEs and drug-related discontinuations were very rare (median 0.3 and 0.9%, respectively). Limitations included the inability to stratify by age group, particularly neonates.
Ledipasvir/Sofosbuvir: A Review in Chronic Hepatitis C

Lesley J. Scott

ABSTRACT
Oral once-daily, fixed-dose, ledipasvir/sofosbuvir (Harvoni®) [± ribavirin] is approved in several countries for the treatment of chronic hepatitis C (CHC) in adults and adolescents aged 12 to < 18 years, with direct-acting antiviral (DAA) regimens resulting in a paradigm shift in the treatment of the disease. In the clinical trial and/or clinical practice setting, ledipasvir/sofosbuvir (± ribavirin) was associated with high sustained virological response rates 12 weeks post-treatment (SVR12) in treatment-naive and -experienced adults and adolescents with chronic hepatitis C virus (HCV) genotype (GT) 1 infection, including in those with compensated cirrhosis or who were co-infected with HIV. SVR12 rates in real-world studies were consistent with those in trials. In other trials, ledipasvir/sofosbuvir (± ribavirin) was associated with high SVR12 rates in various CHC populations, including patients with HCV GT2, 3, 4, 5 or 6 infection, cirrhosis, pre and/or post liver or renal transplantation, inherited blood disorders or failure after prior DAA and/or interferon therapy. Thus, ledipasvir/sofosbuvir (± ribavirin) is a valuable effective and generally well tolerated option for adolescent and adult patients with HCV GT1, 4, 5 or 6 infection, including those with HIV co-infection or cirrhosis, with evidence also supporting its use in patients with chronic HCV GT2 or 3 infection.

MenB-FHbp Meningococcal Group B Vaccine (Trumenba®): A Review in Active Immunization in Individuals Aged ≥ 10 Years

Matt Shirley, Muhamed-Kheir Taha

ABSTRACT
MenB-FHbp (bivalent rLP2086; Trumenba®) is a recombinant protein-based vaccine targeting Neisseria meningitidis serogroup B (MenB), which has recently been licensed in the EU for active immunization to prevent invasive disease caused by MenB in individuals ≥ 10 years of age. The vaccine, which contains a variant from each of the two identified subfamilies of the meningococcal surface protein factor H-binding protein (fHBP), has been licensed in the USA for active immunization in individuals 10–25 years of age since 2014. This article reviews the immunogenicity, reactogenicity and tolerability of MenB-FHbp, with a focus on the EU label and the European setting. As demonstrated in an extensive program of clinical trials in adolescents and young adults, a two-dose or three-dose series of MenB-FHbp elicits a strong immune response against a range of MenB test strains selected to be representative of strains prevalent in Europe and the USA. Follow-up studies investigating the persistence of the MenB-FHbp immune response and the effect of a booster dose of the vaccine indicate that a booster dose should be considered (following a primary vaccine series) in individuals at continued risk of invasive meningococcal disease. MenB-FHbp vaccine appears to be moderately reactogenic but, overall, is generally well tolerated, with most adverse reactions being mild to moderate in severity. Although post-marketing, population-based data will be required to establish the true effectiveness of the vaccine, currently available data indicate that MenB-FHbp, in a two-dose or three-dose series, is likely to provide broad protection against MenB strains circulating in Europe.
Emicizumab-kxwh: First Global Approval
Lesley J. Scott, Esther S. Kim

ABSTRACT
Emicizumab-kxwh (Hemlibra®) is a bispecific humanized monoclonal antibody that restores the function of missing activated FVIII by bridging activated FIX and FX to facilitate effective haemostasis in patients with haemophilia A. Subcutaneous emicizumab-kxwh is approved in the USA for use as routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and paediatric patients with haemophilia A (congenital FVIII deficiency) with FVIII inhibitors. Subcutaneous emicizumab-kxwh is awaiting approval in several countries worldwide, including in the EU and Japan, and is undergoing phase 3 development in haemophilia A without FVIII inhibitors. This article summarizes the milestones in the development of emicizumab-kxwh leading to its first global approval for use as prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A.

Semaglutide: First Global Approval
Sohita Dhillon

ABSTRACT
Novo Nordisk has developed a subcutaneous formulation of semaglutide (Ozempic®), a modified human glucagon-like peptide-1 (GLP-1) analogue, for the treatment of type 2 diabetes mellitus. It has been developed using Novo Nordisk’s proprietary protein-acylation technology, and is administered using an injection device. Semaglutide lowers blood glucose by stimulating the release of insulin and also lowers body weight. Once-weekly subcutaneous semaglutide has recently been approved in the US, Puerto Rico and Canada, and has received a positive opinion in the EU for the treatment of patients with type 2 diabetes. It will be launched as the Ozempic® Pen, a pre-filled device. Semaglutide is also under regulatory review in Japan and Switzerland for the treatment of type 2 diabetes. Clinical development for obesity, non-alcoholic steatohepatitis and non-alcoholic fatty liver disease is underway worldwide. This article summarizes the milestones in the development of semaglutide leading to this first approval for type 2 diabetes.
Outcomes, Access, and Cost Issues Involving PCSK9 Inhibitors to Lower LDL-Cholesterol

Thomas F. Whayne

ABSTRACT

The clinical importance and benefit of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors appears well established for the high-risk cardiovascular (CV) patient. This applies especially to the statin-intolerant patient or the patient who does not attain an appropriate low-density lipoprotein cholesterol (LDL-C) target. Therefore, the barriers to appropriate clinical use of the PCSK9 inhibitors involve cost and not the documented CV benefit or LDL-C lowering. Multiple roadblocks affect many high-risk CV patients in arranging approval of a PCSK9 inhibitor. Overcoming these roadblocks may require legal pressures, some increased regulation, and facilitation by competitive forces.

Overview of Current Drugs and Molecules in Development for Spinal Muscular Atrophy Therapy

Hannah K. Shorrock Thomas H. Gillingswater Ewout J. N. Groen

ABSTRACT

Spinal muscular atrophy (SMA) is a neurodegenerative disease primarily characterized by a loss of spinal motor neurons, leading to progressive paralysis and premature death in the most severe cases. SMA is caused by homozygous deletion of the survival motor neuron 1 (SMN1) gene, leading to low levels of SMN protein. However, a second SMN gene (SMN2) exists, which can be therapeutically targeted to increase SMN levels. This has recently led to the first disease-modifying therapy for SMA gaining formal approval from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Spinraza (nusinersen) is a modified antisense oligonucleotide that targets the splicing of SMN2, leading to increased SMN protein levels, capable of improving clinical phenotypes in many patients. In addition to Spinraza, several other therapeutic approaches are currently in various stages of clinical development. These include SMN-dependent small molecule and gene therapy approaches along with SMN-independent strategies, such as general neuroprotective factors and muscle strength-enhancing compounds. For each therapy, we provide detailed information on clinical trial design and pharmacological/safety data where available. Previous clinical studies are also discussed to provide context on SMA clinical trial development and the insights these provided for the design of current studies.
Pharmacotherapy for Refractory and Super-Refractory Status Epilepticus in Adults

Martin Holtkamp

ABSTRACT
Patients with prolonged seizures that do not respond to intravenous benzodiazepines and a second-line anticonvulsant suffer from refractory status epilepticus and those with seizures that do not respond to continuous intravenous anesthetic anticonvulsants suffer from super-refractory status epilepticus. Both conditions are associated with significant morbidity and mortality. A strict pharmacological treatment regimen is urgently required, but the level of evidence for the available drugs is very low. Refractory complex focal status epilepticus generally does not require anesthetics, but all intravenous non-anesthetizing anticonvulsants may be used. Most descriptive data are available for levetiracetam, phenytoin and valproate. Refractory generalized convulsive status epilepticus is a life-threatening emergency, and long-term clinical consequences are eminent. Administration of intravenous anesthetics is mandatory, and drugs acting at the inhibitory gamma-aminobutyric acid (GABA)A receptor such as midazolam, propofol and thiopental/pentobarbital are recommended without preference for one of those. One in five patients with anesthetic treatment does not respond and has super-refractory status epilepticus. With sustained seizure activity, excitatory N-methyl-d-aspartate (NMDA) receptors are increasingly expressed post-synaptically. Ketamine is an antagonist at this receptor and may prove efficient in some patients at later stages. Neurosteroids such as allopregnanolone increase sensitivity at GABAA receptors; a Phase 1/2 trial demonstrated safety and tolerability, but randomized controlled data failed to demonstrate efficacy. Adjunct ketogenic diet may contribute to termination of difficult-to-treat status epilepticus. Randomized controlled trials are needed to increase evidence for treatment of refractory and super-refractory status epilepticus, but there are multiple obstacles for realization. Hitherto, prospective multicenter registries for pharmacological treatment may help to improve our knowledge.

Efficacy and Safety of Tiotropium in Children and Adolescents

Eckard Hamelmann, Stanley J. Szefler

ABSTRACT
Asthma is one of the most common chronic diseases in children, with a high proportion of patients demonstrating poor control despite the availability of disease management guidelines. Global Initiative for Asthma guidelines include tiotropium as an add-on therapy option at Steps 4 and 5 in patients aged ≥ 12 years with a history of exacerbations, and tiotropium delivered via the Respimat® Soft Mist™ Inhaler has recently been approved for use as once-daily maintenance therapy for children with asthma over the age of 6 years in the USA. A large clinical trial program has been conducted in children, adolescents, and adults across the spectrum of asthma severity. Findings from these clinical studies and pooled analyses in children and adolescents with symptomatic moderate or severe asthma have demonstrated that tiotropium Respimat® as add-on to inhaled corticosteroids, with or without other maintenance therapies, is a well-tolerated and efficacious bronchodilator, showing improved lung function and trends towards improved asthma control, mirroring findings in adult studies. This review discusses the evidence to date for tiotropium Respimat® for the management of asthma in adolescents and children with symptomatic moderate and severe asthma, and considers the challenges of asthma management in these patients. Factors affecting this population group, such as poor adherence, underreporting of symptoms, and social and psychological issues, are highlighted, along with the need for active review and management of treatment to help achieve optimal control.
Chronic postsurgical pain affects between 5 and 75% of patients, often with an adverse impact on quality of life. While the transition of acute to chronic pain is a complex process—involving multiple mechanisms at different levels—the current strategies for prevention have primarily been restricted to perioperative pharmacological interventions. In the present paper, we first present an up-to-date narrative literature review of these interventions. In the second section, we develop several ways by which we could overcome the limitations of the current approaches and enhance the outcome of our surgical patients, including the better identification of individual risk factors, tailoring treatment to individual patients, and improved acute and subacute pain evaluation and management. The third and final section covers the treatment of established CPSP. Given that evidence for the current therapeutic options is limited, we need high-quality trials studying multimodal interventions matched to pain characteristics.

**Belimumab: A Review in Systemic Lupus Erythematous**

Hannah A. Blair, Sean T. Duggan

**ABSTRACT**

Belimumab (Benlysta®) is a human immunoglobulin G1λ monoclonal antibody that inhibits the binding of soluble B lymphocyte stimulator to B cells. It is the only biological agent currently approved for the treatment of non-renal systemic lupus erythematosus (SLE). Belimumab is approved in the EU, the USA and other countries as add-on therapy in adult patients with active, autoantibody-positive SLE despite standard therapy. In phase III trials, treatment with IV or SC belimumab plus standard therapy was effective in terms of reducing overall disease activity and reducing the incidence and severity of flares, without worsening of patients’ overall condition or the development of significant disease activity in new organ systems. Sustained disease control was maintained during longer-term (up to 10 years) treatment with IV belimumab. Belimumab also demonstrated steroid-sparing effects and was associated with clinically meaningful improvements in health-related quality of life and fatigue. Belimumab was generally well tolerated in clinical trials, with low rates of immunogenicity. In view of the flexibility regarding the route of administration and the convenience of the once-weekly, self-administered, SC regimen, add-on therapy with belimumab is a useful treatment option for patients with active, autoantibody-positive SLE despite standard therapy.
Eculizumab: A Review in Generalized Myasthenia Gravis

Sohita Dhillon

ABSTRACT
The humanized monoclonal antibody eculizumab (Soliris®) is a complement inhibitor indicated for use in anti-acetylcholine receptor (AChR) antibody-positive adults with generalized myasthenia gravis (gMG) in the USA, refractory gMG in the EU, or gMG with symptoms that are difficult to control with high-dose IVlg therapy or PLEX in Japan. It is the first complement inhibitor to be approved for use in these patients. In the well-designed, 26-week REGAIN study in patients with anti-AChR-positive refractory gMG, although a statistically significant benefit of eculizumab over placebo in the prespecified primary endpoint analysis (change from baseline in MG-activities of daily living (ADL) score assessed by worst-rank ANCOVA) was not formally demonstrated, preplanned and post hoc sensitivity analyses of this outcome, as well as other secondary outcomes supported the efficacy of eculizumab. Overall, patients receiving eculizumab experienced significant improvements in the ADL, muscle strength and health-related quality of life (HR-QOL) parameters relative to patients receiving placebo. Moreover, an ongoing extension of REGAIN showed that treatment benefits with eculizumab were sustained during continued therapy for at least 52 weeks. Eculizumab was generally well tolerated in these studies, with a tolerability profile similar to that reported previously in other indications. Although several questions remain, such as duration of treatment, cost effectiveness and long-term efficacy and tolerability, current evidence indicates that eculizumab is a valuable emerging therapy for patients with refractory gMG.

Landiolol: A Review in Tachyarrhythmias

Yahiya Y. Syed

ABSTRACT
Intravenous landiolol [Rapibloc® (EU)], an ultra short-acting highly cardioselective β1-blocker, is approved in the EU for the rapid short-term control of tachyarrhythmias in the perioperative and intensive care settings. It has long been used in Japan to treat perioperative tachyarrhythmias. The efficacy of landiolol has been demonstrated in a large number of randomized controlled clinical trials. Landiolol significantly reduced heart rate in patients with postoperative or intraoperative supraventricular tachycardia relative to placebo and in those with atrial fibrillation/flutter and left ventricular dysfunction relative to digoxin. It was more effective than diltiazem in converting postoperative atrial fibrillation (POAF) to normal sinus rhythm. Perioperative prophylactic administration of landiolol significantly reduced the incidence of POAF during the first week after cardiac and other surgeries, compared with diltiazem, placebo or no landiolol treatment. Landiolol also attenuated adverse haemodynamic and other responses to invasive procedures such as percutaneous coronary intervention, tracheal intubation, extubation and electroconvulsive therapy. Landiolol was generally well tolerated, with a relatively low risk of hypotension and bradycardia. Landiolol has more favourable pharmacological properties than esmolol, a short-acting β-blocker commonly used for the rapid control of heart rate. Although additional comparative studies are warranted to define the place of landiolol relative to esmolol, current evidence suggest that landiolol is a useful option for the rapid short-term control of tachyarrhythmias. Landiolol offers a simple dosage scheme and is available in two easy-to-use formulations (concentrate and powder).
Netarsudil Ophthalmic Solution 0.02%: First Global Approval

Sheridan M. Hoy

ABSTRACT
Netarsudil ophthalmic solution 0.02% (hereafter referred to as netarsudil 0.02%) [Rhopressa®] is a Rho-associated protein kinase inhibitor that is thought to lower intraocular pressure (IOP) by increasing aqueous humour outflow through the trabecular meshwork. It has been developed by Aerie Pharmaceuticals and was recently approved in the USA for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The recommended dosage is one drop in the affected eye(s) once daily in the evening. Phase III development in the EU and phase II development in Japan are underway for this indication. This article summarizes the milestones in the development of netarsudil 0.02% leading to this first approval for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

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Generic Substitution of Orphan Drugs for the Treatment of Rare Diseases: Exploring the Potential Challenges

Antonello Di Paolo, Elena Arrigoni

ABSTRACT
Generic drugs are important components of measures introduced by healthcare regulatory authorities to reduce treatment costs. In most patients and conditions the switch from a branded drug to its generic counterpart is performed with no major complications. However, evidence from complex diseases suggests that generic substitution requires careful evaluation in some settings and that current bioequivalence criteria may not always be adequate for establishing the interchangeability of branded and generic products. Rare diseases, also called orphan diseases, are a group of heterogeneous diseases that share important characteristics: in addition to their scarcity, most are severe, chronic, highly debilitating, and often present in early childhood. Finding a treatment for a rare disease is challenging. Thanks to incentives that encourage research and development programs in rare diseases, several orphan drugs are currently available. The elevated cost of orphan drugs is a highly debated issue and a cause of limited access to treatment for many patients. As patent protection and the exclusivity period of several orphan drugs will expire soon, generic versions of orphan drugs should reach the market shortly, with great expectations about their impact on the economic burden of rare diseases. However, consistent with other complex diseases, generic substitution may require thoughtful considerations and may be even contraindicated in some rare conditions. This article provides an overview of rare disease characteristics, reviews reports of problematic generic substitution, and discusses why generic substitution of orphan drugs may be challenging and should be undertaken carefully in rare disease patients.
Recent Advances in Pharmacotherapy for Migraine Prevention: From Pathophysiology to New Drugs

Jonathan Jia Yuan Ong Diana Yi-Ting Wei Peter J. Goadsby

ABSTRACT

Migraine is a common and disabling neurological disorder, with a significant socioeconomic burden. Its pathophysiology involves abnormalities in complex neuronal networks, interacting at different levels of the central and peripheral nervous system, resulting in the constellation of symptoms characteristic of a migraine attack. Management of migraine is individualised and often necessitates the commencement of preventive medication. Recent advancements in the understanding of the neurobiology of migraine have begun to account for some parts of the symptomatology, which has led to the development of novel target-based therapies that may revolutionise how migraine is treated in the future. This review will explore recent advances in the understanding of migraine pathophysiology, and pharmacotherapeutic developments for migraine prevention, with particular emphasis on novel treatments targeted at the calcitonin gene-related peptide (CGRP) pathway.

Therapeutic Drug Monitoring of Beta-Lactams and Other Antibiotics in the Intensive Care Unit: Which Agents, Which Patients and Which Infections?

Anouk E. Muller Benedikt Huttner Angela Huttner

ABSTRACT

Antibiotics are among the medications most frequently administered to the critically ill, a population with high levels of intra- and inter-individual pharmacokinetic variability. Our knowledge of the relationships among antibiotic dosing, exposure and clinical effect in this population has increased in recent decades. Therapeutic drug monitoring (TDM) of serum antibiotic concentrations is the most practical means of assessing adequate antibiotic exposure, though until recently, it has been underutilised for this end. Now TDM is becoming more widespread, particularly for the beta-lactam antibiotics, a class historically thought to have a wide therapeutic range. We review the basic requirements, indications, and targets for effective TDM of the glycopeptides, aminoglycosides, quinolones and beta-lactam antibiotics in the adult intensive-care setting, with a special focus on TDM of the beta-lactam antibiotics, the most widely used antibiotic class.
Effect of Ezetimibe Monotherapy on Plasma Lipoprotein (a) Concentrations in Patients with Primary Hypercholesterolemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Kamal Awad, Dimitri P. MikhailidisNiki KatsikiPaul MuntnerMaciej Banachon behalf of Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group

ABSTRACT

Background and Aims: Ezetimibe reduces plasma low-density lipoprotein cholesterol (LDL-C) levels by up to 20%. However, its effect on plasma lipoprotein (a) [Lp(a)] concentrations in patients with primary hypercholesterolemia has not been defined.

Objective: Therefore, we performed a systematic review and meta-analysis to assess this effect based on the available randomized controlled trials (RCTs).

Methods: We searched the PubMed and SCOPUS databases from inception until 28 February 2017 to identify RCTs that investigated the effect of ezetimibe monotherapy on plasma Lp(a) concentrations in patients with primary hypercholesterolemia. We pooled mean percentage changes in plasma Lp(a) concentrations as a mean difference (MD) with a 95% confidence interval (CI).

Results: Seven RCTs with 2337 patients met the selection criteria and were included in the analysis. Overall pooled analysis suggested that ezetimibe 10 mg significantly reduced plasma Lp(a) concentrations in patients with primary hypercholesterolemia by −7.06% (95% CI −11.95 to −2.18; p = 0.005) compared with placebo. No significant heterogeneity was observed ($\chi^2 = 5.34; p = 0.5$). Excluding one study from the analysis resulted in insignificant differences between the two groups (p = 0.2). Meta-regression did not find a significant association between the mean percentage changes in Lp(a) and other potential moderator variables, which included the mean percentage changes of LDL-C concentrations (p = 0.06) and baseline Lp(a) mean values (p = 0.46).

Conclusions: Ezetimibe monotherapy (10 mg/day) showed a small (7.06%) but statistically significant reduction in the plasma levels of Lp(a) in patients with primary hypercholesterolemia. According to current literature, this magnitude of reduction seems to have no clinical relevance. However, further studies are warranted to clarify the mechanism mediating this effect of ezetimibe and to investigate its efficacy in combination with other drugs that have shown promise in lowering Lp(a) levels.
Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Hillel P. Cohen, Andrew BlauveltRobert M. RifkinSilvio DaneseSameer B. GokhaleGillian Woollett

ABSTRACT

Introduction: To evaluate the possibility that switching from reference biologic medicines to biosimilars could lead to altered clinical outcomes, including enhanced immunogenicity, compromised safety, or diminished efficacy for patients, a systematic literature review was conducted of all switching studies between related biologics (including biosimilars).

Methods: A systematic search was conducted using the Medline® and Embase® databases up to 30 June 2017 employing specific medical subject heading terms. Additionally, the snowball method and a hand search were also applied. Publications were considered if they contained efficacy or safety information related to a switch from a reference medicine to a biosimilar. Non-English, non-human studies, editorials, notes, and short surveys were excluded.

