What's new in drug therapy

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GENERAL DRUG THERAPY

Impact of the PREVENT calculator on cardiovascular risk reclassification and eligibility for antihypertensive drug therapy (November 2024)

- In patients with hypertension, decisions about initiating antihypertensive drug therapy depend upon the level of blood pressure elevation and the patient's atherosclerotic cardiovascular disease (ASCVD) risk; among those with stage 1 hypertension, one criterion to initiate drug therapy is a calculated 10-year ASCVD risk ≥10 percent. The American Heart Association (AHA) now recommends using the new Predicting Risk of Cardiovascular Disease Events (PREVENT) calculator, which systematically produces a lower calculated risk than the previously used 2013 combined cohorts equation. In a large United States cohort, more than half of participants were reclassified to a lower risk category using the PREVENT calculator [1]. If applied broadly across the US, an estimated 2.6 million people with hypertension would initially be managed with lifestyle changes alone.

ADVERSE REACTIONS AND WARNINGS

First-generation antihistamines and seizure risk (November 2024)

- Compared with newer, nonsedating antihistamines, older, first-generation antihistamines (eg, chlorpheniramine or hydroxyzine) have similar efficacy for treatment of allergic rhinitis, pruritus, or urticaria, but known central nervous effects in children include sedation, paradoxical agitation, and cognitive impairment (table 1). Despite these risks, they are widely available and used. In a new crossover study of nearly 3200 children presenting to the emergency department for seizure events, recent prescriptions of a first-generation antihistamine prior to the ED visit were associated with an increased risk of seizures compared with no prescription, especially in children ages 6 to 24 months [9]. These findings suggest seizures as another adverse effect of first-generation antihistamines in predisposed children and support existing recommendations to avoid them in the pediatric population.

RECENT APPROVALS - ONCOLOGIC

Inavolisib in hormone receptor-positive, HER2-negative breast cancer (November 2024)

- Trials are evaluating novel treatment strategies in those with advanced hormone receptor (HR)-positive/HER2-negative breast cancer with endocrine therapy-resistant disease, with promising results among those with *PIK3CA*-mutated cancers. In a randomized trial in 325 such patients who experienced recurrence on or within 12 months of adjuvant endocrine therapy, the addition of the alpha isoform-specific PI3K inhibitor and degrader inavolisib to fulvestrant and palbociclib improved progression-free survival (15 versus 7.3 months) [34]. There was a trend favoring overall survival that did not reach statistical significance, although survival data are immature (hazard ratio 0.64). Grade ≥3 adverse events occurred in 88 versus 82 percent. For patients with locally advanced or metastatic, endocrine therapy-resistant *PIK3CA*-mutated, HR-positive, HER2-negative breast cancer, we consider the combination of inavolisib with palbociclib and fulvestrant to be appropriate option, which now has regulatory approval in the United States [35].

VACCINES

Lower age cutoff for pneumococcal vaccine indications (November 2024)

- In October 2024, the United States Advisory Committee (ACIP) extended pneumococcal vaccination recommendations to include all adults ≥50 years of age, regardless of risk factors (table 2) [59]. Previously, the age threshold was ≥65 years for healthy adults and ≥19 years for those at risk for pneumococcal infection or severe complications from pneumococcal infection. This decision is based on knowledge that the incidence of pneumococcal disease starts to increase at age 50 (table 3) and the predicted reduction in invasive pneumococcal disease cases in certain underrepresented ethnic/racial groups within the United States. We agree with the new guidelines from the ACIP and now suggest pneumococcal vaccination beginning at age 50 for all adults.

DRUG OR INDICATION WITHDRAWALS

Voxelotor withdrawn from the market (October 2024)

- The sickle cell disease medication voxelotor, which was approved by the US Food and Drug Administration in 2019, has been voluntarily withdrawn from the market in the United States and Europe [8]. Information from the company states an unfavorable risk-benefit ratio. The drug's mechanism of action involved reducing sickle hemoglobin polymerization and increasing total hemoglobin. Additional drugs with this and other mechanisms of action are under investigation.