Results: Primary data were available from 90 studies that enrolled 14,225 unique individuals. They included protein medicines used in supportive care as well as those used as therapeutic agents. The medicines contained seven different molecular entities that were used to treat 14 diseases. The great majority of the publications did not report differences in immunogenicity, safety, or efficacy. The nature and intensity of safety signals reported after switching from reference medicines to biosimilars were the same as those already known from continued use of the reference medicines alone. Three large multiple switch studies with different biosimilars did not show differences in efficacy or safety after multiple switches between reference medicine and biosimilar. Two publications reported a loss of efficacy or increased dropout rates.

Conclusions: While use of each biologic must be assessed individually, these results provide reassurance to healthcare professionals and the public that the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine.

Ferric Carboxymaltose: A Review in Iron Deficiency

Lesley J. Scott

ABSTRACT

Intravenous ferric carboxymaltose (Ferinject®; Injectafer®) is a colloidal solution of nanoparticles which consist of a polynuclear iron (III)-(oxyhydr)oxide core stabilized by carboxymaltose and may be given as a single high-dose, 15-min infusion. This article reviews the clinical use of ferric carboxymaltose in various patient populations with iron deficiency (ID) [± anaemia] and briefly summarizes its pharmacological properties. Based on extensive experience in the clinical trial and real-world settings, ferric carboxymaltose is an effective and generally well tolerated treatment for rapidly replenishing iron stores and correcting anaemia in patients with ID (± anaemia) of various aetiologies, including patients with chronic heart failure (CHF), chronic kidney disease, inflammatory bowel disease or perioperative anaemia, and women with ID during pregnancy, postpartum or associated with heavy uterine bleeding. As it may be given as a single high-dose infusion, ferric carboxymaltose has the potential to provide cost savings from a healthpayer perspective. Thus, ferric carboxymaltose remains an important option for the treatment of ID in adults and, where approved, children aged ≥ 14 years, when oral iron preparations are ineffective or cannot be used.
Brodalumab: A Review in Moderate to Severe Plaque Psoriasis

Hannah A. Blair

ABSTRACT
Brodalumab (Kyntheum®) is a human anti-interleukin-17 receptor A (IL-17RA) monoclonal antibody available for use in patients with moderate to severe plaque psoriasis. In the phase III AMAGINE trials in this patient population, 12 weeks of induction therapy with subcutaneous brodalumab was superior to placebo in terms of the proportion of patients with $\geq 75\%$ improvement in the Psoriasis Area and Severity Index score (PASI 75) and the proportion of patients with a static Physician Global Assessment score of 0 or 1. Brodalumab was also superior to ustekinumab for PASI 100 (i.e. complete skin clearance) at week 12. Health-related quality of life (HR-QOL) outcomes improved to a significantly greater extent with brodalumab than with placebo. Moreover, brodalumab was more effective than placebo in patients with difficult-to-treat nail or scalp psoriasis. Brodalumab was generally well tolerated, with low rates of immunogenicity. Efficacy was sustained and brodalumab remained well tolerated during up to 52 weeks of maintenance therapy. Thus, subcutaneous brodalumab is a useful addition to the treatment options currently available for patients with moderate to severe plaque psoriasis.

Benralizumab: First Global Approval
A. Markham

ABSTRACT
Kyowa Hakko Kirin, AstraZeneca and subsidiaries are developing benralizumab (Fasenra™)—a humanised anti-interleukin-5 receptor alpha chain (IL-5Rα) monoclonal antibody—as a treatment of severe eosinophilic asthma and chronic obstructive pulmonary disease (COPD). Eosinophilia is a characteristic of certain asthma and COPD phenotypes and depletion of eosinophils has demonstrated therapeutic benefit. Benralizumab was recently approved by the US FDA as add-on maintenance therapy for patients with severe asthma who have an eosinophilic phenotype. This article summarizes the milestones in the development of benralizumab leading to this first approval for the treatment of severe eosinophilic asthma.

Ertugliflozin: First Global Approval
Anthony Markham

ABSTRACT
Ertugliflozin (Steglatro™) is an orally active sodium glucose co-transporter type 2 inhibitor being developed by Merck and Pfizer as a treatment for type 2 diabetes mellitus (T2DM). Ertugliflozin as monotherapy and in combination with various other antidiabetic drugs was associated with improvements in glycaemic control and secondary outcome measures in the VERTIS phase III clinical trial program. Ertugliflozin and fixed-dose combinations of ertugliflozin and metformin (Segluromet™) and ertugliflozin and sitagliptin (Steglujan™) have recently been approved by the US FDA as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. These products have also received a positive opinion from the EU Committee for Medicinal Products for Human Use (CHMP). This article summarizes the milestones in the development of ertugliflozin leading to its first approval for T2DM.
Treatment of Tardive Dyskinesia: A General Overview with Focus on the Vesicular Monoamine Transporter 2 Inhibitors

Nicki NiemannJoseph Jankovic

ABSTRACT

Tardive dyskinesia (TD) encompasses the spectrum of iatrogenic hyperkinetic movement disorders following exposure to dopamine receptor-blocking agents (DRBAs). Despite the advent of atypical or second- and third-generation antipsychotics with a presumably lower risk of complications, TD remains a persistent and challenging problem. Prevention is the first step in mitigating the risk of TD, but early recognition, gradual withdrawal of offending medications, and appropriate treatment are also critical. As TD is often a persistent and troublesome disorder, specific antidyskinetic therapies are often needed for symptomatic relief. The vesicular monoamine transporter 2 (VMAT2) inhibitors, which include tetrabenazine, deutetetrabenazine, and valbenazine, are considered the treatment of choice for most patients with TD. Deutetetrabenazine—a deuterated version of tetrabenazine—and valbenazine, the purified parent product of one of the main tetrabenazine metabolites, are novel VMAT2 inhibitors and the only drugs to receive approval from the US FDA for the treatment of TD. VMAT2 inhibitors deplete presynaptic dopamine and reduce involuntary movements in many hyperkinetic movement disorders, particularly TD, Huntington disease, and Tourette syndrome. The active metabolites of the VMAT2 inhibitors have high affinity for VMAT2 and minimal off-target binding. Compared with tetrabenazine, deutetetrabenazine and valbenazine have pharmacokinetic advantages that translate into less frequent dosing and better tolerability. However, no head-to-head studies have compared the various VMAT2 inhibitors. One of the major advantages of VMAT2 inhibitors over DRBAs, which are still being used by some clinicians in the treatment of some hyperkinetic disorders, including TD, is that they are not associated with the development of TD. We also briefly discuss other treatment options for TD, including amantadine, clonazepam, Gingko biloba, zolpidem, botulinum toxin, and deep brain stimulation. Treatment of TD and other drug-induced movement disorders must be individualized and based on the severity, phenomenology, potential side effects, and other factors discussed in this review.
Episodic Breathlessness in Patients with Advanced Cancer: Characteristics and Management
Sebastiano Mercadante

ABSTRACT

The aim of this review is to present the way in which episodic breathlessness (EB) has been recognized over the years, with regard to definition, characteristics, and management of these acute episodes that have serious consequences for patients. EB is characterized by a sudden increase in intensity of dyspnea over a short duration of time, leading to high levels of anxiety. A significant aggravation of dyspnea may occur in patients with a background of dyspnea or intermittently even without basal breathlessness. Often, known precipitating factors may trigger EB. Flares of breathlessness are accompanied by degrees of psychological distress, although it is unclear whether psychological factors may precede or be induced by EB. In any case, there is a reinforcing circuit. The duration of EB ranges from 10–30 min. Given the specific temporal pattern, requiring rapid intervention, substances with a short onset of action are suitable to overlap this phenomenon. Short-onset opioids could provide a clinical effect overlapping the onset and duration of an episode, resembling what has been largely reported for breakthrough pain. Although data are still insufficient to suggest specific recommendations, strategies such as avoiding exertion, pacing or using devices, or keeping calm have been described. Few controlled studies have investigated the effects of different formulations of opioids. Some data were gathered from studies assessing the pre-emptive use of rapid onset opioids, such as transmucosal preparations of fentanyl, followed by a provocative test, while other studies attempted to reproduce real-life conditions, given as needed. All these trials were insufficiently powered to address the efficacy of fentanyl products over oral morphine or placebo, reflecting the difficulties in patient recruiting and finalizing the studies. Strategies to prevent the occurrence of EB should be taken into consideration, including optimization of the condition of persistent dyspnea or treating psychologic or environmental causes.

BRAF and MEK Inhibitors: Use and Resistance in BRAF-Mutated Cancers
Jaquelyn N. SanchezTon WangMark S. Cohen

ABSTRACT

The mitogen activated protein kinase/extracellular signal-related kinase (MAPK/ERK) signaling pathway serves an integral role in growth, proliferation, differentiation, migration, and survival of all mammalian cells. Aberrant signaling of this pathway is often observed in several types of hematologic and solid malignancies. The most frequent insult to this signaling cascade, leading to its constitutive activation, is to the serine/threonine kinase rapidly accelerating fibrosarcoma (RAF). Considering this, the development and approval of various small-molecule inhibitors targeting the MAPK/ERK pathway has become a mainstay of treatment as either mono- or combination therapy in these cancers. Although effective initially, a major clinical barrier with these inhibitors is the relapse of patients due to drug resistance. Knowledge of the mechanisms of resistance to these drugs is still premature, highlighting the need for a more in-depth understanding of how patients become insensitive to these pharmacologic interventions. Herein, we will succinctly summarize the milestones in the approval of select MAPK/ERK pathway inhibitors, their use in patients, and major modes of resistance.
The 2017 American College of Cardiology/American Heart Association hypertension guidelines diagnose hypertension if systolic blood pressure (SBP) is ≥130 mmHg or diastolic blood pressure (DBP) is ≥80 mmHg. Increased BP is SBP 120–129 mmHg with DBP < 80 mmHg. Lifestyle measures should be used to treat individuals with increased BP. Lifestyle measures plus BP-lowering drugs should be used for secondary prevention of recurrent cardiovascular events in individuals with clinical cardiovascular disease (coronary heart disease, congestive heart failure, or stroke) and an average SBP ≥130 mmHg or an average DBP ≥80 mmHg. Lifestyle measures plus BP-lowering drugs should be used for primary prevention of cardiovascular disease in individuals with an estimated 10-year risk of atherosclerotic cardiovascular disease (ASCVD) ≥10% and an average SBP ≥130 mmHg or an average DBP ≥80 mmHg. Lifestyle measures plus BP-lowering drugs should be used for primary prevention of cardiovascular disease in individuals with an estimated 10-year risk of ASCVD <10% and an average SBP ≥140 mmHg or an average DBP ≥90 mmHg. White coat hypertension must be excluded before starting antihypertensive drug treatment in individuals with hypertension with a low risk for ASCVD. BP should be lowered to <130/80 mmHg in patients with coronary heart disease, heart failure, or chronic kidney disease; after renal transplantation; for secondary stroke prevention; in lacunar stroke, peripheral arterial disease, and diabetes mellitus; and in ambulatory community-dwelling adults aged >65 years. The selection of antihypertensive drug treatment is discussed.

Sofosbuvir/Velpatasvir/Voxilaprevir: A Review in Chronic Hepatitis C
Young-A Heo, Emma D. Deeks

A fixed-dose combination of the hepatitis C virus (HCV) NS5B polymerase inhibitor sofosbuvir, the HCV NS5A inhibitor velpatasvir and the HCV NS3/4A protease inhibitor voxilaprevir (sofosbuvir/velpatasvir/voxilaprevir; Vosevi®) is approved in the EU for the treatment of chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection in adults. In the phase III POLARIS trials, in patients who had HCV genotype 1–6 infection with or without compensated cirrhosis, overall rates of sustained virological response at 12 weeks post-treatment (SVR12) with sofosbuvir/velpatasvir/voxilaprevir were high after 8 weeks of treatment in direct-acting antiviral (DAA)-naïve patients and 12 weeks of treatment in DAA-experienced patients. However, 8 weeks of sofosbuvir/velpatasvir/voxilaprevir was inferior to 12 weeks of sofosbuvir/velpatasvir in cirrhotic or non-cirrhotic DAA-naïve patients with HCV genotype 1, 2, 4, 5 or 6 infection and non-cirrhotic DAA-naïve patients with HCV genotype 3 infection, mostly due to an insufficient treatment period. Sofosbuvir/velpatasvir/voxilaprevir was generally well tolerated, with most adverse events being of mild or moderate intensity. The most common adverse events included headache, fatigue, nausea and diarrhoea. In conclusion, sofosbuvir/velpatasvir/voxilaprevir is an important and effective option for the treatment of HCV genotype 1–6 infection in adults, especially those who have previously failed a DAA therapy with or without an HCV NS5A inhibitor.
OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine

James E. Frampton, Stephen Silberstein

ABSTRACT

An intramuscular formulation of onabotulinumtoxinA (onabotA; Botox®) is currently the only therapy specifically approved for the prevention of headaches in adults with chronic migraine (CM) in the EU and North America. This article provides a narrative review of relevant data on the drug in this indication from an EU perspective. OnabotA was originally approved on the basis of pooled data from two phase III studies (PREEMPT 1 and 2). In these pivotal studies, injection of up to five cycles of onabotA (155–195 U/cycle) at 12-week intervals was generally well tolerated and effective in producing statistically significant and clinically meaningful improvements in headache symptoms, acute headache pain medication usage, headache impact and health-related quality of life in adults with CM, of whom approximately two-thirds were acute medication overusers and approximately one-third had failed to respond to ≥3 prior oral prophylactic therapies. More recently, the efficacy and tolerability of onabotA over a period of 1 year in the PREEMPT programme has been substantiated and extended by the results of a long-term phase IV study (COMPEL), in which patients received up to nine treatment cycles over a period of 2 years, and by findings from several real-world clinical practice studies from Europe, including the prospective multinational REPOSE and CM-PASS studies. In conclusion, the totality of evidence from clinical trials and real-world studies indicates that onabotA is an effective and generally well tolerated option for the prevention of CM that may be particularly useful for patients who have previously failed to respond to or are intolerant of commonly prescribed oral prophylactics.
Role of Methotrexate in the Management of Psoriatic Arthritis
Musaab Elmamoun Vinod Chandran

ABSTRACT
Methotrexate is known to be safe and efficacious in the management of rheumatoid arthritis and psoriasis and thus has been used for the management of psoriatic arthritis despite a lack of evidence to support efficacy in psoriatic arthritis from randomized controlled trials. Although the largest randomized trial to date did not support its use as a disease-modifying therapy, observational studies have supported its role, and current treatment recommendations approve of its use as a first-line agent for the management of psoriatic arthritis with predominant peripheral arthritis. The first treat-to-target study in psoriatic arthritis, comparing tight control with standard care, has shown the efficacy of methotrexate as monotherapy in the first 12 weeks. This trial demonstrated the effectiveness of methotrexate with improvement in peripheral arthritis, skin and nail disease, enthesitis, and dactylitis over the course of 12 weeks. There is conflicting evidence about the role of combination (concomitant methotrexate and anti-tumor necrosis factor) therapy. However, drug survival and immunogenicity of certain anti-tumor necrosis factors seem to be better when used in combination with methotrexate. This report reviews the available evidence on the efficacy and effectiveness of methotrexate in psoriatic arthritis and its role in treating psoriatic arthritis to target, as well as in combination with biologic agents. Ideally, randomized placebo-controlled clinical trials evaluating methotrexate (using subcutaneous route of delivery) would provide much-needed clarity on the role of methotrexate in the management of psoriatic arthritis; however, issues around using a placebo in patients with active psoriatic arthritis may render such a trial unfeasible.

Individualising Therapy to Minimize Bacterial Multidrug Resistance
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ABSTRACT
The scourge of antibiotic resistance threatens modern healthcare delivery. A contributing factor to this significant issue may be antibiotic dosing, whereby standard antibiotic regimens are unable to suppress the emergence of antibiotic resistance. This article aims to review the role of pharmacokinetic and pharmacodynamic (PK/PD) measures for optimising antibiotic therapy to minimise resistance emergence. It also seeks to describe the utility of combination antibiotic therapy for suppression of resistance and summarise the role of biomarkers in individualising antibiotic therapy. Scientific journals indexed in PubMed and Web of Science were searched to identify relevant articles and summarise existing evidence. Studies suggest that optimising antibiotic dosing to attain defined PK/PD ratios may limit the emergence of resistance. A maximum aminoglycoside concentration to minimum inhibitory concentration (MIC) ratio of > 20, a fluoroquinolone area under the concentration–time curve to MIC ratio of > 285 and a β-lactam trough concentration of > 6 × MIC are likely required for resistance suppression. In vitro studies demonstrate a clear advantage for some antibiotic combinations. However, clinical evidence is limited, suggesting that the use of combination regimens should be assessed on an individual patient basis. Biomarkers, such as procalcitonin, may help to individualise and reduce the duration of antibiotic treatment, which may minimise antibiotic resistance emergence during therapy. Future studies should translate laboratory-based studies into clinical trials and validate the appropriate clinical PK/PD predictors required for resistance suppression in vivo. Other adjunct strategies, such as biomarker-guided therapy or the use of antibiotic combinations require further investigation.
Herbal Dietary Supplements for Erectile Dysfunction: A Systematic Review and Meta-Analysis

Francesca Borrelli, Cristiano ColaltoDomenico V. DelfinoMarcello IritiAngelo A. Izzo

ABSTRACT

Purpose: Erectile dysfunction (ED) is a common condition that significantly affects quality of life and interpersonal relationships.

Objective: Our objective was to perform a systematic review and meta-analysis to evaluate the efficacy of herbal dietary supplements in the treatment of ED.

Materials and Methods: We searched five databases to identify randomized controlled trials (RCTs) that evaluated the clinical efficacy of herbal medicines in ED. Quality was assessed and risk of bias was estimated using the Jadad score and the Cochrane risk-of-bias tool.

Results: In total, 24 RCTs, including 2080 patients with ED, were identified. Among these, 12 evaluated monopreparations (five ginseng [n = 399], three saffron [n = 397], two Tribulus terrestris [n = 202], and one each Pinus pinaster [n = 21] and Lepidium meyenii [n = 50]), seven evaluated formulations (n = 544), and five investigated dietary supplements in combination with pure compounds (n = 410). Ginseng significantly improved erectile function (International Index of Erectile Function [IIEF]-5 score: 140 ginseng, 96 placebo; standardized mean difference [SMD] 0.43; 95% confidence interval [CI] 0.15–0.70; P < 0.01; I2 = 0). P. pinaster and L. meyenii showed very preliminary positive results, and saffron and T. terrestris treatment produced mixed results. Several herbal formulations were associated with a decrease of IIEF-5 or IIEF-15, although the results were preliminary. The quality of the included studies varied, with only seven having a prevalent low risk of bias. The median methodological quality Jadad score was three out of a maximum of five. Adverse events were recorded in 19 of 24 trials, with no significant differences between placebo and verum in placebo-controlled studies.

Conclusions: Encouraging evidence suggests that ginseng may be an effective herbal treatment for ED. However, further, larger, and high-quality studies are required before firm conclusions can be drawn. Promising (although very preliminary) results have also been generated for some herbal formulations. Overall, more research in the field, adhering to the CONSORT statement extension for reporting trials, is justified before the use of herbal products in ED can be recommended.
Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative Bacterial Infections
Matt Shirley

ABSTRACT

Ceftazidime-avibactam (Zavicefta®) is an intravenously administered combination of the third-generation cephalosporin ceftazidime and the novel, non-β-lactam β-lactamase inhibitor avibactam. In the EU, ceftazidime-avibactam is approved for the treatment of adults with complicated urinary tract infections (cUTIs) [including pyelonephritis], complicated intra-abdominal infections (cIAIs), hospital-acquired pneumonia (HAP) [including ventilator-associated pneumonia (VAP)], and other infections caused by aerobic Gram-negative organisms in patients with limited treatment options. This article discusses the in vitro activity and pharmacological properties of ceftazidime-avibactam, and reviews data on the agent’s clinical efficacy and tolerability relating to use in these indications, with a focus on the EU label. Ceftazidime-avibactam has excellent in vitro activity against many important Gram-negative pathogens, including many extended-spectrum β-lactamase-, AmpC-, Klebsiella pneumoniae carbapenemase- and OXA-48-producing Enterobacteriaceae and drug-resistant Pseudomonas aeruginosa isolates; it is not active against metallo-β-lactamase-producing strains. The clinical efficacy of ceftazidime-avibactam in the treatment of cUTI, cIAI and HAP (including VAP) in adults was demonstrated in pivotal phase III non-inferiority trials with carbapenem comparators. Ceftazidime-avibactam treatment was associated with high response rates at the test-of-cure visit in patients with infections caused by ceftazidime-susceptible and -nonsusceptible Gram-negative pathogens. Ceftazidime-avibactam was generally well tolerated, with a safety and tolerability profile consistent with that of ceftazidime alone and that was generally typical of the injectable cephalosporins. Thus, ceftazidime-avibactam represents a valuable new treatment option for these serious and difficult-to-treat infections.

Baloxavir: First Global Approval
Young-A Heo

ABSTRACT

Baloxavir marboxil (Xofluza™; baloxavir) is an oral cap-dependent endonuclease inhibitor that has been developed by Roche and Shionogi. The drug blocks influenza virus proliferation by inhibiting the initiation of mRNA synthesis. In February 2018, baloxavir received its first global approval in Japan for the treatment of influenza A or B virus infections. Phase III development is underway in the USA, EU and other countries for this indication. This article summarized the milestones in the development of baloxavir leading to this first global approval for influenza A or B virus infections.
Apalutamide: First Global Approval
Zaina T. Al-Salama

ABSTRACT
Apalutamide (Erleada™) is a next-generation oral androgen receptor (AR) inhibitor that is being developed by Janssen for the treatment of prostate cancer (PC). It binds directly to the ligand-binding domain of the AR and blocks the effects of androgens. In February 2018, apalutamide received its first global approval in the USA for the treatment of non-metastatic castration-resistant PC (nmCRPC). Apalutamide is undergoing phase III investigation in chemotherapy-naive patients with metastatic CRPC (in combination with abiraterone acetate plus prednisone), patients with high-risk localized or locally advanced PC receiving primary radiation therapy, and in patients with metastatic hormone-sensitive PC and biochemically-relapsed PC. This article summarizes the milestones in the development of apalutamide leading to this first approval in nmCRPC.

Burosumab: First Global Approval
Yvette N. Lamb

ABSTRACT
Burosumab (Crysvita®; Kyowa Hakko Kirin Co., Ltd. and Ultragenyx Pharmaceutical Inc.) is a fully human monoclonal antibody directed at fibroblast growth factor 23 (FGF23). Excessive FGF23 production has been implicated in various hypophosphataemic diseases. Inhibition of FGF23 by burosumab results in increased renal phosphate reabsorption and increased serum levels of phosphorus and active vitamin D. In February 2018, the EMA granted subcutaneous burosumab conditional marketing authorization for the treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. In April 2018, the US FDA approved burosumab for the treatment of XLH in adults and children one year of age and older. Multinational phase III trials of burosumab are currently underway in adult and paediatric patients with XLH. Burosumab is also being evaluated in the phase II setting in adults with tumour-induced osteomalacia and epidermal nevus syndrome in the USA, as well as in Japan and Korea. This article summarizes the milestones in the development of burosumab leading to its first global approval in the EU for XLH in paediatric patients.
The Potential Role of SGLT2 Inhibitors in the Treatment of Type 1 Diabetes Mellitus

Hadi Fattah, Volker Vallon

ABSTRACT

Type 1 diabetes mellitus is a difficult disease to treat due to the relative paucity of therapeutic options other than injectable insulin. The latter, however, can induce hypoglycemia, which has been linked to enhanced cardiovascular risk. Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of oral anti-hyperglycemic medications that do not increase the hypoglycemia risk and are US Food and Drug Administration (FDA) approved in type 2 diabetes mellitus. SGLT2 inhibitors may also be of benefit in type 1 diabetic patients, in addition to insulin, although they have not yet been approved for this indication. By blocking SGLT2 in the early proximal tubules of the kidney, these drugs decrease renal glucose retention, which is enhanced in hyperglycemia, thereby improving blood glucose control, in type 1 and type 2 diabetic patents. Their low hypoglycemia risk is due to the compensating reabsorption capacity of another glucose transporter, SGLT1, in the downstream late proximal tubule and the body’s metabolic counter-regulation, which remains intact during SGLT2 inhibition. When insulin dosage is lowered too much, SGLT2 inhibitors can enhance ketogenesis to the extent that the risk of diabetic ketoacidosis increases, particularly in type 1 diabetic patients. SGLT2 inhibitors improve the renal and cardiovascular outcome in type 2 diabetic patients. The mechanisms likely include a reduction in glomerular hyperfiltration, blood pressure, volume overload, and body weight, as well as lowering blood glucose without increasing the hypoglycemia risk. The same mechanistic effects are induced in type 1 diabetic patients. More studies are needed with SGLT2 inhibitors in type 1 diabetic patients, including renal and cardiovascular clinical outcome trials, to fully evaluate their therapeutic potential in this specific population.

The Expanding Role of Ketamine in the Emergency Department

Sophia Sheikh, Phyllis Hendry

ABSTRACT

Patients frequently come to the emergency department for pain. For decades, ketamine has been used in the emergency department for procedural sedation but is now receiving attention as a potential alternative to opioids because of its unique analgesic effects. Additionally, ketamine’s dissociative properties have made it a popular choice for sedating profoundly agitated patients. In this narrative review, these new roles for ketamine in the emergency department are discussed.
Chemotherapy-Induced Neutropenia as a Prognostic and Predictive Marker of Outcomes in Solid-Tumor Patients
Pashtoon Murtaza KasiAxel Grothey

ABSTRACT
Chemotherapy诱导的中性粒细胞减少症（CIN）是癌症患者最常见的副作用之一。作为一种不良事件，它被认为是有害的，因为它经常导致治疗延迟和/或剂量减少。它还与来自诊断工作和治疗患者的化疗诱发的发热中性粒细胞减少症（CIFN）中的一种经济成本相关。中性粒细胞减少症通常伴随着由其他造血干细胞减少而来的贫血（和/或血小板减少症）。将化疗药物的剂量给予患者，是基于其毒性程度而定的。根据中性粒细胞减少症的严重程度，化疗药物也可以被推迟，直到计数恢复和生长因子支持可能被允许以允许进行剂量计划。然而，中性粒细胞减少症似乎比只是另一种不良事件更大。虽然CIFN本身可能是一个不良事件，但中性粒细胞减少症可能不一定是预示不良结果的标记。实际上，它似乎是一个治疗反应和/或生存率的可能预测标志。对于化疗药物引起的不良事件，通过不同的肿瘤类型和/或治疗计划，在不同治疗方案中，CIN对改善结果的影响。如果CIN是一个治疗反应的预测标志，那么化疗药物的剂量可能需要被调整以实现中性粒细胞减少症。另外，考虑到安全性问题，生长因子支持的增加和替代的给药方案可能是需要考虑的策略。

Apatinib: A Review in Advanced Gastric Cancer and Other Advanced Cancers
Lesley J. Scott

ABSTRACT
Apatinib [Aitan® (brand name in China)], also known as rivoceranib, is a novel, small molecule, selective vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor and is the second anti-angiogenic drug to be approved in China for the treatment of advanced or metastatic gastric cancer. This article summarizes the pharmacological properties of apatinib and reviews its clinical use in chemotherapy-experienced patients with advanced gastric adenocarcinoma, including gastroesophageal adenocarcinoma (GEA), or with other advanced cancers such as non-small cell lung cancer (NSCLC), breast cancer, gynaecological cancers, hepatocellular carcinoma (HCC), thyroid cancer and sarcomas. As third- or subsequent-line therapy, oral apatinib significantly prolonged median progression-free survival (PFS) and overall survival (OS) compared with placebo and had a manageable safety profile in Chinese patients with advanced or metastatic gastric cancer or GEA participating in randomized, double-blind, multicentre, phase 2 and 3 trials. More limited evidence also supports it use as subsequent-line treatment in Chinese patients with other advanced or metastatic solid tumours, including NSCLC, breast cancer and HCC. Further clinical experience and long-term pharmacovigilance data are required to more definitively establish the efficacy and safety profile of apatinib, including its use in combination with other chemotherapy agents and its role in the management of other types of advanced or metastatic solid tumours. In the meantime, given its convenient administration regimen and the limited treatment options and poor prognosis for patients with advanced or metastatic solid tumours, apatinib is an important, emerging treatment option for adult patients with advanced gastric adenocarcinoma or GEA who have progressed or relapsed after chemotherapy.
Baricitinib: A Review in Rheumatoid Arthritis

Zaina T. Al-Salama, Lesley J. Scott

ABSTRACT

Baricitinib (Olumiant®) is an oral, targeted synthetic DMARD that inhibits JAK1 and JAK2, which are implicated in the pathogenesis of rheumatoid arthritis (RA). This novel, small molecule is approved for use as monotherapy, or in combination with methotrexate, for the treatment of adults with moderate to severe active RA who responded inadequately to or were intolerant of ≥ 1 DMARD. In pivotal multinational trials, once-daily baricitinib 4 mg, with/without methotrexate (± another csDMARD), improved the signs and symptoms of RA, disease activity and physical function in DMARD-naive patients and in patients with an inadequate response to methotrexate, csDMARDs or TNF inhibitors; baricitinib treatment also slowed structural joint damage in DMARD-naive patients and in those with an inadequate response to methotrexate and csDMARDs. Baricitinib plus methotrexate was more effective than adalimumab plus methotrexate in patients with an inadequate response to methotrexate. The onset of these benefits was generally rapid and sustained over time. Baricitinib was generally well tolerated during up to 5.5 years’ treatment; the most commonly reported adverse drug reactions were upper respiratory tract infections, increased LDL cholesterol, nausea and thrombocytosis. Thus, once-daily baricitinib, as monotherapy or in combination with methotrexate, is an effective and generally well tolerated emerging treatment for patients with moderate to severe active RA who have responded inadequately to or are intolerant of ≥ 1 DMARD, and extends the options available for this population.

Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension

Sheridan M. Hoy

ABSTRACT

Latanoprostene bunod ophthalmic solution 0.024% (hereafter referred to as latanoprostene bunod 0.024%) [Vyzulta™] is a nitric oxide (NO)-donating prostaglandin F2α analogue approved in the USA for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension. It is thought to lower IOP by increasing aqueous humour outflow through the uveoscleral pathway (mediated by latanoprost acid) and increasing the facility of aqueous humour outflow through the trabecular meshwork pathway (mediated by NO). Results from two multinational, phase III studies (APOLLO and LUNAR) and a pooled analysis of these studies demonstrated the noninferiority of latanoprostene bunod 0.024% to timolol ophthalmic solution 0.5% (hereafter referred to as timolol 0.5%) in terms of IOP-lowering efficacy over 3 months in patients with OAG or ocular hypertension, with the superiority of latanoprostene bunod 0.024% over timolol 0.5% subsequently demonstrated in APOLLO and the pooled analysis. Moreover, there was no apparent loss of IOP-lowering effect in subsequent safety extension periods of up to 9 months. The IOP-lowering efficacy seen in APOLLO and LUNAR was confirmed in a phase III study (JUPITER) in Japanese patients, with IOP reductions observed early (week 4) and maintained over the longer-term (12 months). Latanoprostene bunod 0.024% was well tolerated over up to 12 months in these studies, with most ocular treatment-emergent adverse events (TEAEs) being mild to moderate in severity. Thus, current evidence indicates once-daily latanoprostene bunod 0.024% is an effective and well tolerated treatment option for the reduction of IOP in adults with OAG or ocular hypertension.
Ibalizumab: First Global Approval
Anthony Markham

ABSTRACT
TaiMed Biologics is developing ibalizumab (Trogarzo™, ibalizumab-uiyk)—a humanised IgG4 monoclonal antibody—as a treatment for HIV-1 infection. Ibalizumab blocks HIV entry into CD4 cells while preserving normal immunological function and is the first CD4-directed post-attachment HIV-1 inhibitor and the first humanised monoclonal antibody for the treatment of HIV/AIDS. This article summarizes the milestones in the development of ibalizumab leading to this first approval in HIV-1 treatment.

Colorectal Cancer: Why Does Side Matter
Claire GalloisSimon PernotAziz ZaananJulien Taieb

ABSTRACT
Colorectal cancer (CRC) is a heterogeneous disease, and the search for clinical and molecular prognostic and predictive factors is thus necessary to better tailor each individual patient’s management. Primary tumor location (PTL) seems to act as a master prognostic factor pooling different clinical, pathological, and molecular poor prognostic factors. In fact, right-sided (RS) CRC patients are more frequently female and elderly with microsatellite unstable, BRAF mutated, CpG island methylator phenotype (CIMP)-high, poorly differentiated tumors, compared to left-sided (LS) CRC patients. PTL does not seem to clearly influence disease-free survival (DFS) in localised colon cancer even though the opposite prognostic value of RS tumors on DFS depending on RAS/BRAF mutational status has been recently suggested in these patients. In metastatic CRC (mCRC), the poor prognosis associated with RS tumors is confirmed in the most recent publications in the era of double and triple chemotherapeutic regimens and targeted agents. Concerning the predictive value of PTL, in patients with RAS wild-type mCRC in the first-line setting, anti-epidermal growth factor receptor (EGFR) therapy combined with chemotherapy appears to be more effective than bevacizumab in LS CRC, while patients with RS CRC benefit less from anti-EGFR therapy, and intensive chemotherapy plus bevacizumab may be more appropriate but EGFR antibodies remain an option if objective response is needed. Due to the limitation of the current data (unplanned and retrospective analyses), these conclusions must be interpreted with caution. Clinical trials in RS CRC may be of interest to clarify what is the best treatment strategy in these patients.
Vaccines Targeting PCSK9: A Promising Alternative to Passive Immunization with Monoclonal Antibodies in the Management of Hyperlipidaemia
Stefan WeisshaarMarkus Zeitlinger

ABSTRACT
Hypercholesterolaemia is frequently observed in patients with cardiovascular diseases (CVD) and is associated with increased mortality. Statin treatment has been the standard of care for reducing low-density lipoprotein cholesterol (LDL-C) to improve cardiovascular outcomes. However, statins have limited effects in some patients and may be discontinued due to adverse effects resulting in LDL-C above target levels. The proprotein convertase subtilisin kexin type 9 (PCSK9) is a pivotal regulator in the LDL-C metabolism by degrading the LDL-C receptor on hepatocytes. Inhibition of PCSK9 by monoclonal antibodies (mAb) significantly lowers LDL-C levels and is considered to reduce the likelihood of adverse cardiac events. However, such treatment regimens are not cost-effective, and require frequent administrations at high doses that may be associated with side effects and poor drug adherence. Furthermore, it has been shown that these PCSK9 medicines may trigger the formation of antidrug antibodies followed by a significant attenuation of the LDL-C-lowering effect. Active vaccination inducing high-affinity antibodies against PCSK9 with less frequent administration intervals may be a novel promising therapeutic approach to overcome the drawback of passive immunization with PCSK9 mAb. However there is a paucity of available clinical safety and efficacy data. This article discusses challenges in the development of PCSK9 vaccines and their potential therapeutic benefits by reviewing clinical studies that evaluated the safety and efficacy of PCSK9 mAb.

Treatment of Eosinophilic Granulomatosis with Polyangiitis: A Review
Loïc RaffrayLoïc Guillemin

ABSTRACT
Eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome) is a rare type of anti-neutrophil cytoplasm antibody-associated vasculitis. Nevertheless, eosinophilic granulomatosis with polyangiitis stands apart because it has features of vasculitis and eosinophilic disorders that require targeted therapies somewhat different from those used for other anti-neutrophil cytoplasm antibody-associated vasculitides. Considerable advances have been made in understanding the underlying pathophysiology of eosinophilic granulomatosis with polyangiitis that have highlighted the key role of eosinophils and opened new therapeutic opportunities. Its conventional treatment relies mainly on agents that decrease inflammation: corticosteroids and immunosuppressant adjunction for severe manifestations. New therapeutic approaches are needed for refractory disease, relapses and issues associated with corticosteroid dependence, especially for asthma manifestations. Drugs under evaluation mostly target eosinophils and B cells. Results of low-evidence-based trials suggested possible efficacies of biologicals: B-cell-blocking rituximab and anti-immunoglobulin E omalizumab. Recently, the first large-scale randomised controlled trial on eosinophilic granulomatosis with polyangiitis proved the efficacy of anti-interleukin-5 mepolizumab. That finding opens a new era in eosinophilic granulomatosis with polyangiitis management, with mepolizumab approval but also in future drug evaluations and trial designs for eosinophilic granulomatosis with polyangiitis. Additional studies are needed to determine which patients would benefit most from targeted therapies and achieve personalised treatment for patients with eosinophilic granulomatosis with polyangiitis. Herein, we review eosinophilic granulomatosis with polyangiitis characteristics and provide an overview of established and novel pharmacological agents.
Management of Embolic Stroke of Undetermined Source (ESUS)

Tobias Geisler, Annerose MengelUlf ZiemannSven Poli

ABSTRACT

According to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, embolic stroke of undetermined source (ESUS) has refined the old definition of cryptogenic stroke. More sophisticated criteria and a well-defined diagnostic workup point out the embolic nature of this disease. Because ESUS is associated with a high stroke recurrence, a clear risk prediction and management is of utmost importance to improve prognosis. To date, standard pharmacotherapy consists of antiplatelet drugs and statins. This review attempts to provide an overview on the diagnostic criteria, prognosis, and current clinical trials evaluating the value of direct oral anticoagulants for secondary prevention after ESUS.

Mirabegron: A Review in Overactive Bladder Syndrome

Emma D. Deeks

ABSTRACT

The first-in-class β3-adrenoceptor agonist mirabegron is indicated in the EU (Betmiga™), Japan (Betanis™) and several other countries for the management of overactive bladder (OAB) syndrome. Evidence for its use in this setting includes several large phase 3 trials. Compared with placebo, oral mirabegron for 12 weeks reduced the frequency of micturition and generally also that of incontinence, with other benefits including reduced urgency, increased void volume and improved health related quality-of-life (HR-QOL). Mirabegron comparisons versus tolterodine are descriptive; however, in a 12-week powered comparison versus solifenacin in patients dissatisfied with antimuscarinic efficacy, mirabegron did not demonstrate noninferiority in reducing micturition frequency or significantly differ in terms of improving other urinary symptoms. Urinary and HR-QOL benefits of mirabegron were sustained over up to 52 weeks of treatment and the drug was generally well tolerated, with a numerically lower incidence of dry mouth than antimuscarinics. Real-world data support the trial findings and indicate possible persistence and adherence benefits for mirabegron over antimuscarinics. Mirabegron use is not generally restricted by patient age, sex or antimuscarinic treatment status, although data in men (from a phase 4 study and phase 3 trial subanalyses) are variable; additional studies in older and male OAB patients are awaited with interest. Although further longer-term efficacy and tolerability data would be beneficial, current clinical evidence indicates that mirabegron provides an alternative to antimuscarinics for the management of OAB in adults, including those for whom antimuscarinics have proven unsuitable.
Tildrakizumab: First Global Approval

Anthony Markham

ABSTRACT

Merck & Company Inc. have developed tildrakizumab (tildrakizumab-asmn; Ilumya™), a high-affinity, humanised IgG1 κ monoclonal antibody that specifically targets interleukin-23 p19, as a treatment for chronic plaque psoriasis. The drug was recently approved for marketing by the US FDA based on positive results from the phase III reSURFACE clinical trial programme in patients with chronic plaque psoriasis. This article summarizes the milestones in the development of tildrakizumab leading to this first approval for the treatment of adults with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

Drugs in Development for Malaria

Elizabeth A. Ashley, Aung Pyae Phyo

ABSTRACT

The last two decades have seen a surge in antimalarial drug development with product development partnerships taking a leading role. Resistance of Plasmodium falciparum to the artemisinin derivatives, piperaquine and mefloquine in Southeast Asia means new antimalarials are needed with some urgency. There are at least 13 agents in clinical development. Most of these are blood schizonticides for the treatment of uncomplicated falciparum malaria, under evaluation either singly or as part of two-drug combinations. Leading candidates progressing through the pipeline are artefenomel–ferroquine and lumefantrine-KAF156, both in Phase 2b. Treatment of severe malaria continues to rely on two parenteral drugs with ancient forebears: artesunate and quinine, with sevuparin being evaluated as an adjuvant therapy. Tafenoquine is under review by stringent regulatory authorities for approval as a single-dose treatment for Plasmodium vivax relapse prevention. This represents an advance over standard 14-day primaquine regimens; however, the risk of acute haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency remains. For disease prevention, several of the newer agents show potential but are unlikely to be recommended for use in the main target groups of pregnant women and young children for some years. Latest predictions are that the malaria burden will continue to be high in the coming decades. This fact, coupled with the repeated loss of antimalarials to resistance, indicates that new antimalarials will be needed for years to come. Failure of the artemisinin-based combinations in Southeast Asia has stimulated a reappraisal of current approaches to combination therapy for malaria with incorporation of three or more drugs in a single treatment under consideration.
Inhibition of Tissue Factor Pathway Inhibitor (TFPI) as a Treatment for Haemophilia: Rationale with Focus on Concizumab
Pratima Chowdary

ABSTRACT
Replacement therapy with missing factor (F) VIII or IX in haemophilia patients for bleed management and preventative treatment or prophylaxis is standard of care. Restoration of thrombin generation through novel mechanisms has become the focus of innovation to overcome limitations imposed by protein replacement therapy. Tissue factor pathway inhibitor (TFPI) is a multivalent Kunitz-type serine protease inhibitor that regulates tissue factor (TF)-induced coagulation through a FXa-dependent feedback inhibition of the TF.FVIIa complex in plasma and on endothelial surfaces. Concizumab is a monoclonal, humanised antibody, specific for the second Kunitz domain of TFPI that binds and inhibits FXa, abolishing the inhibitory effect of TFPI. Concizumab restored thrombin generation in FVIII and FIX deficient plasmas and decreased blood loss in a rabbit haemophilia model. Phase 1 single and multiple dose escalation studies in haemophilia patients demonstrated a dose dependent decrease in TFPI levels and a pro-coagulant effect with increasing d-dimers and prothrombin fragment 1 + 2. A dose dependent increase in peak thrombin and endogenous thrombin potential was observed with values in the normal range when plasma TFPI levels were nearly undetectable. A few haemophilia patients in the highest dose cohorts with complete inhibition of plasma TFPI showed a decreased fibrinogen concentration with normal levels of anti-thrombin and platelets and no evidence of thrombosis. Pharmacokinetic parameters were influenced by binding to the target (TFPI), demonstrating target mediated drug disposition. A trend towards decreasing bleeding tendency was observed and this preventative effect is being studied in Phase 2 studies with additional data gathered to improve our understanding of the therapeutic window and potential for thrombosis.