RECENT APPROVALS - HEMATOLOGIC AND ANTICOAGULANT

Asciminib for high-risk chronic-phase chronic myeloid leukemia (October 2024)

- Asciminib, the first tyrosine kinase inhibitor (TKI) that binds the myristoyl pocket of BCR::ABL1 rather than the ATP binding site (which is bound by all other TKIs), is efficacious and well tolerated in patients with chronic myeloid leukemia (CML) who develop mutations in the ATP binding site. In a trial of front-line therapy in 201 patients with chronic-phase (CP) CML, molecular responses and survival after 16 months were comparable with asciminib versus the investigator's choice of a second-generation (2G) TKI, but fewer patients taking asciminib required treatment discontinuation [21]. The US Food and Drug Administration recently approved asciminib for front-line therapy of CP CML. Although we consider asciminib an acceptable option for selected patients with CP CML, we favor a 2G-TKI for high-risk CML if treatment-free remission (TFR) is the goal, given no reports of TFR using asciminib as initial therapy.

RECENT APPROVALS - HEMATOLOGIC AND ANTICOAGULANT

New gene therapy for hemophilia B (October 2024)

- Fidanacogene elaparvovec is an adeno-associated virus (AAV) vector containing the *F9* Padua variant, a naturally occurring mutation in the *F9* gene that increases factor IX activity. In a new study involving 45 patients with hemophilia B and factor IX activity <2 percent treated with this therapy, the annualized bleeding rate decreased by 71 percent; mean factor IX level was 27 percent [22]. Increases in alanine aminotransferase, decreases in factor IX activity, or both led to the use of glucocorticoids in 62 percent. There were no infusion-related serious adverse events, thromboses, or factor IX inhibitors. This construct was approved by the US Food and Drug Administration in April 2024 for adults with hemophilia B meeting certain criteria; it is the second gene therapy construct approved for hemophilia B.

RECENT APPROVALS - NEUROLOGIC AND PSYCHIATRIC

Xanomeline-trospium for schizophrenia (October 2024)

- Xanomeline-trospium, a new antipsychotic agent that is the first to exclusively target muscarinic receptors, was recently approved by the US Food and Drug Administration for the treatment of schizophrenia in adults [27]. Approval was based on two placebo-controlled trials that demonstrated improvements in schizophrenia symptoms over five weeks with xanomeline-trospium [28,29]. Adverse effects included urinary retention, increased heart rate, decreased gastric motility, nausea, vomiting, constipation, and hypertension. However, it is associated with fewer side effects (eg, extrapyramidal symptoms) than most commonly used dopamine blocking agents and has minimal effect on the QTc interval. Studies of longer duration are needed to inform long term efficacy and tolerability.

RECENT APPROVALS - NEUROLOGIC AND PSYCHIATRIC

Efgartigimod alfa-hyaluronidase in patients with CIDP (July 2024, Modified October 2024)

- Long-term management of chronic inflammatory demyelinating polyneuropathy (CIDP) often requires a non-steroid immunomodulatory agent, and novel therapies are under investigation. Efgartigimod alfa is a biologic agent designed to promote degradation of autoantibodies that was first approved for myasthenia gravis. In a placebo-controlled trial of 322 patients with CIDP, weekly subcutaneous infusion of efgartigimod alfa-hyaluronidase improved symptoms in 66 percent by 12 weeks and lowered the rate of clinical deterioration at 48 weeks compared with placebo (28 versus 54 percent) [30]. These results led to approval by the US Food and Drug Administration [31]and support efgartigimod alfa-hyaluronidase as an additional treatment option for CIDP.

VACCINES

RSV vaccine effective in mild to moderately immunocompromised individuals (October 2024)

- The respiratory syncytial virus (RSV) vaccine is recommended for immunocompromised individuals aged 60 and above, although the data on the efficacy of the RSV vaccine in this population is limited. In an electronic health records-based observational study that included over 10,000 predominantly mild to moderately immunocompromised individuals ≥60 years old (46 percent of whom had a malignancy), the adjusted RSV vaccine effectiveness against respiratory virus-associated hospitalizations in the first year of follow-up was 73 percent [60]. This study provides preliminary evidence of vaccine efficacy in this patient population and supports vaccination against RSV in immunocompromised individuals aged 60 and above.