Targeting EGFR in Lung Cancer: Current Standards and Developments
Asunción Díaz-Serrano Pablo Gella Elisabeth Jiménez Jon Zugazagoitia Luis Paz-Ares Rodríguez

ABSTRACT
Lung cancer is the second most common malignant tumor and the leading cause of cancer death. Epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) is a distinct subtype of lung cancer comprising approximately 15–40% of non-squamous tumors. The development of first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) has been a significant step forward in the treatment of patients with EGFR-mutant tumors, and over the last few years has been the therapy of choice in the initial management of patients with activating mutations in EGFR, with some differences in efficacy and toxicity profile. Up to 50% of patients treated with first- and second-generation TKIs develop an EGFR exon 20 T790M mutation at the time of progression. In this context, osimertinib has shown a great benefit in terms of progression-free survival (PFS) in the second-line setting, including central nervous system metastasis control. The FLAURA trial, which compared osimertinib to first-generation inhibitors as first-line therapy, showed a clear PFS advantage for osimertinib and a trend towards an increased overall survival (OS) assessed by investigator review. Although T790M mutation is the most common mechanism of resistance to first- and second-generation EGFR TKIs, other EGFR-dependent and -independent mechanisms have been described, such as HER2 and MET amplifications or BRAF and MEK mutations. Some mechanisms of resistance to osimertinib and other third-generation TKIs have also been described. Several fourth-generation TKIs, targeted drug combinations and immunotherapy strategies are under investigation to overcome resistance to EGFR TKIs in order to improve EGFR-mutant NSCLC patient outcomes.
CGRP and Migraine: The Role of Blocking Calcitonin Gene-Related Peptide Ligand and Receptor in the Management of Migraine
Kasra Maasumi, Rebecca L. MichaelAlan M. Rapoport

ABSTRACT
Migraine is a highly prevalent, complex neurological disorder. The burden of disease and the direct/indirect annual costs are enormous. Thus far, treatment options have been inadequate and mostly based on trial and error, leaving a significant unmet need for effective therapies. While the underlying pathophysiology of migraine is incompletely understood, blocking the calcitonin gene-related peptide (CGRP) using monoclonal antibodies targeting CGRP or its receptor and small molecule CGRP receptor antagonists (gepants) have emerged as a promising therapeutic opportunity for the management of migraine. In this review, we discuss new concepts in the pathophysiology of migraine and the role of CGRP, the current guidelines for treating migraine preventively, the medications that are being used, and their limitations. We then discuss small molecule CGRP receptor antagonists, monoclonal antibodies to CGRP ligand and receptor, as well as the detailed results of Phase II and III trials involving these novel treatments. We conclude with a discussion of the implications of blocking CGRP and its receptor.

Sarilumab: A Review in Moderate to Severe Rheumatoid Arthritis
Yvette N. Lamb, Emma D. Deeks

ABSTRACT
Sarilumab (Kevzara®), a monoclonal antibody against the interleukin-6 (IL-6) receptor, is approved in various countries, including the USA, those of the EU, and Japan, as a subcutaneous treatment administered every 2 weeks for moderately to severely active rheumatoid arthritis (RA) in adults who have responded inadequately to, or are intolerant of, one or more DMARDs. In placebo-controlled trials, sarilumab improved the signs and symptoms of RA, as well as physical function and health-related quality-of-life (HR-QOL), when administered in combination with conventional synthetic DMARD (csDMARD) therapy in patients with an inadequate response to methotrexate or an inadequate response to, or intolerance of, at least one tumour necrosis factor (TNF) inhibitor; benefits were sustained over ≤3 years’ therapy in an open-label extension. Sarilumab plus methotrexate inhibited the progression of structural damage in patients who had inadequately responded to methotrexate. As monotherapy in patients who were inappropriate for continued treatment with methotrexate, sarilumab was more effective than adalimumab in reducing the signs and symptoms of RA and improving physical function. The safety profile of sarilumab was consistent with the anticipated effects of IL-6 inhibition. In the minority of patients who tested positive for anti-drug antibodies (ADAs), ADAs did not impact efficacy or increase adverse reactions. Thus, sarilumab extends the available treatment options for adults with moderately to severely active RA who have responded inadequately to, or are intolerant of, at least one DMARD.
Telotristat Ethyl: A Review in Carcinoid Syndrome Diarrhoea

Katherine A. Lyseng-Williamson

ABSTRACT
Telotristat ethyl (Xermelo®), a first-in-class peripheral tryptophan hydroxylase (TPH) inhibitor, is approved to treat carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy alone. Some neuroendocrine tumours secrete serotonin (5-HT) into the blood, resulting in frequent bowel movements (BMs) and other symptoms. Telotristat ethyl inhibits TPH, thereby reducing the production of 5-HT and improving carcinoid syndrome diarrhoea. In the 12-week placebo-controlled phase of randomized trials in patients with carcinoid syndrome diarrhoea (most of whom were receiving SSA therapy), the addition of oral telotristat ethyl 250 three times daily provided significant reductions in the frequency of BMs and levels of urinary 5-hydroxyindolacetic acid (u5-HIAA; a metabolite of 5-HT) relative to placebo. Telotristat ethyl 250 mg three times daily was well tolerated, with the proportion of patients reporting at least one treatment-emergent adverse event being similar to that with placebo. With regard to adverse events of special interest, relative to placebo, telotristat ethyl had a comparable incidence of depression-related symptoms, a somewhat higher incidence of gastrointestinal (GI) disorders and a higher incidence of elevated hepatic enzyme levels.

Regorafenib: A Review in Hepatocellular Carcinoma

Young-A. Heo, Yahiya Y. Syed

ABSTRACT
Regorafenib (Stivarga®), a small molecule inhibitor of multiple kinases, is the first drug to be approved for the treatment of hepatocellular carcinoma (HCC) in patients who have progressed during or after sorafenib therapy. Its approval was based on the results of the randomized, double-blind, placebo-controlled, multinational, phase III RESORCE trial in patients with HCC who had progressed during sorafenib therapy. In RESORCE, regorafenib significantly prolonged overall survival (OS; primary endpoint), progression-free survival (PFS) and time to progression (TTP) compared with placebo, with the OS benefit appearing to be largely due to disease stabilization. Regorafenib had an acceptable tolerability profile. The most common treatment-related adverse events in the regorafenib group included hand-foot skin reaction, fatigue, diarrhoea and hypertension. No fatal hepatic failure was reported with regorafenib in patients with HCC in RESORCE. In conclusion, current evidence suggests that regorafenib is an important new targeted therapy option for the treatment of HCC patients who have progressed on sorafenib therapy.
Fostamatinib: First Global Approval
Anthony Markham

ABSTRACT
Rigel Pharmaceuticals are developing the spleen tyrosine kinase (SYK) inhibitor fostamatinib (TAVALISSE™) as a treatment for immune thrombocytopenia (ITP), autoimmune haemolytic anaemia and IgA nephropathy. Based on positive results in the phase III FIT clinical trial program, the drug was recently approved in the US as a treatment for thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment. This article summarizes the milestones in the development of fostamatinib leading to this first approval.

The Evolution of Lung Transplant Immunosuppression
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ABSTRACT
Advances in immunosuppression have been a key component to the ongoing success of lung transplantation. The demographics of patients receiving a lung transplant have evolved with older, more critically ill patients and those with previously contraindicated indications, now becoming recipients. Despite the lack of new classes of maintenance immunosuppression drugs becoming available, advances have been made in the prescribing of traditional immunosuppressive therapies. Developments in immunosuppressive regimens have seen changes in the route of administration, approaches to monitoring and combinations used. Long-term complications of immunosuppression, such as nephrotoxicity and malignancy can limit the success of lung transplantation, and strategies have evolved in recent years to minimise their long-term impact. Although survival outcomes have been steadily improving, chronic lung allograft dysfunction remains a barrier to long-term success. However, treatments for antibody-mediated rejection are emerging as a potential new therapeutic target to decrease the incidence of chronic lung allograft dysfunction. This article provides an update on the current status of immunosuppression after lung transplantation and reviews the evidence for immunosuppressive regimens and the implications for practice.
Postural Orthostatic Tachycardia Syndrome: Prevalence, Pathophysiology, and Management
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ABSTRACT
Postural orthostatic tachycardia syndrome (POTS) is a debilitating disease that predominantly affects young women. It is a multifactorial disorder that is characterized by severe tachycardia and orthostatic intolerance. Patients with POTS experience a variety of cardiac, neurological, and immunological symptoms that significantly reduce quality of life. In this review, a comprehensive framework is provided to aid in helping identify and treat patients with POTS. Given its heterogenous nature, it is crucial to understand each component of POTS in relation to one another instead of distinct parts. The framework highlights the overlap among the five main subtypes of POTS based on its pathophysiology (neuropathic, hypovolemic, primary hyperadrenergic, joint-hypermobility-related, and immune-related). Emphasis is placed on incorporating a multidisciplinary approach when treating patients with POTS, especially with a new focus towards immunotherapy. Although research has advanced our knowledge of POTS, there is still a critically unmet need to further our understanding and provide patients with the relief they need.

Current and Emerging Therapeutics for the Management of Endometriosis
Simone Ferrero, Fabio BarraUmberto Leone Roberti Maggiore

ABSTRACT
Endometriosis is a chronic benign disease that affects women of reproductive age. Medical therapy is often the first line of management for women with endometriosis in order to ameliorate symptoms or to prevent post-surgical disease recurrence. Currently, there are several medical options for the management of patients with endometriosis. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of chronic inflammatory conditions, being efficacious in relieving primary dysmenorrhea. Combined oral contraceptives (COCs) and progestins, available for multiple routes of administration, are effective first-line hormonal options. In fact, several randomized controlled trials (RCTs) demonstrated that they succeed in improving pain symptoms in the majority of patients, are well tolerated and not expensive. Second-line therapy is represented by gonadotropin-releasing hormone (GnRH) agonists. Even if these drugs are efficacious in treating women not responding to COCs or progestins, they are not orally available and have a less favorable tolerability profile (needing an appropriate add-back therapy). The use of danazol is limited by the large availability of other better-tolerated hormonal drugs. Because few data are available on long-term efficacy and safety of aromatase inhibitors they should be administered only in women with symptoms refractory to other conventional therapies in a clinical research setting. Promising preliminary data have emerged from multicenter Phase III trials on elagolix, a new oral GnRH antagonist but non-inferiority RCT data are required to compare elagolix with first-line therapies for endometriosis.
Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection

Emma D. Deeks

ABSTRACT

Darunavir/cobicistat/emtricitabine/tenofovir AF (Symtuza®) is the first protease inhibitor (PI)-based single-tablet regimen (STR) available for the treatment of adults and adolescents (aged ≥ 12 years) with HIV-1 infection. It combines the PI darunavir (which has a high genetic barrier to resistance) with the pharmacokinetic booster cobicistat and the nucleos(t)ide reverse transcriptase inhibitors emtricitabine and tenofovir alafenamide (tenofovir AF), the latter being associated with less off-target tenofovir exposure than its predecessor tenofovir disoproxil fumarate (tenofovir DF). Over 48 weeks in phase 3 trials, darunavir/cobicistat/emtricitabine/tenofovir AF was noninferior to darunavir/cobicistat plus emtricitabine/tenofovir DF in establishing virological suppression in antiretroviral therapy (ART)-naïve adults and, likewise, was noninferior to an ongoing boosted PI, emtricitabine plus tenofovir DF regimen in preventing virological rebound in virologically-suppressed, ART-experienced adults. Resistance did not emerge to the STR components, with the exception being an emtricitabine resistance-associated mutation (RAM) [M184I/V] in one of seven recipients who experienced virological failure (although M184V was a minority variant at screening in this patient). Darunavir/cobicistat/emtricitabine/tenofovir AF was generally well tolerated, with renal and bone profile improvements but less favourable effects on some lipids versus tenofovir DF-based regimens. Thus, although longer-term and cost-effectiveness data would be beneficial, darunavir/cobicistat/emtricitabine/tenofovir AF is a welcome addition to the STRs available for the treatment of adults and adolescents with HIV-1 infection, being the first to combine the high genetic resistance barrier of darunavir with the renal/bone profile of tenofovir AF, thus expanding the patient population for whom an STR may be suitable.

Lisdexamfetamine Dimesylate: A Review in Paediatric ADHD

James E. Frampton

ABSTRACT

Lisdexamfetamine dimesylate (lisdexamfetamine; Elvanse®, Tyvense®), an orally-active dexamfetamine prodrug, is indicated in the EU for the treatment of attention-deficit hyperactivity disorder (ADHD) in children aged ≥ 6 years (including adolescents) when the response to previous methylphenidate (MPH) treatment is clinically inadequate. The original approval of the drug was based on the results of phase III trials in children and adolescents with ADHD who had an inadequate response to previous pharmacotherapy (e.g. MPH) or were treatment naïve. In these studies, short-term treatment with flexibly-dosed lisdexamfetamine demonstrated greater efficacy than atomoxetine, based on a prospective comparison, and osmotic-release oral system (OROS)-MPH, based on a post hoc comparison. Improvements in ADHD symptoms were accompanied by improvements in health-related quality of life and functioning that were maintained as long as treatment with lisdexamfetamine was continued in a long-term extension of one of these trials. In subsequent phase IV head-to-head studies in adolescents with ADHD and an inadequate response to previous pharmacotherapy, lisdexamfetamine demonstrated greater efficacy than OROS-MPH when both medications were force-titrated, but not when they were flexibly-titrated. Lisdexamfetamine was generally well tolerated, with an adverse event profile (e.g. decreased appetite, headache, weight reduction, insomnia and irritability) typical of that reported for other stimulants. Thus, lisdexamfetamine provides an alternative option for the treatment of children and/or adolescents with ADHD who have not responded adequately to previous ADHD pharmacotherapies.
Empagliflozin: A Review in Type 2 Diabetes

James E. Frampton

ABSTRACT

Empagliflozin (Jardiance®), a potent, highly selective, sodium glucose cotransporter-2 (SGLT2) inhibitor, is an effective and generally well tolerated antihyperglycaemic agent approved for the treatment of adults with type 2 diabetes (T2D) in the EU, USA and Japan, among other parts of the world. As with other members of its class, empagliflozin offers the convenience of once-daily oral administration and carries a low inherent risk of hypoglycaemia as a result of its insulin-independent mechanism of action, enabling it to be used as monotherapy and as a component of combination therapy with other antidiabetic agents with complementary modes of action to improve glycaemic control in patients with T2D. Beyond lowering glucose, empagliflozin exerts a favourable effect on a number of nonglycaemic outcomes, including modest reductions in bodyweight and blood pressure. As an adjunct to standard care, it demonstrated cardioprotective and renoprotective properties largely independent of glycaemic control in patients with T2D and established cardiovascular disease (CVD) in a mandated cardiovascular (CV) outcomes trial (EMPA-REG OUTCOME). Empagliflozin is generally well tolerated as monotherapy or as add-on therapy and, unlike canagliflozin (the only other SGLT2 inhibitor that has so far shown CV and renal benefits), it has not been associated with an increased risk of amputation or bone fractures. In conclusion, empagliflozin is a valuable treatment option for the management of T2D. Given its demonstrable cardioprotective benefits, the drug is worthy of preferential consideration in patients at high CV risk who require an (additional) antidiabetic medication in order to attain their glycaemic goal.

Andexanet Alfa: First Global Approval

Young-A Heo

ABSTRACT

Intravenous andexanet alfa [coagulation factor Xa (recombinant), inactivated-zhzo; Andexxa®] is a first-in-class recombinant modified factor Xa protein that has been developed by Portola Pharmaceuticals as a universal antidote to reverse anticoagulant effects of direct or indirect factor Xa inhibitors. In May 2018, andexanet alfa received its first global approval in the USA for use in patients treated with rivaroxaban and apixaban, when reversal of anticoagulant effects is required in life-threatening or uncontrolled bleeding. Intravenous andexanet alfa is under regulatory review in the EU and is undergoing clinical development in Japan. This article summarizes the milestones in the development of andexanet alfa leading to this first global approval for reversing anticoagulation of rivaroxaban and apixaban in adults.
Anlotinib: First Global Approval

Yahiya Y. Syed

ABSTRACT

Jiangsu Chia-Tai Tianqing Pharmaceutical and Advenchen Laboratories are co-developing anlotinib (Focus V®) for the treatment of advanced cancer. Anlotinib is an oral small molecule inhibitor of multiple receptor tyrosine kinases, with a broad spectrum of inhibitory effects on tumour angiogenesis and growth. Anlotinib is approved in China for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have undergone progression or recurrence after ≥2 lines of systemic chemotherapy. Anlotinib is also undergoing phase II and/or III clinical development for various sarcomas and carcinomas in China, USA and Italy. This article summarizes the milestones in the development of anlotinib leading to this first approval for NSCLC.

The Significance of the Intestinal Microbiome for Vaccinology: From Correlations to Therapeutic Applications

Vanessa C. Harris

ABSTRACT

Despite unprecedented advances in understanding the intestinal microbiome, its potential to improve fields such as vaccinology has yet to be realized. This review briefly outlines the immunologic potential of the intestinal microbiome for vaccinology and highlights areas where the microbiome holds specific promise in vaccinology. Oral rotavirus vaccine effectiveness in low-income countries is used as a case study to describe how the intestinal microbiome may be employed to improve a vaccine’s immunogenicity. A top-down, evidence-based approach is proposed to identify effective microbiota-based applications for vaccine improvement. Applying evidence from field studies in pertinent populations that correlate microbiome composition with vaccine effectiveness to appropriate experimental platforms will lead to the identification of safe, vaccine-supporting microbiota targets that are relevant to populations in need of improvement in vaccine-induced immunity.

The Future of IL-1 Targeting in Kidney Disease

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ABSTRACT

Interleukin (IL)-1α and IL-1β are proinflammatory cytokines that play a role in many diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, gout, and periodic inflammatory syndromes, including familial Mediterranean fever and Muckle-Wells syndrome. Drugs targeting IL-1 such as recombinant IL-1Ra (anakinra), neutralizing anti-IL-1β antibodies (canakinumab) and IL-1β traps (rilonacept) are in clinical use to treat these diseases. Additionally, experimental evidence suggests a role of IL-1 in kidney disease and hypertension and targeting IL-1 showed promising results in high cardiovascular risk patients, hemodialysis and renal transplantation patients. We now summarize knowledge on the potential role of IL-1 targeting in patients with kidney disease.
New Developments in the Management of Cytomegalovirus Infection after Transplantation
Atibordee MeesingRaymund R. Razonable

ABSTRACT
Cytomegalovirus (CMV) continues to be one of the most important pathogens that universally affect solid organ and allogeneic hematopoietic stem cell transplant recipients. Lack of effective CMV-specific immunity is the common factor that predisposes to the risk of CMV reactivation and clinical disease after transplantation. Antiviral drugs are the cornerstone for prevention and treatment of CMV infection and disease. Over the years, the CMV DNA polymerase inhibitor, ganciclovir (and valganciclovir), have served as the backbone for management, while foscarnet and cidovirof are reserved for the management of CMV infection that is refractory or resistant to ganciclovir treatment. In this review, we highlight the role of the newly approved drug, letermovir, a viral terminase inhibitor, for CMV prevention after allogeneic hematopoietic stem cell transplantation. Advances in immunologic monitoring may allow for an individualized approach to management of CMV after transplantation. Specifically, the potential role of CMV-specific T-cell measurements in guiding the need for the treatment of asymptomatic CMV infection and the duration of treatment of CMV disease is discussed. The role of adoptive immunotherapy, using ex vivo-generated CMV-specific T cells, is highlighted. This article provides a review of novel drugs, tests, and strategies in optimizing our current approaches to prevention and treatment of CMV in transplant recipients.

Centrally Acting Agents for Obesity: Past, Present, and Future
Ann A. CoulterCandida J. RebelloFrank L. Greenway

ABSTRACT
For many years, obesity was believed to be a condition of overeating that could be resolved through counseling and short-term drug treatment. Obesity was not recognized as a chronic disease until 1985 by the scientific community, and 2013 by the medical community. Pharmacotherapy for obesity has advanced remarkably since the first class of drugs, amphetamines, were approved for short-term use. Most amphetamines were removed from the obesity market due to adverse events and potential for addiction, and it became apparent that obesity pharmacotherapies were needed that could safely be administered over the long term. This review of central nervous system (CNS) acting anti-obesity drugs evaluates current therapies such as phentermine/topiramate, which act through multiple neurotransmitter pathways to reduce appetite. In the synergistic mechanism of bupropion/naltrexone, naltrexone blocks the feed-back inhibitory circuit of bupropion to give greater weight loss. Lorcaserin, a selective agonist of a serotonin receptor that regulates food intake, and the glucagon-like-peptide-1 (GLP-1) receptor agonist liraglutide are reviewed. Future drugs include tesofensine, a potent triple reuptake inhibitor in Phase III trials for obesity, and semaglutide, an oral GLP-1 analog approved for diabetes and currently in trials for obesity. Another potential new pharmacotherapy, setmelanotide, is a melanocortin-4 receptor agonist, which is still in an early stage of development. As our understanding of the communication between the CNS, gut, adipose tissue, and other organs evolves, it is anticipated that obesity drug development will move toward new centrally acting combinations and then to drugs acting on peripheral target tissues.
Assessment of the Risk of Rhabdomyolysis and Myopathy During Concomitant Treatment with Ticagrelor and Statins

Dorota Danielak, Marta Karaźniewicz-ŁadaFranciszek Główka

ABSTRACT

The introduction of ticagrelor, one of the first directly-acting oral antiplatelet drugs, provided new possibilities in the prevention of thrombotic events in patients with acute coronary syndromes (ACS). Current guidelines recommend ticagrelor in dual antiplatelet therapy with aspirin over clopidogrel for prevention of stent thrombosis in patients with ACS. Moreover, in the management of ACS, lipid-lowering treatment with high-intensity statin therapy is advised for secondary prevention of cardiovascular events over the long term. Despite the apparent advantages of combined antiplatelet and lipid-lowering treatments, a possible interaction between statins and ticagrelor may lead to myopathy and rhabdomyolysis. In this review, relevant information was gathered on the ticagrelor–statin interaction that might lead to this life-threatening condition. This review focuses on the most widely used statins—simvastatin, atorvastatin, and rosuvastatin. Possible mechanisms of this interaction are discussed, including CYP3A4 isoenzymes, organic anion transporter polypeptide (OATPs), P-glycoprotein and glucuronidation. PubMed database was searched for relevant case reports and all data gathered from the introduction of ticagrelor to March 2018 are presented and discussed. In summary, co-administration of statins and ticagrelor was found to be relatively safe in routinely prescribed doses. However, caution should be exercised, especially in elder populations.

Regorafenib: A Review in Metastatic Colorectal Cancer

Sohita Dhillon

ABSTRACT

Regorafenib (Stivarga®) is an oral small-molecule multiple kinase inhibitor. It is indicated worldwide for patients with metastatic colorectal cancer (mCRC). In the EU and USA it is indicated for patients with mCRC who have been previously treated with, or are not considered candidates for available therapies, including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and, if RAS wild-type, an anti-EGFR therapy. In Japan, it is indicated for the treatment of unresectable, advanced/recurrent CRC. The addition of regorafenib to best supportive care prolonged median overall survival (OS; by up to 2.5 months) and progression-free survival (PFS; by up to 1.5 months) relative to the addition of placebo in double-blind phase 3 studies (CORRECT and CONCUR) in patients with mCRC who had progressed after failure of standard therapy. Health-related quality of life was not adversely affected with regorafenib relative to placebo. A large open-label phase 3 study (CONSIGN) and several large real-world studies supported the efficacy of regorafenib in this setting. Regorafenib had a generally manageable tolerability profile, which was consistent with the profile of a typical small-molecule multiple kinase inhibitor. Treatment-related adverse events (AEs), mostly of mild or moderate severity, were reported in the majority of patients receiving regorafenib, with dermatological toxicities and liver enzyme elevations among the most common AEs. Although identification of biomarkers/parameters predicting efficacy outcomes with regorafenib will help to individualize therapy, current evidence indicates that regorafenib is a valuable treatment option for patients with refractory mCRC who have a very poor prognosis.
Vismodegib: A Review in Advanced Basal Cell Carcinoma

James E. Frampton, Nicole Basset-Séguin

ABSTRACT

Vismodegib (Erivedge®) is the first-in-class, oral small molecule inhibitor of the Hedgehog (Hh) pathway, abnormal activation of which is associated with basal cell carcinoma (BCC). In the USA, vismodegib is indicated for the treatment of adults with metastatic BCC (mBCC) or with locally-advanced BCC (LaBCC) that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. Similarly, in the EU, vismodegib is indicated for the treatment of adult patients with symptomatic mBCC, or with laBCC inappropriate for surgery or radiotherapy. The full European approval of vismodegib was based on the results of two phase II, open-label, noncomparative, international trials (ERIVANCE BCC and STEVIE), both of which showed high rates of tumour control in the indicated patient populations, including individuals with or without Gorlin syndrome. These studies also showed that vismodegib has an acceptable and manageable tolerability profile characterized by a number of class-related treatment-emergent adverse events, including muscle spasms, taste disturbances, alopecia, weight loss and asthenia (fatigue). Primary and secondary resistance to vismodegib has been documented, albeit at a low rate compared with some other targeted therapies. Vismodegib is therefore an effective and generally well tolerated systemic therapy for patients with mBCC and laBCC that can no longer be suitably controlled with surgery and/or radiotherapy. Historically, it is the first member of a class of drugs (Hh pathway inhibitors) that are now considered to be first-line treatment options for such individuals.

Erenumab: First Global Approval

Anthony Markham

ABSTRACT

Amgen and Novartis are developing erenumab (AIMOVIG™, erenumab-aooe)—a fully human monoclonal antibody calcitonin gene-related peptide (CGRP) receptor antagonist—for the prevention of migraine. CGRP is a vasodilatory neuropeptide implicated in the pathophysiology of migraine and treatment with erenumab was associated with significant reductions in migraine frequency in phase II and III clinical trials. Based on these positive results erenumab was recently approved in the US for the preventive treatment of migraine in adults and has received a positive opinion in the EU for the prophylaxis of migraines in adults who have at least 4 migraine days per month. This article summarizes the milestones in the development of erenumab leading to this first approval.
Avatrombopag: First Global Approval
Matt Shirley

ABSTRACT
Avatrombopag (Doptelet®) is an orally bioavailable, small molecule thrombopoietin receptor agonist that has been developed by Dova Pharmaceuticals for the treatment of thrombocytopenic disorders. In May 2018 avatrombopag received its first global approval, in the USA, for use in the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. A Marketing Authorization Application for use of avatrombopag in this indication was submitted to the EMA in April 2018. Clinical development of avatrombopag in the treatment of other thrombocytopenic disorders, including immune thrombocytopenic purpura and chemotherapy-induced thrombocytopenia, is ongoing. This article summarizes the milestones in the development of avatrombopag leading to this first approval for the treatment of thrombocytopenia in adult patients with CLD.

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Targeting Gastrointestinal Transport Proteins to Control Hyperphosphatemia in Chronic Kidney Disease
Denis FouqueMarc VervloetMarkus Ketteler

ABSTRACT
Management of hyperphosphatemia in patients with dialysis-dependent chronic kidney disease remains a major challenge, requiring a multifaceted approach that includes dietary phosphate restriction, dialysis, and phosphate binders. However, these treatments fail to meet serum phosphate targets in many patients, potentially further exacerbating the significant morbidity and mortality burden associated with the disease. Recent advances in our understanding of the mechanisms underlying phosphate homeostasis have shed new light on the issue and suggest that gastrointestinal transport proteins may be promising targets for new hyperphosphatemia treatments. Drugs that inhibit or downregulate these transport proteins, and thus reduce phosphate uptake from the gut, may overcome some of the limitations of existing phosphate-lowering strategies, such as interdialytic rises in serum phosphate levels, poor adherence to dietary and phosphate-binder regimens, and maladaptive responses that can increase gastrointestinal phosphate absorption. Here, we review the latest preclinical and clinical data for two candidates in this novel drug class: tenapanor, a small-molecule inhibitor of the sodium/hydrogen ion-exchanger isofrom 3, and nicotinamide, an inhibitor of sodium–phosphate-2b cotransporters. We also discuss how potential synergies in their mechanisms of action suggest that coadministering phosphate binders with sodium–phosphate-2b cotransporter inhibitors may yield additive benefits over traditional phosphate-binder therapy.
Adult-Onset Still’s Disease: Molecular Pathophysiology and Therapeutic Advances
Paolo Sfriso, Sara BindoliPaola Galozzi

ABSTRACT
Adult-onset Still’s disease (AOSD) is a rare inflammatory disorder of unknown etiology generally characterized by persistent high spiking fever, evanescent rash, and polyarthritis. The pathogenesis of AOSD is only partially known. The pivotal role of macrophage cell activation, which leads to T-helper 1 (Th1) cell cytokine activation, is now well-established in AOSD. Moreover, pro-inflammatory cytokines such as interleukin (IL)-1, -6, and -18 seem to play a key role in this disorder, giving rise to the development of new targeted therapies. For years, treatment of AOSD has been largely empirical, using nonsteroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs. Patients with steroid- and methotrexate-refractory AOSD can now benefit from efficient and well-tolerated biologic agents such as IL-1, IL-6, and tumor necrosis factor-α antagonists.

Metastatic Melanoma: Recent Therapeutic Progress and Future Perspectives
Nausicaa MalissenJean-Jacques Grob

ABSTRACT
The prognosis of patients with metastatic melanoma has dramatically improved in recent years with the introduction of two new therapeutic strategies. BRAF and MEK inhibitors are small molecules that are able to block the mitogen-activated protein kinase (MAPK) pathway, which is constitutively activated by recurrent BRAF V600 mutations in 45% of melanoma patients. These agents were shown to provide a rapid and strong response but are often limited by a high rate of secondary resistance. Monoclonal antibodies against the immune checkpoints cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) can restore an efficient and durable anti-tumor immunity, even following treatment discontinuation. Anti-PD-1 antibodies were shown to prolong survival of metastatic melanoma patients and a real cure seems to be obtainable in some patients. Many more therapies are currently under investigation, given that 50% of patients still do not have long-term benefits from approved treatments. The main goal is to avoid or circumvent primary or secondary immune resistance to anti-PD-1 therapy not only by targeting other players in the tumor microenvironment but also by optimizing treatment sequencing and combining anti-PD-1 with other treatments, especially with BRAF and MEK inhibitors. The unexpected major successes of immunotherapies in melanoma have opened the way for the development of these treatments in other cancers. In this review, we describe the different available treatments, their toxicities, and the key components of our decisional algorithms, and give an overview of what we expect to be the near future of melanoma treatment.
Treating Chronic Pain: An Overview of Clinical Studies Centered on the Buprenorphine Option
Mellar P. Davis, Gavril PasternakBertrand Behm

ABSTRACT

The buprenorphine receptor binding profile is unique in that it binds to all three major opioid receptors (mu, kappa, delta), and also binds to the orphan-like receptor, the receptor for orphanin FQ/nociceptin, with lower affinity. Within the mu receptor group, buprenorphine analgesia in rodents is dependent on the recently discovered arylepoxamide receptor target in brain, which involves a truncated 6-transmembrane mu receptor gene protein, distinguishing itself from morphine and most other mu opioids. Although originally designed as an analgesic, buprenorphine has mainly been used for opioid maintenance therapy and only now is increasingly recognized as an effective analgesic with an improved therapeutic index relative to certain potent opioids. Albeit a second-, third-, or fourth-line analgesic, buprenorphine is a reasonable choice in certain clinical situations. Transdermal patches and buccal film formulations are now commercially available as analgesics. This review discusses buprenorphine pharmacodynamics and pharmacokinetics, use in certain populations, and provides a synopsis of systematic reviews and randomized analgesic trials. We briefly discuss postoperative management in patients receiving buprenorphine maintenance therapy, opioid equivalence to buprenorphine, rotations to buprenorphine from other opioids, and clinical relevance of buprenorphine-related QTc interval changes.

Perioperative Use of Intravenous Lidocaine
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ABSTRACT

Lidocaine is an amide local anaesthetic initially used intravenously as an antiarrhythmic agent. At some point it was proposed that intravenous lidocaine (IVL) had an analgesic effect that could be potentially beneficial in perioperative settings. Since these preliminary reports, a large body of evidence confirmed that IVL had anti-inflammatory and opiate-sparing effects, a combination of characteristics leading to an array of effects such as a decrease in postoperative pain and opiate consumption, and a reduction in the duration of digestive ileus. Additional studies demonstrated IVL to possess antithrombotic, antimicrobial and antitumoral effects. Beneficial effects of IVL have been characterized in abdominal surgery but remain controversial in other types of surgeries. Because the quality of evidence was limited, due to inconsistency, imprecision and study quality, recent conclusions from meta-analysis pooling together all types of surgery stated the uncertainty about IVL benefits. Additional indications such as the prevention of propofol-induced injection pain, prevention of hyperalgesia, protection against bronchial reactivity by bronchotracheal relaxation during surgery, and the increase in depth of general anaesthesia have since emerged. IVL is rapidly distributed in the body and metabolized by the liver. With the commonly recommended doses, lidocaine’s therapeutic index remains very high and the plasma concentrations stay largely below the cardiotoxic and neurotoxic threshold levels, a notion that may be used by clinicians to draw conclusions on the benefit-risk profile of IVL in comparison to other analgesic strategies. The purpose of this review is to address the pharmacokinetic and pharmacodynamic properties of lidocaine in healthy and pathological conditions.
Alectinib: A Review in Advanced, ALK-Positive NSCLC
Julia Paik, Sohita Dhillon

ABSTRACT
Alectinib (Alecensa®) is a potent and highly selective anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor. Oral alectinib monotherapy is approved in the EU as first-line treatment for adults with advanced ALK-positive non-small cell lung cancer (NSCLC) and for the treatment of adults with advanced ALK-positive NSCLC previously treated with crizotinib. In the USA, alectinib is indicated for the treatment of adults with ALK-positive metastatic NSCLC. The recommended dosage for alectinib in the EU and USA is 600 mg twice daily. Well-designed phase III studies in patients with ALK-positive NSCLC showed that during up to ≈ 19 months’ follow-up, progression-free survival (PFS) was significantly improved with alectinib relative to crizotinib as first-line therapy (ALEX study), and relative to chemotherapy in patients previously treated with crizotinib and platinum-doublet chemotherapy (ALUR study). Central nervous system (CNS)-related outcomes were significantly improved with alectinib in both these settings. Two phase II registrational studies (NP28673 and NP28761) in patients previously treated with crizotinib also demonstrated the efficacy of alectinib, as assessed by objective response rates (ORRs), during up to 21 months’ follow-up. Overall, alectinib had a manageable tolerability profile in these settings, with most adverse events (AEs) of mild or moderate severity. Current evidence indicates that alectinib is an important treatment option for patients with advanced ALK-positive NSCLC who are previously untreated or those previously treated with crizotinib. Given its efficacy and tolerability, current guidelines include alectinib as a treatment option in these settings, with the NCCN guidelines recommending it as a preferred option for first-line therapy.

Meropenem/Vaborbactam: A Review in Complicated Urinary Tract Infections
Sohita Dhillon

ABSTRACT
The global threat of the spread of carbapenem resistance in Enterobacteriaceae has led to the search for new antibacterials. Intravenous meropenem/vaborbactam (Vabomere™) is the first carbapenem/β-lactamase inhibitor combination approved in the USA for use in patients with complicated urinary tract infections (cUTIs), including pyelonephritis. Vaborbactam is a potent inhibitor of class A serine carbapenemases, which, when combined with the antibacterial meropenem, restores the activity of meropenem against β-lactamase producing Enterobacteriaceae, particularly Klebsiella pneumoniae carbapenemase (KPC)-producing Enterobacteriaceae. Meropenem/vaborbactam demonstrated excellent in vitro activity against Gram-negative clinical isolates, including KPC- and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. In the phase 3, noninferiority TANGO I trial in patients with cUTIs, intravenous meropenem/vaborbactam was noninferior to intravenous piperacillin/tazobactam for overall success (composite of clinical cure and microbial eradication; FDA primary endpoint) and microbial eradication (EMA primary endpoint). In subsequent superiority testing, meropenem/vaborbactam was superior to piperacillin/tazobactam for overall success. Meropenem/vaborbactam was generally well tolerated, with a tolerability profile generally similar to that of piperacillin/tazobactam. TANGO I did not assess the efficacy of meropenem/vaborbactam for the treatment of infections caused by carbapenem-resistant Enterobacteriaceae and meropenem/vaborbactam is currently not indicated for these patients. Available evidence indicates that meropenem/vaborbactam is a useful treatment option for patients with cUTIs.
Danoprevir: First Global Approval
Anthony MarkhamSusan J. Keam

ABSTRACT
Ascletis has developed danoprevir (Ganovo®), an orally-administered hepatitis C virus NS3 protease inhibitor, as a treatment for hepatitis C. Based on positive results in phase II and phase III trials in patients with hepatitis C, danoprevir, in combination with ritonavir, peginterferon alfa and ribavirin was recently approved for marketing in China for the treatment of treatment-naive patients with non-cirrhotic genotype 1b chronic hepatitis C. This article summarizes the milestones in the development of danoprevir leading to this first approval.

Encorafenib and Binimetinib: First Global Approvals
Matt Shirley

ABSTRACT
Encorafenib (Braftovi™), a BRAF inhibitor, and binimetinib (Mektovi®), a MEK inhibitor, are two orally bioavailable drugs developed by Array BioPharma. In June 2018 they each received their first global approval, in the USA, for use in combination, for patients with unresectable or metastatic melanoma with a BRAFV600E or -V600K mutation as detected by an FDA-approved test. Registration applications for encorafenib and binimetinib for use in combination in the treatment of BRAF-mutation-positive advanced melanoma have also been submitted in the EU, Australia, Switzerland and Japan, with the EMA Committee for Medicinal Products for Human Use adopting a positive opinion in July 2018 towards granting the drugs marketing authorizations in the EU. Encorafenib plus binimetinib combination therapy is also in ongoing phase III clinical development in the treatment of metastatic colorectal cancer. This article summarizes the milestones in the development of encorafenib and binimetinib leading to these first approvals for the treatment of BRAFV600E or -V600K-mutation-positive unresectable or metastatic melanoma.
Fenofibrate and Dyslipidemia: Still a Place in Therapy
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ABSTRACT
Dyslipidemia is one of the major cardiovascular risk factors, but beyond statin treatment—which represents the cornerstone of therapy—a relevant practical uncertainty regards the use of fibrate derivatives. In the lack of successful results from the main cardiovascular trials, guidelines recommend the use of peroxisome proliferator-activated receptor agonists in selected cases, i.e. patients with true atherogenic dyslipidemia. However, recent observations indicate that fenofibrate treatment may provide a reliable complementary support against residual cardiovascular risk. We therefore summarize current evidence on fenofibrate, seeking to provide an updated interpretation of recent studies in the field.

Extending the Breadth of Influenza Vaccines: Status and Prospects for a Universal Vaccine
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ABSTRACT
Despite the widespread use of seasonal influenza vaccines, there is urgent need for a universal influenza vaccine to provide broad, long-term protection. A number of factors underpin this urgency, including threats posed by zoonotic and pandemic influenza A viruses, suboptimal effectiveness of seasonal influenza vaccines, and concerns surrounding the effects of annual vaccination. In this article, we discuss approaches that are being investigated to increase influenza vaccine breadth, which are near-term, readily achievable approaches to increase the range of strains recognized within a subtype, or longer-term more challenging approaches to produce a truly universal influenza vaccine. Adjuvanted and neuraminidase-optimized vaccines are emerging as the most feasible and promising approaches to extend protection to cover a broader range of strains within a subtype. The goal of developing a universal vaccine has also been advanced with the design of immunogenic influenza HA-stem constructs that induce broadly neutralizing antibodies. However, these constructs are not yet sufficiently immunogenic to induce lasting universal immunity in humans. Advances in understanding how T cells mediate protection, and how viruses are packaged, have facilitated the rationale design and delivery of replication-incompetent virus vaccines that induce broad protection mediated by lung-resident memory T cells. While the lack of clear mechanistic correlates of protection, other than haemagglutination-inhibiting antibodies, remains an impediment to further advancing novel influenza vaccines, the pressing need for such a vaccine is supporting development of highly innovative and effective strategies.
Antithrombotic Therapy after Percutaneous Coronary Intervention in Atrial Fibrillation: The Triple Trouble
Massimo Leggio, Augusto Fusco Paolo Severi Mario Lombardi Elisa Caldare Stefania D’Emidio Massimo Armeni Daniela Mereu Maria Grazia Bendini Andrea Mazza

ABSTRACT
One of the most common conundrums in all cardiovascular medicine pertains to the care of patients with atrial fibrillation after percutaneous coronary intervention, because of both dual antiplatelet therapy and oral anticoagulant therapy would seem to be necessary to reduce risks of stent thrombosis and thromboembolism, respectively, but also with an inevitable trade-off of more bleeding. Patients who require triple therapy are at high risk of both ischaemia and bleeding; therefore, defining a personalised secondary prevention strategy aimed at achieving the best net clinical benefit is essential. The good news is that we have entered an era of increased perceived and tangible safety that applies to both non-vitamin K-antagonist oral anticoagulants and newer drug-eluting stents. Even if the consistency across the major trials and the significantly lower risk of bleeding with dual therapy make it hard to argue that triple therapy should be used routinely, the aggregate evidence suggests that the net clinical benefit of dual therapy should give cardiologists confidence to drop aspirin when they are using a contemporary percutaneous coronary intervention strategy with drug-eluting stents. Waiting for more randomised trials and meta-analyses, for the time being, in patients not in clinical trials, full-dose oral triple therapy with dual antiplatelet agents and full-dose anticoagulation should be avoided as a routine practice, and the choice of the proper, that is, safer, oral anticoagulant, namely a non-vitamin K-antagonist oral anticoagulant, may be regarded by now as an additional bleeding avoiding strategy in patients with atrial fibrillation undergoing percutaneous coronary intervention.

Pharmacotherapy for Focal Seizures in Children and Adolescents
Clare E. Stevens Carl E. Stafstrom

ABSTRACT
Focal-onset seizures are among the most common forms of seizures in children and adolescents and can be caused by a wide diversity of acquired or genetic etiologies. Despite the increasing array of antiseizure drugs available, treatment of focal-onset seizures in this population remains problematic, with as many as one-third of children having seizures refractory to medications. This review discusses contemporary concepts in focal seizure classification and pathophysiology and describes the antiseizure medications most commonly chosen for this age group. As antiseizure drug efficacy is comparable in children and adults, here we focus on pharmacokinetic aspects, drug–drug interactions, and side effect profiles. Finally, we provide some suggestions for choosing the optimal medication for the appropriate patient.
Supervised Injectable Opioid Treatment for the Management of Opioid Dependence

James Bell, Vendula BelackovaNicholas Lintzeris

ABSTRACT

Since the 1990s, there have been seven clinical trials, and considerable clinical experience, in supervised injectable opioid treatment (SIOT) for individuals who, despite previous treatments, continue to inject illicit heroin and experience harmful health and social consequences. Most studies prescribed pharmaceutical heroin (diacetyl morphine, or DAM). This paper critically reviews randomised trials, long-term follow-up studies and qualitative reports of SIOT, and briefly reviews evidence regarding other medications used in injectable treatment as an alternative to DAM. It seeks to identify critical, unresolved issues regarding this treatment. Randomised trials comparing DAM with oral methadone (OM) report that while in treatment, participants randomised to DAM used less street heroin; reported spending less money on drugs, committed fewer crimes, and experienced improved health. Similar findings pertain to SIOT with hydromorphone. Because of the risks of overdose, diversion, and misuse, all recent trials of injected DAM involved supervised administration. This contributes to treatment being expensive to deliver. There is conflicting evidence regarding societal cost effectiveness, with some studies estimating that the reduction in crime more than compensates for the expense of the treatment. The critical, unresolved issues concerning this modality of treatment relate to the way in which it is approached—either as a medium-term, intensive intervention where other treatment has failed, designed to bring people into conventional opioid agonist treatment (OAT); or an indefinite support aimed at reducing social and personal harm. The former seems in line with the available findings on long-term effectiveness of SIOT and might be more acceptable given its rather moderate cost.

An Update on the Clinical Use of CDK4/6 Inhibitors in Breast Cancer

Marie Robert, Jean-Sébastien FrenelEmmanuelle BourboulouxDominique Berton RigaudAnne PatsourisPaule AugereauCarole GourmelonMario Campone

ABSTRACT

Deregulated cell division, resulting in aberrant cell proliferation, is one of the key hallmarks of cancer. Cyclin-dependent kinases (CDKs) play a central role in cell cycle progression in cancer, and the clinical development of the CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib has changed clinical practice in the setting of endocrine-receptor positive breast cancer. Results of pivotal phase II and III trials investigating these CDK4/6 inhibitors in patients with endocrine receptor-positive, advanced breast cancer have demonstrated a significant improvement in progression-free survival, with a safe toxicity profile. No validated biomarkers of sensitivity or resistance exist at the moment. Future development of CDK4/6 inhibitors in breast cancer should focus on the identification of predictive biomarkers, the development of drug combinations to overcome resistance, and the application of CDK4/6 inhibitors to other breast cancer subtypes.
Peramivir: A Review in Uncomplicated Influenza

Lesley J. Scott

ABSTRACT
Intravenous peramivir (Alpivab™; Rapivab®; Rapiacta®; PeramiFlu®), the most recent globally approved inhibitor of influenza neuraminidase, is indicated for the treatment of uncomplicated influenza in adults and children from the age of 2 years. This article, written from an EU perspective, reviews the clinical use of peramivir in this indication and summarizes its pharmacological properties. In large, randomized, double-blind, multicentre trials in previously healthy adults with uncomplicated influenza, a single infusion of peramivir 600 mg significantly shortened the median time to resolution of influenza symptoms compared with placebo and was noninferior to the recommended oseltamivir regimen in terms of this primary outcome. Albeit data are limited, results from a noncomparative phase 3 trial in paediatric patients (≈95% of whom were aged ≥2 years) with acute uncomplicated influenza receiving the recommended dose of peramivir were generally consistent with those in adults. Peramivir was generally well tolerated in children and adults participating in these clinical trials, with most adverse events of mild to moderate intensity. Given its simple single-dose regimen and with intravenous administration offering a potential advantage over oral administration in individuals with nausea, vomiting or having difficulty in swallowing, peramivir provides an additional option for treating uncomplicated influenza infection in adults and children from the age of 2 years.

Inotersen: First Global Approval

Susan J. Keam

ABSTRACT
Ionis Pharmaceuticals and Akcea Therapeutics have developed inotersen (Tegsedi™), an antisense oligonucleotide inhibitor of mutant and wild-type human transthyretin (TTR), for the treatment of hereditary transthyretin amyloidosis (hATTR). Mutation of the TTR gene results in accumulation of TTR protein fragments as amyloid deposits throughout the organs in patients with hATTR, including the peripheral nervous system and the heart. Treatment with inotersen, which selectively binds to TTR mRNA, prevents the synthesis of TTR protein in the liver, thus reducing further amyloid deposition throughout the body. Subcutaneous administration of inotersen significantly reduced neurological progression and improved health-related quality of life in patients with hATTR and polyneuropathy in a phase III trial. Based on these results, inotersen was recently approved in the EU for the treatment of stage 1 or 2 polyneuropathy in adult patients with hATTR and is under evaluation in the USA and Canada for a similar indication. This article summarizes the milestones in the development of inotersen leading to this first approval.
Tecovirimat: First Global Approval
Sheridan M. Hoy

ABSTRACT
Tecovirimat (TPOXX®) is an orthopoxvirus-specific antiviral drug developed by SIGA Technologies in conjunction with the US Department of Health and Human Services’ Biomedical Advances Research and Development Authority. It acts by inhibiting the activity of the orthopoxvirus VP37 envelope wrapping protein, thereby preventing the formation of egress-competent enveloped virions, which are essential for dissemination of the virus in the host. In July 2018, oral tecovirimat was approved in the USA for the treatment of human smallpox disease caused by variola virus in adults and paediatric patients weighing ≥ 13 kg. Tecovirimat was approved under the US FDA’s Animal Rule, in which marketing approval is based on its efficacy in relevant animal models. An intravenous formulation of tecovirimat is undergoing phase I development for the treatment of smallpox infection. This article summarises the milestones in the development of tecovirimat leading to this first approval for the treatment of human smallpox disease in adults and paediatric patients weighing ≥ 13 kg.

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Human Papillomavirus Vaccines: Successes and Future Challenges
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ABSTRACT
Over a decade has passed since the first human papillomavirus (HPV) vaccine was introduced. These vaccines have received unequivocal backing from the scientific and medical communities, yet continue to be debated in the media and within the general public. The current review is an updated examination that the authors made five years ago on some of the key sociocultural and behavioral issues associated with HPV vaccine uptake and acceptability, given the changing HPV vaccine policies and beliefs worldwide. We explore current worldwide HPV vaccination rates, outline HPV vaccine policies, and revisit critical issues associated with HPV vaccine uptake including: risk compensation, perceptions of vaccine safety and efficacy, age of vaccination, and healthcare provider (HCP) recommendation and communication. While public scrutiny of the vaccine has not subsided, empirical evidence supporting its safety and efficacy beyond preventing cervical cancer has amassed. There are conclusive findings showing no link that vaccinated individuals engage in riskier sexual behaviors as a result of being immunized (risk compensation) both at the individual and at the policy level. Finally, HCP recommendation continues to be a central factor in HPV vaccine uptake. Studies have illuminated how HCP practices and communication enhance uptake and alleviate misperceptions about HPV vaccination. Strategies such as bundling vaccinations, allowing nurses to vaccinate via “standing orders,” and diversifying vaccination settings (e.g., pharmacies) may be effective steps to increase rates. The successes of HPV vaccination outweigh the controversy, but as the incidence of HPV-related cancers rises, it is imperative that future research on HPV vaccine acceptability continues to identify effective and targeted strategies to inform HPV vaccination programs and improve HPV coverage rates worldwide.
Beyond the TNF-α Inhibitors: New and Emerging Targeted Therapies for Patients with Axial Spondyloarthritis and their Relation to Pathophysiology

Susanne Juhl Pedersen, Walter P. Maksymowych

ABSTRACT

Axial spondyloarthritis (axSpA) is a complex disease that affects the joints and entheses of axial and peripheral joints, and is associated with inflammation in extra-articular sites such as the gut. Improved knowledge on genetics and immunology has improved treatment options with the availability of treatments targeting tumor necrosis factor-α (TNF-α) and interleukin (IL)-17. However, these agents do not provide clinical benefit for about 40% of patients, and additional therapeutic options are necessary. Theories on pathogenesis includes misfolding of HLA-B*27 during its assembly leading to endoplasmic reticulum stress and autophagy/unfolded protein response (UPR). HLA-B*27 may express free heavy chain on the cell surface, which activates innate immune receptors on T, natural killer, and myeloid cells with pro-inflammatory effects. Activation of UPR genes is associated with increased TNF-α, interleukin-23 (IL-23), IL-17, interferon-γ expression, and expansion of T helper (Th)-17 cells. Certain genotypes of endoplasmic reticulum aminopeptidase (ERAP) 1 and 2 are associated with ankylosing spondylitis (AS) and functionally interact with the HLA-B27 peptidome. Innate immune cells type 3, which express RORyt, regulate expression of IL-17 and IL-22 in T cells. Stimulation of gamma-delta T cells with IL-23 also induces IL-17. Mucosa-associated invariant T cells residing in the gut mucosa express IL-17 in AS patients after stimulation with IL-7. Prostaglandin E2 induces IL-17A independent of IL-23 via IL-1β and IL-6. The pathogenic role of gut inflammation, zonulin and microbiota, which has a different composition in AS patients, remains to be elucidated. This article also includes a comprehensive review on the mechanism of action and efficacy of the biological treatments currently approved for axSpA (TNF-α inhibitors and IL-17 inhibitors) and future targets for treatment (other IL-17 family member(s), Janus kinase, IL-23, and phosphodiesterase 4).

Approaches to the Pharmacological Management of Jet Lag

Josephine Arendt

ABSTRACT

For many years now a treatment mitigating the debilitating effects of jet lag has been sought. Rapid travel across time zones leads, in most people, to temporary symptoms, in particular poor sleep, daytime alertness and poor performance. Mis-timed circadian rhythms are considered to be the main factor underlying jet-lag symptoms, together with the sleep deprivation from long haul flights. Virtually all aspects of physiology are rhythmic, from cells to systems, and circadian rhythms are coordinated by a central pacemaker or clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN adapts slowly to changes in time zone, and peripheral clocks or oscillators adapt at different rates, such that the organism is in a state of desynchrony from the external environment and internally. Light exposure is the main factor controlling the circadian system and needs to be considered together with any pharmacological interventions. This review covers the relatively new chronobiotic drugs, which can hasten adaptation of the circadian system, together with drugs directly affecting alertness and sleep propensity. No current treatment can instantly shift circadian phase to a new time zone; however, adaptation can be hastened. The melatonergic drugs are promising but larger trials in real-life situations are needed. For short stopovers it is recommended to preserve sleep and alertness without necessarily modifying the circadian system. New research suggests that modification of clock function via genetic manipulation may one day have clinical applications.
Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia
G. Di StefanoA. TruiniG. Cruccu

ABSTRACT

Trigeminal neuralgia is a representative neuropathic facial pain condition, characterised by unilateral paroxysmal pain in the distribution territory of one or more divisions of the trigeminal nerve, triggered by innocuous stimuli. A subgroup of patients with trigeminal neuralgia [TN (previously defined as atypical TN)] also suffer from concomitant continuous pain, i.e. a background pain between the paroxysmal attacks. The aim of this review is to provide current, evidence-based, knowledge about the pharmacological treatment of typical and atypical TN, with a specific focus on drugs in development. We searched for relevant papers within PubMed, EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials database (ClinicalTrials.gov), taking into account publications up to February 2018. Two authors independently selected studies for inclusions, data extraction, and bias assessment. Carbamazepine and oxcarbazepine are the first-choice drugs for paroxysmal pain. When sodium channel blockers cannot reach full dosage because of side effects, an add-on treatment with lamotrigine or baclofen should be considered. In patients with atypical TN, both gabapentin and antidepressants are expected to be efficacious and should be tried as an add-on to oxcarbazepine or carbamazepine. Although carbamazepine and oxcarbazepine are effective in virtually the totality of patients, they are responsible for side effects causing withdrawal from treatment in an important percentage of cases. A new, better tolerated, Nav1.7 selective state-dependent, sodium channel blocker (vixotrigine) is under development. Future trials testing the effect of combination therapy in patients with TN are needed, especially in patients with concomitant continuous pain and in TN secondary to multiple sclerosis.

Immune Checkpoint Inhibitors: Toward New Paradigms in Renal Cell Carcinoma
Ronan FlippotBernard EscudierLaurence Albiges

ABSTRACT

Immune modulatory treatment regimens, led by immune checkpoint inhibitors, have transformed the treatment of clear-cell renal cell carcinoma. First-in-class, the PD-1 inhibitor nivolumab improved overall survival in advanced renal cell carcinoma following prior anti-angiogenic therapy, an important shift in the management of clear-cell renal cell carcinoma. Further improvements of long-term outcomes will be driven by combinations in the first-line setting, including PD-1/PD-L1 associated with antiangiogenic therapies, or PD1/PD-L1 inhibitors with other immune checkpoint inhibitors such as anti-CTLA-4, anti-LAG-3 or TIM-3 targeted therapies. The first two randomized Phase 3 trials assessing these combinations have now challenged sunitinib in first-line setting. First, the CheckMate 214 trial demonstrated an objective response rate and overall survival benefit for the combination of nivolumab plus ipilimumab in the intermediate- and poor-risk patients. Second, the IMMmotion 151 study demonstrated a progression-free survival benefit for the atezolizumab plus bevacizumab combination by investigator assessment. Further Phase 3 trials are awaited with tyrosine kinase and immune checkpoint inhibitor combinations. Clinical trials of immune checkpoint inhibitors are also actively investigated in the localized adjuvant or neoadjuvant setting. Nevertheless, the search for biomarkers along with new clinical trial designs will be crucial to better select the patients that may derive the greatest benefit from these advances. The continuing improvement of antitumor immunity comprehension and the emergence of new immune modulatory treatments will deeply change the management of renal cell carcinoma for the years to come.
Assessing and Treating Chronic Pain in Patients with End-Stage Renal Disease

Flaminia Coluzzi

ABSTRACT

Pain is one of the most common symptoms among patients with end-stage renal disease (ESRD), and is often under recognized and not adequately managed in hemodialysis (HD) patients. Barriers to adequate pain management include poor awareness of the problem, insufficient medical education, fears of possible drug-related side effects, and common misconceptions about the inevitability of pain in elderly and HD patients. Caregivers working in HD should be aware of the possible consequences of inadequate pain assessment and management. Common pain syndromes in HD patients include musculoskeletal diseases and metabolic neuropathies, associated with typical intradialytic pain. Evaluating the etiology, nature, and intensity of pain is crucial for choosing the correct analgesic. A mechanism-based approach to pain management may result in a better outcome. Pharmacokinetic considerations on clearance alterations and possible toxicity in patients with ESRD should drive the right analgesic prescription. Comorbidities and polymedications may increase the risk of drug–drug interactions, therefore drug metabolism should be taken into account when selecting analgesic drugs. Automedication is common among HD patients but should be avoided to reduce the risk of hazardous drug administration. Further research is warranted to define the efficacy and safety of analgesic drugs and techniques in the context of patients with ESRD as generalizing information from studies conducted in the general population could be inappropriate and potentially dangerous. A multidisciplinary approach is recommended for the management of complex pain syndromes in frail patients, such as those suffering from ESRD.

Elotuzumab: A Review in Relapsed and/or Refractory Multiple Myeloma

Yvette N. Lamb

ABSTRACT

Intravenous elotuzumab (Empliciti™), a monoclonal antibody targeting the signalling lymphocytic activation molecule F7 (SLAMF7) glycoprotein, is approved for use in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in previously-treated adult patients. In the pivotal, multinational, phase III ELOQUENT-2 trial in adults with relapsed and/or refractory multiple myeloma, elotuzumab in combination with lenalidomide and dexamethasone significantly prolonged median progression-free survival (PFS) and increased overall response rate (ORR; co-primary endpoints) compared with lenalidomide and dexamethasone alone. The clinical benefit of elotuzumab was maintained over the longer term (≤ 4 years’ minimum follow-up); final overall survival data are awaited. Health-related quality of life was not negatively impacted by the addition of elotuzumab. Elotuzumab combination therapy had a generally manageable tolerability profile and the most common adverse events (AEs) of grade ≥ 3 severity were haematological (e.g. lymphocytopenia, anaemia, thrombocytopenia, neutropenia). Elotuzumab plus lenalidomide and dexamethasone extends the treatment options available for the management of relapsed and/or refractory multiple myeloma.
Capsaicin 8% Dermal Patch: A Review in Peripheral Neuropathic Pain

Hannah A. Blair

ABSTRACT
The adhesive capsaicin dermal patch (Qutenza®) delivers a high concentration (8% w/w) of synthetic capsaicin, a highly selective agonist of transient receptor potential vanilloid-1 (TRPV-1), directly to the site of pain. The capsaicin 8% dermal patch is indicated in the EU for the treatment of peripheral neuropathic pain (PNP) in adults, either alone or in combination with other medicinal products for pain. In patients with painful diabetic peripheral neuropathy, a single 30-min application of the capsaicin 8% dermal patch provided 12 weeks of pain relief and improved sleep quality compared with placebo. Repeat treatment with the capsaicin 8% dermal patch plus standard of care over 52 weeks provided sustained pain relief, with no negative neurological effects compared with standard of care alone. The capsaicin 8% dermal patch was non-inferior to oral pregabalin in relieving pain in patients with non-diabetic PNP, with a faster onset of action and greater treatment satisfaction. A single 60-min application of the capsaicin 8% dermal patch provided rapid and sustained pain relief in patients with postherpetic neuralgia. Results in patients with HIV-associated neuropathy were equivocal, with a significant improvement in pain intensity observed in one trial, but not in the other. The capsaicin 8% dermal patch was generally well tolerated; transient application-site reactions were the most common adverse events. In conclusion, the capsaicin 8% dermal patch is a useful addition to the treatment options currently available for patients with PNP.

Elagolix: First Global Approval

Yvette N. Lamb

ABSTRACT
Elagolix (ORILISSA™), an orally bioavailable, second-generation, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist, is being developed AbbVie and Neurocrine Biosciences for the treatment of reproductive hormone-dependent disorders in women. In July 2018, the US FDA approved elagolix tablets for the management of moderate to severe pain associated with endometriosis. This approval was based on positive results in two replicate phase III trials; additional phase III trials in the USA, Canada and Puerto Rico are currently evaluating elagolix as both monotherapy and in combination with low-dose hormone add-back therapy in the same indication. Elagolix with and without low-dose hormone add-back therapy is also undergoing phase III clinical development for heavy menstrual bleeding associated with uterine fibroids in the aforementioned locations. This article summarizes the milestones in the development of elagolix leading to its first approval for the management of moderate to severe pain associated with endometriosis.
Ivosidenib: First Global Approval
Sohita Dhillon

ABSTRACT
Ivosidenib (Tibsovo®) is a small molecule, orally available inhibitor of mutated cytosolic isocitrate dehydrogenase 1 (IDH1) that is being developed by Agios Pharmaceuticals for the treatment of cancer in patients with IDH1 mutations. The mutated form of the IDH1 enzyme produces a metabolite, 2-hydroxyglutarate (2-HG), which is thought to play a role in the formation and progression of acute myeloid leukaemia (AML), gliomas and other cancers. Elevated 2-HG levels interfere with cellular metabolism and epigenetic regulation, thereby contributing to oncogenesis. Ivosidenib targets the IDH1 metabolic pathway to prevent a build-up of the oncometabolite 2-HG. This article summarizes the milestones in the development of ivosidenib leading to this first approval in the USA for the treatment of patients with relapsed or refractory AML with a susceptible IDH1 mutation. Clinical development for AML, cholangiocarcinoma, glioma, myelodysplastic syndromes and solid tumours is ongoing worldwide.

Tafenoquine: First Global Approval
James E. Frampton

ABSTRACT
Tafenoquine (Krintafel™, Arakoda™), an orally-active 8-aminoquinoline anti-malarial drug, is a long-acting analogue of primaquine with activity against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of Plasmodium species that include Plasmodium vivax (P. vivax) and Plasmodium falciparum. It has been developed by GlaxoSmithKline (formerly SmithKline Beecham) for the radical cure of P. vivax malaria and by 60 Degrees Pharmaceuticals for the prophylaxis of malaria. The exact mechanism(s) of action underlying the anti-Plasmodium activity of tafenoquine are unknown, although it may exert its effect by inhibiting haematin polymerization and, additionally, by inducing mitochondrial dysfunction leading to the apoptotic-like death of the organism. In July 2018, tafenoquine was approved in the USA for the radical cure of P. vivax malaria in patients aged ≥ 16 years who are receiving appropriate antimalarial therapy for acute P. vivax malaria. Subsequently, in August 2018, tafenoquine was approved in the USA for the prophylaxis of malaria in patients aged ≥ 18 years. This article primarily summarizes the milestones in the development of tafenoquine leading to its first global approval for the radical cure of P. vivax malaria.
Targeted Therapies for Autoimmune Bullous Diseases: Current Status
Kyle T. Amber, Roberto MaglieFarzan SolimaniRüdiger EmingMichael Hertl

ABSTRACT
Autoimmune bullous skin disorders are rare but meaningful chronic inflammatory diseases, many of which had a poor or devastating prognosis prior to the advent of immunosuppressive drugs such as systemic corticosteroids, which down-regulate the immune pathogenesis in these disorders. Glucocorticoids and adjuvant immunosuppressive drugs have been of major benefit for the fast control of most of these disorders, but their long-term use is limited by major side effects such as blood cytopenia, osteoporosis, diabetes mellitus, hypertension, and gastrointestinal ulcers. In recent years, major efforts were made to identify key elements in the pathogenesis of autoimmune bullous disorders, leading to the identification of their autoantigens, which are mainly located in desmosomes (pemphigus) and the basement membrane zone (pemphigoids). In the majority of cases, immunoglobulin G, and to a lesser extent, immunoglobulin A autoantibodies directed against distinct cutaneous adhesion molecules are directly responsible for the loss of cell-cell and cell-basement membrane adhesion, which is clinically related to the formation of blisters and/or erosions of the skin and mucous membranes. We describe and discuss novel therapeutic strategies that directly interfere with the production and regulation of pathogenic autoantibodies (rituximab), their catabolism (intravenous immunoglobulins), and their presence in the circulation and extravascular tissues such as the skin (immunoadsorption), leading to a significant amelioration of disease. Moreover, we show that these novel therapies have pleiotropic effects on various proinflammatory cells and cytokines. Recent studies in bullous pemphigoid suggest that targeting of immunoglobulin E autoantibodies (omalizumab) may be also beneficial. In summary, the introduction of targeted therapies in pemphigus and pemphigoid holds major promise because of the high efficacy and fewer side effects compared with conventional global immunosuppressive therapy.

Therapeutic Advances and Challenges in the Treatment of Progressive Multiple Sclerosis
Laura E. BaldassariRobert J. Fox

ABSTRACT
Despite the fact that majority of patients with multiple sclerosis (MS) have relapsing-remitting disease, many transition to secondary progressive disease (SPMS) over time. This transition is thought to be related to neurodegenerative processes increasingly predominating over inflammatory processes as the driving forces of disability. However, some patients initially present with primary progressive disease (PPMS) that is characterized by a gradual accumulation of neurological symptoms and subsequent disability accumulation. The treatment of both PPMS and SPMS, collectively referred to as progressive MS, has proven quite challenging due to the multifactorial and poorly understood pathophysiology of multiple sclerosis in general, specifically that of progressive disease. The purpose of this article is to discuss important clinical and pathophysiologic differences between relapsing and progressive forms of MS, review previous notable trials of drugs in progressive MS, examine current literature regarding recent and promising progressive MS treatments, and discuss future considerations for progressive MS therapeutics and management. Specifically, the current evidence regarding treatment of progressive MS with ocrelizumab, simvastatin, ibudilast, alpha-lipoic acid, high-dose biotin, siponimod, and cell-based therapies are discussed.
Cardiovascular Safety of Antihyperglycemic Agents: “Do Good or Do No Harm”
Antonis A. ManolisTheodora A. ManolisAntonis S. Manolis

ABSTRACT
Results from recent cardiovascular outcome trials have ushered in a new era in the management of type 2 diabetes mellitus, moving from a focus on glycemic control to the cardiovascular safety of antihyperglycemic agents. Several new antihyperglycemic drugs have been shown to exert either neutral or cardioprotective effects in patients with diabetes. Among them, the sodium–glucose co-transporter-2 (SGLT-2) inhibitors (gliflozins) and selected agents from the incretin mimetics or enhancers, such as the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins), appear to confer cardiovascular safety and/or protection in patients with underlying, or at high risk for, cardiovascular disease. Metformin remains the standard first-line drug treatment for patients with diabetes because of its established effectiveness and cardiovascular safety. However, this initial drug therapy may not prove adequate as this disease appears to be progressive with a decline in function of the pancreatic beta cells, necessitating the addition of other agents to better control rising glucose levels. With the advent of several new classes of antihyperglycemic drugs and the completion of their respective cardiovascular outcome trials, the therapeutic armamentarium against this disease pandemic appears to be greatly expanding and moving closer to the direction of the Hippocratic aphorism “Do Good or Do No Harm”. In this review, we discuss all these issues and summarize the contemporary literature on cardiovascular safety and outcomes of the available glucose-lowering agents.
Antibiotics and Cure Rates in Childhood Febrile Urinary Tract Infections in Clinical Trials: A Systematic Review and Meta-analysis

Konstantinos Vazouras, Romain BasmaciJulia BielickiLaura FolgornTheoklis ZaoutisMike SharlandYingfen Hsia

ABSTRACT

Purpose: Urinary tract infections (UTIs) are common bacterial infections among children.

Objective: To systematically review the antimicrobials used for febrile UTIs in paediatric clinical trials and meta-analyse the observed cure rates and reasons for treatment failure.

Materials and Methods: We searched Medline, Embase and Cochrane central databases between January 1, 1990, and November 24, 2016, combining MeSH and free-text terms for: “urinary tract infections”, AND “therapeutics”, AND “clinical trials” in children (age range 0–18 years). Two independent reviewers assessed study quality and performed data extraction. The major outcome measures were clinical and microbiological cure rates according to different antibiotics.

Results: We identified 2762 published studies and included 30 clinical trials investigating 3913 cases of paediatric febrile urinary tract infections. Children with no underlying condition were the main population included in the trials (n = 2602; 66.5%). Cephalosporins were the most frequent antibiotics studied in trials (22/30, 73.3%). Only a few antibiotics active against resistant UTIs have been tested in randomised clinical trials, mainly aminoglycosides. The average point cure rate of all investigational drugs was estimated to 95.3% (95% CI 93.5–96.9%). Among 3002 patients for whom cure and failure rates were reported, only 3.9% (3.9%; 118/3002) were considered clinically to have treatment failure, while 135 (4.5%; 135/3002) had microbiological failure.

Conclusions: We observed high treatment cure rates, regardless of the investigational drug chosen, the route of administration, duration and dosing. This suggests that future research should prioritise observational studies and clinical trials on children with multi-drug-resistant infections.

Sodium Zirconium Cyclosilicate: A Review in Hyperkalaemia

Sheridan M. Hoy

ABSTRACT

Sodium zirconium cyclosilicate (Lokelma™) [hereafter referred to as SZC] is a non-absorbed, non-polymer zirconium silicate compound that preferentially exchanges hydrogen and sodium for potassium and ammonium ions in the gastrointestinal tract (GIT), thereby increasing faecal potassium excretion and lowering serum potassium levels. It is available as a powder for oral suspension (in water) and is approved in the EU and the USA for the treatment of hyperkalaemia in adults. In two multinational, phase III studies in adults with hyperkalaemia, SZC 10 g three times daily lowered serum potassium levels to within the normal range (3.5–5.0 mmol/L) during the first 48 h of treatment, and SZC 5 and 10 g once daily maintained normokalaemia over ≤28 days’ therapy. These beneficial effects were consistent across all patient subgroups (e.g. chronic kidney disease, diabetes, heart failure, concomitant use of RAAS inhibitor therapy), and appeared to be maintained over the longer term (≤12 months). SZC was generally well tolerated in adults with hyperkalaemia. Its tolerability profile was generally similar to that seen with placebo over ≤28 day, and its safety profile appeared to remain consistent over the longer term (≤12 months). Moreover, the incidence of hypokalaemia was low. Current evidence indicates that SZC is a promising therapy for the management of hyperkalaemia in adults.
Dinoprostone Vaginal Insert: A Review in Cervical Ripening

Matt Shirley

ABSTRACT

Dinoprostone vaginal insert (Cervidil®; Propess®), a retrievable vaginal pessary containing 10 mg of dinoprostone [prostaglandin E2 (PGE2)] in a controlled-release drug delivery device, is approved in many countries worldwide for the initiation (or continuation) of cervical ripening in patients at term prior to labour induction. The device is designed to provide a constant and sustained release of dinoprostone to the cervix to promote the complex processes involved in cervical ripening. The vaginal insert is attached to a retrieval system that facilitates easy removal of the device at the onset of labour or in the event of complications. The effectiveness of dinoprostone vaginal insert has been demonstrated in a vast range of randomized clinical trials in women at term. The agent is well tolerated, with a generally favourable safety profile, both maternal and foetal/neonatal. As with all prostaglandin agents used in cervical ripening, dinoprostone vaginal insert is associated with a risk of uterine hyperstimulation. However, this is generally rapidly reversible upon removal of the insert. The demonstrated effectiveness and safety of the device, combined with the benefits of controlled drug release from a simple, single application, and efficient dose control, suggest that dinoprostone vaginal insert is a valuable option for promoting cervical ripening in patients with an unfavourable cervix at term.

Patisiran: First Global Approval

Sheridan M. Hoy

ABSTRACT

Patisiran (ONPATTRO™) is a double-stranded small interfering RNA encapsulated in a lipid nanoparticle for delivery to hepatocytes. By specifically binding to a genetically conserved sequence in the 3’ untranslated region of mutant and wild-type transthyretin (TTR) messenger RNA, patisiran causes its degradation (via RNA interference) and subsequently a reduction in serum TTR protein levels and tissue TTR protein deposits. Patisiran has been developed by Alnylam Pharmaceuticals; it was recently approved in the USA for the treatment of the polyneuropathy of hereditary TTR-mediated amyloidosis (hATTR) in adults and subsequently approved in the EU for the treatment of hATTR in adults with stage 1 or 2 polyneuropathy. The recommended dosage, administered as a single intravenous infusion over approximately 80 min, is 0.3 mg/kg once every 3 weeks for patients weighing <100 kg and 30 mg once every 3 weeks for patients weighing ≥100 kg. This article summarizes the milestones in the development of patisiran leading to these approvals.
Lanadelumab: First Global Approval

Yahiya Y. Syed

ABSTRACT

Shire is developing lanadelumab (Takhzyro™) for the prevention of hereditary angioedema (HAE) attacks. Lanadelumab is a fully human monoclonal antibody that inhibits plasma kallikrein. Mutations in the SERPING1 gene lead to C1 inhibitor deficiency or dysfunction, resulting in uncontrolled plasma kallikrein activity, which in turn produces excessive bradykinin, a vasodilator thought to cause angioedema symptoms. Subcutaneous administration of lanadelumab significantly reduced HAE attacks versus placebo in patients aged ≥ 12 years with type I or II HAE in a phase III trial. Based on these results, lanadelumab is recently approved in the USA for the prevention of HAE attacks in patients aged ≥ 12 years. It is also preregistered in the EU, Canada, Australia and Switzerland. This article summarizes the milestones in the development of lanadelumab leading to this first approval.

Caplacizumab: First Global Approval

Sean Duggan

ABSTRACT

Ablynx, a Sanofi Company, has developed the anti-von Willebrand factor Nanobody® caplacizumab (Cablivi™) for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP). Based on positive results in phase II and III trials in patients with aTTP, caplacizumab was recently approved in the EU for the treatment of adults experiencing an episode of aTTP, in conjunction with plasma exchange and immunosuppression. This article summarizes the milestones in the development of caplacizumab leading to this first approval.

Doravirine: First Global Approval

Emma D. Deeks

ABSTRACT

Doravirine is a new non-nucleoside reverse transcriptase inhibitor (NNRTI) developed by Merck & Co for the treatment of HIV-1 infection. The drug is approved in the USA both as a single-agent tablet (Pifelatro™) and as a fixed-dose combination tablet with the nucleos(t)ide reverse transcriptase inhibitors lamivudine and tenofovir disoproxil fumarate (Delstrigo™). Each formulation is indicated in the USA for treating HIV-1 infection in adults with no prior antiretroviral treatment, has received a positive opinion in the EU for treating HIV-1 infection in adults without resistance to NNRTIs or (in the case of the fixed-dose combination tablet) lamivudine or tenofovir, and is also under regulatory review for the treatment of HIV-1 infection in Canada. This article summarizes the milestones in the development of doravirine leading to this first approval for the treatment of HIV-1 infection in treatment-naive adults.
Targeting Bruton’s Tyrosine Kinase Across B-Cell Malignancies
Caspar da Cunha-BangCarsten Utoft Niemann

ABSTRACT
Bruton’s tyrosine kinase (BTK) is crucial in B-cell development and survival. The role of BTK as a downstream kinase in the B-cell receptor (BCR) signaling pathway is well described. As a key player in the pathogenesis of B-cell malignancies, targeting of dysregulated BCR signaling has been explored by development of inhibitors of downstream mediators. Discovery of the biological function of BTK and the development of covalent inhibitors for clinical use, ibrutinib as the lead agent and acalabrutinib as the second clinically approved BTK inhibitor, have revolutionized the treatment options for B-cell malignancies. Currently, ibrutinib is approved for mantle cell lymphoma, chronic lymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, small lymphocytic lymphoma, marginal zone lymphoma and chronic graft versus host disease, while acalabrutinib is approved for mantle cell lymphoma. Potential expansion of indications in other diseases is under investigation in several clinical trials, while combination of BTK inhibitors with either chemoimmunotherapy or other targeted agents is being systematically explored in B-cell malignancies.

Dolutegravir/Rilpivirine: A Review in HIV-1 Infection
Hannah A. Blair

ABSTRACT
Dolutegravir/rilpivirine (Juluca®) is the first two-drug single-tablet regimen (STR) to be approved for the treatment of HIV-1 infection in adults. The fixed-dose STR combines the integrase strand transfer inhibitor dolutegravir with the non-nucleoside reverse transcriptase inhibitor rilpivirine. In two phase III non-inferiority trials (SWORD-1 and SWORD-2) in treatment-experienced patients already virologically suppressed on their current antiretroviral (ART) regimen, switching to once-daily dolutegravir plus rilpivirine maintained virological suppression over 48 weeks. Switching to a two-drug regimen of dolutegravir plus rilpivirine was also associated with high rates of virological suppression in real-world observational studies. Switching to once-daily dolutegravir plus rilpivirine was generally well tolerated and associated with more favourable renal and bone parameters than remaining on the current ART regimen. Longer-term, dolutegravir plus rilpivirine demonstrated durable maintenance of virological suppression and remained generally well tolerated for up to 100 weeks. Thus, dolutegravir/rilpivirine provides a convenient alternative treatment option for some adults with HIV-1 infection and no history of virological failure who are already virologically suppressed on (and wish to switch from) their current ART regimen.
Cannabinoid receptors, endocannabinoids and the enzymes responsible for their biosynthesis and degradation constitute the endocannabinoid system. In recent decades, the endocannabinoid system has attracted considerable interest as a potential therapeutic target in numerous pathological conditions. Its involvement in several physiological processes is well known, such as in energy balance, appetite stimulation, blood pressure, pain modulation, embryogenesis, nausea and vomiting control, memory, learning and immune response, among others, as well as in pathological conditions where it exerts a protective role in the development of certain disorders. As a result, it has been reported that changes in endocannabinoid levels may be related to neurological diseases such as Parkinson’s disease, Huntington’s disease, Alzheimer’s disease and multiple sclerosis, as well as anorexia and irritable bowel syndrome. Alterations in the endocannabinoid system have also been associated with cancer, affecting the growth, migration and invasion of some tumours. Cannabinoids have been tested in several cancer types, including brain, breast and prostate cancers. Cannabinoids have shown promise as analgesics for the treatment of both inflammatory and neuropathic pain. There is also evidence for a role of the endocannabinoid system in the control of emotional states, and cannabinoids could prove useful in decreasing and palliating post-traumatic stress disorder symptoms and anxiolytic disorders. The role of the endocannabinoid system in addictions has also been examined, and cannabinoids have been postulated as alternative and co-adjuvant treatments in some abuse syndromes, mainly in ethanol and opioid abuses. The expression of the endocannabinoid system in the eye suggests that it could be a potential therapeutic target for eye diseases. Considering the importance of the endocannabinoid system and the therapeutic potential of cannabinoids in this vast number of medical conditions, several clinical studies with cannabinoid-based medications are ongoing. In addition, some cannabinoid-based medications have already been approved in various countries, including nabilone and dronabinol capsules for the treatment of nausea and vomiting associated with chemotherapy, dronabinol capsules for anorexia, an oral solution of dronabinol for both vomiting associated with chemotherapy and anorexia, a Δ9-tetrahydrocannabinol/cannabidiol oromucosal spray for pain related to cancer and for spasticity and pain associated with multiple sclerosis, and an oral solution of cannabidiol for Dravet and Lennox–Gastaut syndromes. Here, we review the available efficacy, safety and tolerability data for cannabinoids in a range of medical conditions.

ABSTRACT
Tapering and Discontinuation of Biologics in Patients with Psoriatic Arthritis with Low Disease Activity

Weiyu Ye, Laura J. TuckerLaura C. Coates

ABSTRACT

The introduction of biologic disease modifying anti-rheumatic drugs (bMDARDs) have revolutionised the treatment of psoriatic arthritis (PsA). This combined with a ‘treat-to-target’ approach, means that achieving remission is increasingly possible. In patients with well-controlled PsA, there is little consensus on whether bDMARDs should be continued, tapered or discontinued altogether. Tapering or discontinuation of bDMARDs could offer significant financial savings and minimise patient burden and unwanted drug-related side effects. However, there is a risk of loss of remission. The primary focus of this paper is to review the current evidence on bDMARD tapering and discontinuation in PsA. We explore the criteria employed by studies to define patients eligible for bDMARD tapering or discontinuation and the process by which this occurs. We also review the outcomes of bDMARD tapering and discontinuation, the predictors, and the likelihood of restoring remission following relapse. To date, bDMARD tapering seems to be feasible and safe in patients with PsA who are in remission or with low disease activity. Lower disease activity prior to tapering seems to increase the likelihood of successful bDMARD tapering. In contrast, discontinuing bDMARDs appears to carry a substantial risk of loss of remission. Those with higher disease activity at time of tumour necrosis factor inhibitors discontinuation, current smokers, male sex, increased skin involvement, and synovial hypertrophy seen on ultrasound prior to discontinuation are at greater risk of losing remission post-bDMARD discontinuation. In those who lose remission, reinstating the standard dose of bDMARD appears to be effective in restoring remission.

Pyrotinib: First Global Approval

Hannah A. Blair

ABSTRACT

Pyrotinib is an irreversible dual pan-ErbB receptor tyrosine kinase inhibitor developed for the treatment of HER2-positive advanced solid tumours. Based on positive results in a phase II trial, the drug recently received conditional approval in China for use in combination with capecitabine for the treatment of HER2-positive, advanced or metastatic breast cancer in patients previously treated with anthracycline or taxane chemotherapy. This article summarizes the milestones in the development of pyrotinib leading to this first global approval for the treatment of HER2-positive advanced breast cancer.
Chronic Obstructive Pulmonary Disease and Lung Cancer: Underlying Pathophysiology and New Therapeutic Modalities


**ABSTRACT**

Chronic obstructive pulmonary disease (COPD) and lung cancer are major lung diseases affecting millions worldwide. Both diseases have links to cigarette smoking and exert a considerable societal burden. People suffering from COPD are at higher risk of developing lung cancer than those without, and are more susceptible to poor outcomes after diagnosis and treatment. Lung cancer and COPD are closely associated, possibly sharing common traits such as an underlying genetic predisposition, epithelial and endothelial cell plasticity, dysfunctional inflammatory mechanisms including the deposition of excessive extracellular matrix, angiogenesis, susceptibility to DNA damage and cellular mutagenesis. In fact, COPD could be the driving factor for lung cancer, providing a conducive environment that propagates its evolution. In the early stages of smoking, body defences provide a combative immune/oxidative response and DNA repair mechanisms are likely to subdue these changes to a certain extent; however, in patients with COPD with lung cancer the consequences could be devastating, potentially contributing to slower postoperative recovery after lung resection and increased resistance to radiotherapy and chemotherapy. Vital to the development of new-targeted therapies is an in-depth understanding of various molecular mechanisms that are associated with both pathologies. In this comprehensive review, we provide a detailed overview of possible underlying factors that link COPD and lung cancer, and current therapeutic advances from both human and preclinical animal models that can effectively mitigate this unholy relationship.

**Fruquintinib: First Global Approval**

Matt Shirley

**ABSTRACT**

Fruquintinib (Elunate®) is an orally available, potent and highly selective small molecule inhibitor of VEGFR-1, -2 and -3 that was discovered and developed by Hutchison MediPharma for the treatment of solid tumours. In September 2018, fruquintinib received its first global approval, in China, for use in the treatment of metastatic colorectal cancer (CRC) in patients who have failed at least two prior systemic anti-neoplastic therapies. Fruquintinib is in ongoing phase III clinical development for use in the treatment of advanced NSCLC and advanced gastric cancer. This article summarizes the milestones in the development of fruquintinib leading to this first approval for the treatment of metastatic CRC.
Moxetumomab Pasudotox: First Global Approval

Sohita Dhillon

ABSTRACT

Moxetumomab pasudotox-tdfk (LUMOXITI™), an anti CD22 recombinant immunotoxin, has been developed by MedImmune and its parent company AstraZeneca for the treatment of hairy cell leukaemia. The product, discovered at the National Cancer Institute, is an optimised version of immunotoxin CAT-3888. Moxetumomab pasudotox is composed of the Fv fragment of an anti-CD22 monoclonal antibody fused to a 38 kDa fragment of Pseudomonas exotoxin A, PE38. The Fv portion of moxetumomab pasudotox binds to CD22, a cell surface receptor expressed on a variety of malignant B-cells, thereby delivering the toxin moiety PE38 directly to tumour cells. Once internalised, PE38 catalyses the ADP ribosylation of the diphthamide residue in elongation factor-2 (EF-2), resulting in the rapid fall in levels of the anti-apoptotic protein myeloid cell leukaemia 1 (Mcl-1), leading to apoptotic cell death. This article summarizes the milestones in the development of moxetumomab pasudotox leading to this first approval for the treatment of adults with relapsed or refractory hairy cell leukaemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analogue. Development of moxetumomab pasudotox for non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia and precursor cell lymphoblastic leukaemia/lymphoma was discontinued.

Galcanezumab: First Global Approval

Yvette N. Lamb

ABSTRACT

Galcanezumab-gnIm (Emgality™; Eli Lilly and Company), hereafter galcanezumab, is a humanized monoclonal antibody against the calcitonin gene-related peptide (CGRP) ligand. A potent vasodilator, CGRP is implicated in nociceptive transmission and migraine pathogenesis. In September 2018, the US FDA approved galcanezumab as a once-monthly subcutaneous injection for the preventive treatment of migraine in adults. In the same month, the EMA issued a positive opinion for galcanezumab for the prophylaxis of migraine in adults who have at least 4 migraine days per month. Galcanezumab is also undergoing phase III evaluation for the preventive treatment of cluster headache in North America and Europe. This article summarizes the milestones in the development of galcanezumab leading to its first approval for the preventive treatment of migraine in adults.
Why Biologics and Biosimilars Remain So Expensive: Despite Two Wins for Biosimilars, the Supreme Court’s Recent Rulings do not Solve Fundamental Barriers to Competition

Brian K. Chen, Y. Tony Yang Charles L. Bennett

ABSTRACT

Biologics and biosimilars are medicines made from living cells that treat common and serious diseases such as cancer, diabetes, rheumatoid arthritis, and other inflammatory diseases. They are highly targeted, efficacious, and represent an increasingly important part of physicians’ armamentaria in the combat against these medical conditions. Yet they are extremely expensive, costing on average $10,000–$30,000 per year and exceed $500,000 for the most expensive biologics. The advent of biosimilar drugs, or high similar copies of biologics, was supposed to help reduce costs, but thus far the cost of treatment with biologics or biosimilars has not fallen sharply in the USA. We argue that a primary hurdle is the extent of patent protection for the reference biologics that impedes greater numbers of biosimilars entering into the market. To date, of the 12 biosimilars approved for marketing by the US Food and Drug Administration (FDA), only five are commercially available. All but one of the remaining biosimilars are withheld from commercialization due to patent disputes. We argue that the market for biologics and biosimilars will become price competitive only if more biosimilars are available to patients. To this end, the process to eliminate marginally inventive patents held by the reference drug makers must be streamlined and improved. In this perspective article, we suggest actions to improve the pre-FDA approval patent resolution process known as the patent dance, the streamlined patent invalidation process known as Inter Partes Reviews, and the process of granting patents.

A Critical Review of Nebivolol and its Fixed-Dose Combinations in the Treatment of Hypertension

Arrigo F. G. Cicero Masanari Kuwabara Claudio Borghi

ABSTRACT

β-Adrenergic receptor blockers (β-blockers) are well-known useful and cost-effective drugs for managing hypertensive patients with coronary heart disease, stroke, and heart failure. However, it is often difficult to use β-blockers for patients with asthma or chronic obstructive pulmonary disease (COPD). Moreover, most β-blockers negatively influence glucose or lipid metabolism. Nebivolol is a third-generation lipophilic β-1 receptor-selective blocker with nitric oxide-mediated vasodilatory effects, metabolically neutral and usually well tolerated by patients with asthma or COPD. Nebivolol has significant effects of reduction in central blood pressure and improvements in endothelial dysfunction and arterial stiffness. To summarize the merits and demerits of nebivolol in different clinical situations, we conducted a review using the word ‘nebivolol’ on Pubmed and Embase, limiting the search to hypertension, clinical trials, and meta-analyses. This review summarizes the clinical studies on nebivolol itself and on the combination of nebivolol with other antihypertensive drugs, such as hydrochlorothiazide, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and amlodipine. Most studies showed the safety and well-tolerated profile of nebivolol and the combination of nebivolol with other antihypertensive drugs, which suggests that new fixed combinations of nebivolol with other antihypertensive drugs would be useful for patients who are unable to tolerate traditional β-blockers.
Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis

Simona Lattanzi, Francesco BrigoEugen TrinkaGaetano ZaccaraClaudia CagnettiCinzia Del GiovaneMauro Silvestrini

ABSTRACT

Background: Approximately one-third of patients with epilepsy presents seizures despite adequate treatment. Hence, there is the need to search for new therapeutic options. Cannabidiol (CBD) is a major chemical component of the resin of Cannabis sativa plant, most commonly known as marijuana. The anti-seizure properties of CBD do not relate to the direct action on cannabinoid receptors, but are mediated by a multitude of mechanisms that include the agonist and antagonist effects on ionic channels, neurotransmitter transporters, and multiple 7-transmembrane receptors. In contrast to tetrahydrocannabinol, CBD lacks psychoactive properties, does not produce euphoric or intrusive side effects, and is largely devoid of abuse liability.

Objective: The aim of the study was to estimate the efficacy and safety of CBD as adjunctive treatment in patients with epilepsy using meta-analytical techniques.

Methods: Randomized, placebo-controlled, single- or double-blinded add-on trials of oral CBD in patients with uncontrolled epilepsy were identified. Main outcomes included the percentage change and the proportion of patients with ≥ 50% reduction in monthly seizure frequency during the treatment period and the incidence of treatment withdrawal and adverse events (AEs).

Results: Four trials involving 550 patients with Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS) were included. The pooled average difference in change in seizure frequency during the treatment period resulted 19.5 [95% confidence interval (CI) 8.1–31.0; p = 0.001] percentage points between the CBD 10 mg and placebo groups and 19.9 (95% CI 11.8–28.1; p < 0.001) percentage points between the CBD 20 mg and placebo arms, in favor of CBD. The reduction in all-types seizure frequency by at least 50% occurred in 37.2% of the patients in the CBD 20 mg group and 21.2% of the placebo-treated participants [risk ratio (RR) 1.76, 95% CI 1.07–2.88; p = 0.025]. Across the trials, drug withdrawal for any reason occurred in 11.1% and 2.6% of participants receiving CBD and placebo, respectively (RR 3.54, 95% CI 1.55–8.12; p = 0.003) [Chi squared = 2.53, degrees of freedom (df) = 3, p = 0.506; I² = 0.0%]. The RRs to discontinue treatment were 1.45 (95% CI 0.28–7.41; p = 0.657) and 4.20 (95% CI 1.82–9.68; p = 0.001) for CBD at the doses of 10 and 20 mg/kg/day, respectively, in comparison to placebo. Treatment was discontinued due to AEs in 8.9% and 1.8% of patients in the active and control arms, respectively (RR 5.59, 95% CI 1.87–16.73; p = 0.002). The corresponding RRs for CBD at the doses of 10 and 20 mg/kg/day were 1.66 (95% CI 0.22–12.86; p = 0.626) and 6.89 (95% CI 2.28–20.80; p = 0.001). AEs occurred in 87.9% and 72.2% of patients treated with CBD and placebo (RR 1.22, 95% CI 1.11–1.33; p < 0.001). AEs significantly associated with CBD were somnolence, decreased appetite, diarrhea, and increased serum aminotransferases.

Conclusions: Adjunctive CBD in patients with LGS or DS experiencing seizures uncontrolled by concomitant anti-epileptic treatment regimens is associated with a greater reduction in seizure frequency and a higher rate of AEs than placebo.
Tapentadol Prolonged Release: A Review in Pain Management
Emma D. Deeks

ABSTRACT
Tapentadol prolonged release (tapentadol PR) [Palexia® SR in EU] is a long-acting tablet formulation of the strong central analgesic tapentadol, which acts as both a μ-opioid receptor (MOR) agonist and a noradrenaline reuptake inhibitor. Tapentadol PR is approved for chronic pain in various countries, with its EU indication (severe chronic pain manageable only with opioid analgesics) being the focus here. Well-designed trials and clinical practice data support tapentadol PR use in this setting. Short term, tapentadol PR was an effective and generally well tolerated analgesic for moderate to severe pain of varying aetiologies, including neuropathic pain. It provided analgesia at least as good as that of conventional strong opioids and appeared more favourable in terms of gastrointestinal tolerability, likely due to less potent MOR binding. Severe back pain with a neuropathic component responded well to moderate-dose tapentadol PR in some patients, while for others, an increase to the maximum recommended tapentadol PR dosage provided analgesia at least as good as that of moderate-dose tapentadol PR plus pregabalin and appeared to have some CNS tolerability benefits. Data also support the use of tapentadol PR in opioid rotation, including when conventional opioids are intolerable. Longer-term data in musculoskeletal pain conditions indicate continued benefit over up to 2 years’ treatment with tapentadol PR with no evidence of tolerance. Thus, tapentadol PR is a useful option for the management of severe chronic pain.

Bictegravir/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection
Emma D. Deeks

ABSTRACT
Bictegravir is a new integrase strand transfer inhibitor (INSTI) with a high genetic barrier to the development of HIV-1 resistance. The drug is co-formulated with the nucleos (t) ide reverse transcriptase inhibitors emtricitabine and tenofovir alafenamide (AF) in a single-tablet regimen (STR) for the once-daily treatment of HIV-1 infection in adults (bictegravir/emtricitabine/tenofovir AF; Biktarvy®). In phase 3 trials, bictegravir/emtricitabine/tenofovir AF was noninferior to dolutegravir-based therapy (dolutegravir/abacavir/lamivudine or dolutegravir plus emtricitabine/tenofovir AF) in establishing virological suppression in treatment-naïve adults through 96 weeks’ treatment and, similarly, was noninferior to ongoing dolutegravir/abacavir/lamivudine or boosted elvitegravir- or protease inhibitor (PI)-based therapy in preventing virological rebound over 48 weeks in treatment-experienced patients. No resistance emerged to any of the antiretrovirals in the STR. Bictegravir/emtricitabine/tenofovir AF is generally well tolerated, requires no prior HLA-B*5701 testing (making it more suitable for ‘rapid start’ treatment), fulfils the antiretroviral regimen requirement for patients with hepatitis B virus (HBV) co-infection (i.e. contains tenofovir AF and emtricitabine, both of which are active against HBV) and can be used in renally impaired patients with creatinine clearance (CRCL) ≥ 30 mL/min. Thus, although cost-effectiveness analyses would be beneficial, current data indicate that bictegravir/emtricitabine/tenofovir AF is a convenient initial and subsequent treatment option for adults with HIV-1 infection, including those co-infected with HBV, and provides the first non-pharmacologically boosted, INSTI-based, triple-combination STR suitable for patients with CRCL 30–50 mL/min.
Fremanezumab: First Global Approval
Sheridan M. Hoy

ABSTRACT
Fremanezumab-vfrm (hereafter referred to as fremanezumab) [AJOVY™] is a fully humanized monoclonal antibody (IgG2Δa) developed by Teva Pharmaceuticals to selectively target calcitonin gene-related peptide (a vasodilatory neuropeptide involved in the pathophysiology of migraine). Its use has been associated with significant reductions in migraine frequency, the requirement for acute headache medication use and headache-related disability compared with placebo in multinational, phase III studies, and in September 2018 fremanezumab was approved by the US FDA for the preventive treatment of migraine in adults. A regulatory assessment for fremanezumab as a preventive treatment of migraine in adults is underway in the EU. Fremanezumab is also undergoing phase III development for the preventive treatment of cluster headache (although a phase III chronic cluster headache study has been suspended due to the results of a prespecified futility analysis) and phase II development for the preventive treatment of post-traumatic headache disorder. This article summarizes the milestones in the development of fremanezumab leading to this first approval in the USA for the preventive treatment of migraine in adults.

Vibegron: First Global Approval
Susan J. Keam

ABSTRACT
Vibegron is a selective beta 3 adrenergic receptor (β3AR) agonist that is being developed in Japan jointly by Kyorin Pharmaceutical Co., Ltd and Kissei Pharmaceutical Co., Ltd and in other regions worldwide (except in several other Asian countries) by Urovant Sciences for the treatment of overactive bladder (OAB). Based on results from Japanese phase III trials, vibegron received approval in Japan in September 2018 for this indication. This article summarizes the milestones in the development of vibegron leading to this first global approval for the treatment of OAB.

Cemiplimab: First Global Approval
Anthony Markham, Sean Duggan

ABSTRACT
Cemiplimab (LIBTAYO®; cemiplimab-rwlc), a human programmed death receptor-1 (PD-1) monoclonal antibody that binds to PD-1 and blocks its interaction with programmed death ligands 1 (PD-L1) and 2 (PD-L2), is being developed by Regeneron Pharmaceuticals and Sanofi Genzyme. The drug is being investigated as a treatment for various cancers and in September 2018 received approval in the USA for the treatment of patients with metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. This article summarizes the milestones in the development of cemiplimab leading to this first global approval for the treatment of advanced cutaneous squamous cell carcinoma.
Duvelisib: First Global Approval
Hannah A. Blair

ABSTRACT
Duvelisib (Copiktra™) is a small-molecule inhibitor of phosphatidylinositol-3 kinase that has been developed as an oral treatment for various cancer indications. In September 2018, duvelisib received its first global approval in the USA for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) after at least two prior therapies. Duvelisib was also granted accelerated approval in the USA for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. Clinical development for various haematological malignancies is ongoing worldwide, as well as preclinical development for solid tumours in the USA. This article summarizes the milestones in the development of duvelisib leading to these first approvals for CLL/SLL and FL.

Prevention and Management of Bleeding Episodes in Patients with Acquired Hemophilia A
Paul Knöbl

ABSTRACT
Acquired hemophilia A (AHA) is a rare autoimmune disease caused by autoantibodies inhibiting the function of coagulation factor VIII. It is characterized by spontaneous bleeding in patients with no previous family or personal history of bleeding. Although several large registries have collected clinical data on AHA, limited information is available on the optimal management of AHA because controlled clinical trials are lacking. AHA can easily be diagnosed if the problem (prolonged activated partial thromboplastin time in a bleeding patient) is recognized. After the effects of anticoagulants are excluded, low factor VIII activity and the detection of circulating inhibitors confirms the diagnosis. However, lack of familiarity with this rare condition may delay diagnosis and adequate therapy. Treatment of AHA is based on measures for prompt hemostatic control to stop (and prevent) bleeding, immunosuppression to eradicate the autoantibodies, and supportive care for the adverse effects of that treatment and patients’ often complex comorbidities. This article gives a comprehensive overview of the current knowledge about the pathophysiology, diagnosis, and treatment of AHA.
Current and Future Treatment Options for Myelodysplastic Syndromes: More than Hypomethylating Agents and Lenalidomide?
Katja Sockel Uwe Platzbecker

ABSTRACT
Myelodysplastic syndromes are a heterogeneous group of bone marrow disorders that result in cytopenias and a propensity to develop secondary leukemia. While allogeneic transplantation still remains the only potential curative treatment option, it can only be offered to a limited number of patients. For the majority, who are not transplant candidates, treatment strategies cover iron chelation, growth factors, lenalidomide, and hypomethylating agents to improve cytopenia and potentially delay disease progression. These limited options underpin the urgent need for more translational research-based clinical trials in well-defined subgroups of patients with myelodysplastic syndromes. Indeed, myelodysplastic syndromes are a moving target with maximum innovation in the understanding of the complex molecular pathways during the last decade. Compared with other hematological diseases such as myeloma, this has unfortunately not yet translated into approval of novel treatment options. Given the current developments in the field, we are optimistic that recent frustrations will be overcome shortly and this will pave the way for exciting opportunities, especially for patients not responding to first-line therapeutic options.

Daunorubicin/Cytarabine Liposome: A Review in Acute Myeloid Leukaemia
Hannah A. Blair

ABSTRACT
VYXEOS™ is a liposomal-encapsulated formulation of daunorubicin and cytarabine delivering a fixed, synergistic 1:5 molar ratio (hereafter referred to as daunorubicin/cytarabine liposome). Daunorubicin/cytarabine liposome is approved in several countries worldwide for the treatment of adults with therapy-related acute myeloid leukaemia (tAML) and AML with myelodysplasia-related changes (MRC). Approval was based on its clinical benefit in older patients with newly diagnosed high-risk/secondary AML in a pivotal phase III trial. In this study, daunorubicin/cytarabine liposome significantly prolonged overall survival (OS) and event-free survival (EFS) relative to conventional chemotherapy with cytarabine plus daunorubicin (hereafter referred to as 7+3). Daunorubicin/cytarabine liposome was also associated with significantly higher rates of complete remission (CR) and CR with incomplete haematological recovery (CRi) compared with 7+3. Daunorubicin/cytarabine liposome had an acceptable tolerability profile in older patients with newly diagnosed high-risk/secondary AML. The safety profile of daunorubicin/cytarabine liposome, including types and severities of adverse events, was generally similar to that of 7+3. Therefore, daunorubicin/cytarabine liposome is an important treatment option for adults with newly diagnosed tAML or AML-MRC.
Efficacy of Metformin Treatment with Respect to Weight Reduction in Children and Adults with Obesity: A Systematic Review

Y. E. LentferinkC. A. J. KnibbeM. J. van der Vorst

ABSTRACT

Background: Obesity and its related complications are increasing health issues. Since generally only minor weight loss is obtained with lifestyle intervention, additional pharmacological therapies such as metformin are often used.

Objective: We conducted a systematic review to provide an overview of the efficacy of ≥6 months of metformin treatment in children and adults with respect to weight, insulin resistance, and progression toward type 2 diabetes mellitus (T2DM).

Methods: In September 2018, we searched PubMed, Embase, and the Cochrane Library for studies published in English using the keywords metformin, obesity/overweight, and weight loss. Prospective studies reporting weight/body mass index (BMI) as a primary or secondary outcome in patients with overweight/obesity with ≥6 months’ metformin treatment were included. Included subjects were children and adults with overweight/obesity who received ≥6 months of metformin and/or lifestyle intervention, and/or placebo and/or lifestyle intervention, and/or standard care. Studies were independently screened by two reviewers. Data were extracted by one and verified by the other reviewer, and both reviewers assessed the risk of bias using the Cochrane risk-of-bias tool.

Results: Our review includes 15 pediatric and 14 adult studies. In children, after 6 months, more than half the studies reported a greater reduction in BMI with metformin versus controls. Only six studies had an intervention of >6 months, and these studies found no further improvement in BMI in the metformin users, though their BMI was lower than that of controls. Three studies showed a significant improvement in insulin sensitivity in the metformin versus the control group. Adults using metformin experienced and maintained small decreases in weight irrespective of duration of intervention. In 11 of 14 studies, a greater reduction in weight/BMI was observed with metformin than with placebo. Progression toward T2DM was significantly reduced in adults using metformin, ranging from 7 to 31%. The safety and tolerability of metformin, withdrawal of participants, and comparison with other drugs were not taken into account.

Conclusions: The effects of metformin on weight/BMI vary, with smaller reductions in children than in adults. This could be because of differences in adherence, daily dosage, and insulin status. Metformin significantly reduced the progression toward T2DM in adults. Therefore, metformin should be considered as a treatment for obesity and its related complications.
Enzalutamide: A Review in Castration-Resistant Prostate Cancer

Lesley J. Scott

ABSTRACT

Oral enzalutamide (Xtandi®), a second generation androgen receptor inhibitor, is indicated for the treatment of castration-resistant prostate cancer (CRPC) in numerous countries worldwide, with specific indications in this patient population varying between individual countries. Based on extensive experience in the clinical trial and/or real-world settings, oral enzalutamide 160 mg once daily is an effective and generally well tolerated treatment in a broad spectrum of patients with CRPC, including in nonmetastatic and metastatic disease and in chemotherapy-naive and -experienced metastatic CRPC. Enzalutamide is an emerging option for the treatment of men with nonmetastatic CRPC who are at high-risk for developing metastatic disease, and remains an important first-line option in chemotherapy-naive or -experienced patients with metastatic CRPC.

Omideneag Isopropyl Ophthalmic Solution 0.002%: First Global Approval

Sean Duggan

ABSTRACT

Omideneag isopropyl ophthalmic solution 0.002% (EYBELIS®) is a selective prostaglandin E2 receptor 2 agonist with a non-prostaglandin structure that is being developed by Ube Industries and Santen Pharmaceutical in Japan, Singapore and the USA for the treatment of glaucoma and ocular hypertension. Based on results from phase III trials, omidenepag isopropyl ophthalmic solution 0.002% received approval in Japan in September 2018 for this indication. This article summarizes the milestones in the development of omidenepag isopropyl ophthalmic solution 0.002% leading to this first global approval for the treatment of glaucoma and ocular hypertension.

Omadacycline: First Global Approval

Anthony Markham, Susan J. Keam

ABSTRACT

Paratek Pharmaceuticals are developing omadacycline (NUZYRA™), a first-in-class orally active aminomethyleneclcline antibacterial, as a treatment for various bacterial infections. The drug, which is available in intravenous and oral formulations, has a broad spectrum of antibacterial activity and was recently approved in the USA as a treatment for the treatment of community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults. This article summarizes the milestones in the development of omadacycline leading to this first global approval for the treatment of CABP and ABSSSI.
**Talazoparib: First Global Approval**

Sheridan M. Hoy

**ABSTRACT**

Talazoparib (TALZENNA™) is an oral inhibitor of the polyadenosine 5′-diphosphoribose polymerase (PARP) enzymes, which play a critical role in repairing DNA single-strand breaks. It has been developed by Pfizer and was recently approved in the USA for the treatment of adults with deleterious or suspected deleterious germline BRCA-mutated, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer (as detected by a US FDA-approved assay). A regulatory assessment for talazoparib in this patient population is underway in the EU, with talazoparib also undergoing development for use in metastatic castration-resistant prostate cancer and various solid tumours, and as neoadjuvant therapy in early triple negative breast cancer. This article summarizes the milestones in the development of talazoparib leading to its first approval for the treatment of adults with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative, locally advanced or metastatic breast cancer.

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**Dacomitinib: First Global Approval**

Matt Shirley

**ABSTRACT**

Dacomitinib (Vizimpro®) is an orally administered, small-molecule irreversible inhibitor of HER1 (EGFR), HER2 and HER4 that was developed by Pfizer Inc. for the treatment of solid tumours. In September 2018, dacomitinib received its first global approval, in the USA, for use in the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test. Registration applications for the use of dacomitinib as first-line treatment for patients with EGFR-mutation-positive metastatic NSCLC have also been submitted in the EU and Japan. This article summarizes the milestones in the development of dacomitinib leading to this first approval for the first-line treatment of patients with EGFR-mutated metastatic NSCLC.

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End

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