October 2020

Inside this issue:

Thank you to Conner McClain, Lauren Ratliff, & Ben Scalise for their contributions to this newsletter

Pharmacy in the News:

CROWN CORONATION: COVID-19 Research Outcomes Worldwide Network for CORONAavirus PrevenTION (CROWN CORONA)

- CROWN CORONATION is an international, Bayesian platform, adaptive, randomized, placebo-controlled trial assessing the effectiveness of the MR or MMR vaccine in preventing COVID-19 disease in healthcare workers.
- The study plans to enroll 30,000 healthcare workers at risk of contracting SARS-CoV-2. Participants will be randomized into one of two arms:
  - Education and surveillance plus MR or MMR vaccine
  - Education and surveillance plus placebo
- The study will evaluate the incidence of laboratory confirmed, symptomatic COVID-19 over 60 days, severity of COVID-19 over 60 days, and effectiveness of preventing/reducing SARS-CoV-2 infection over 5 months.

Reference

A Framework for Equitable Allocation of Vaccine for the Novel Coronavirus

- The National Academies of Sciences, Engineering and Medicine released a statement on the plan to initiate a COVID-19 vaccine once made available.
- The plan is to vaccinate front-line health care workers and first responders initially, followed by people with underlying conditions that elevate their risk of severe COVID-19 disease, then teachers, childcare providers, and transit workers, and lastly the remaining US population.

Reference

Dapagliflozin in Patients with Chronic Kidney Disease

- An international, multicenter, event-driven, randomized, double-blind, parallel group, placebo-controlled study, evaluated the effect of dapagliflozin versus placebo, both given once daily in addition to standard of care, to prevent the progression of chronic kidney disease (CKD) or cardiovascular/renal death.
- The study was composed of 4304 participants with or without type II diabetes mellitus, with an estimated glomerular filtration rate (eGFR) of 25 to 75 ml/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of 200 to 5000.
- The study evaluated time to a composite endpoint of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes, time to occurrence of any of the components of the composite, and time to death from any cause for up to 4 years.
- Due to efficacy, the independent data monitoring committee recommended to end the trial early. The primary outcome occurred in 197/2152 (9.2%) of the treatment arm versus 312/2152 (14.5%) of the placebo arm (HR 0.61; 95% CI 0.51 to 0.72; p<0.001).

Reference

Newly Approved Drugs

Gavreto (pralsetinib), Blueprint Medicines Corporation; 9/4/2020
Indication: To treat metastatic non-small cell lung cancer

MOA: Kinase inhibitor of wild-type RET (rearranged during transfection) and oncogenic RET fusions and mutations

Dosing: 400 mg by mouth daily until disease progression or unacceptable toxicity

Olinvyk (oliceridine), Trevena, Inc.; 8/7/2020
Indication: To treat acute pain in adults when the pain is severe enough to require an intravenous opioid

MOA: Full opioid receptor agonist, relatively selective for the mu-opioid receptor, with the precise mechanism of analgesia unknown

Dosing: 1.5 mg IV initially, titrate as needed, do not exceed ≥3 mg in a single dose or ≥27 mg per day

Monjuvi (tafasitamab-cxix), MorphoSys US Inc.; 7/31/2020
Indication: To treat relapse or treatment failure diffuse large B-cell lymphoma (DLBCL); for patients who cannot receive a stem cell transplant

MOA: Binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including DLBCL

Dosing: 12 mg/kg IV infusion administered on a cyclic dosing schedule

Winlevi (clascoterone), Cassiopea SpA; 8/26/2020
Indication: To treat acne vulgaris in patients 12 years and older

MOA: Androgen receptor inhibitor; true mechanism of action is unknown

Dosing: Apply a thin, uniform layer of cream to the affected skin area twice a day

Evrysdi (risdiplam), Genentech Inc.; 8/7/2020
Indication: To treat spinal muscular atrophy in patients 2 months or older

MOA: Increases exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein in the brain

Dosing: 0.2 mg/kg from 2 mon to <2 yr, 0.25 mg/kg from ≥2 yr and weighing <20 kg, and 5 mg from ≥2 yr and ≥20 kg taken orally once daily

Xeglyze (abametapir), Dr. Reddy's Laboratories; 7/24/2020
Indication: To treat head lice in patients 6 months and older

MOA: Inhibits critical egg development and survival of lice by metalloproteinase inhibition

Dosing: Apply lotion to dry hair in an amount sufficient to thoroughly coat the hair and scalp; message into scalp and throughout hair; leave on hair and scalp for 10 minutes and rinse off with warm water

Recently Approved Generics:

- Tecfidera (dimethyl fumarate) 120 and 240 mg DR capsules – 8/26/20
- Ciprodex (ciprofloxacin 0.3% /dexamethasone 0.1%) otic suspension – 8/17/20
- Korlym (mifepristone) 300 mg tablets – 8/3/20
- Desmer (metyrosine) 250 mg capsules – 7/24/20
- Jadenu Sprinkle (deferasirox) oral granules 90, 180, and 360 mg – 7/14/20
- Librax (chlordiazepoxide HCl/ Clindinium Br) 5 mg/2.5 mg capsules – 7/7/20

Express Scripts

Drug Information & Wellness Center

Southern Illinois University Edwardsville

Monday – Friday

8 AM – 4:30 PM

druginfo@siue.edu

Apps of the Month

Did you see the last newsletter?

Learn about COVID-19 mental health tips in our July 2020 DIWC Newsletter.

★★★☆☆

SBIRT for Health Professionals

- Utilize interactive training features to learn how to administer the “Screening, Brief Intervention and Referral to Treatment (SBIRT)” validated tool
- Conduct, save, and print SBIRT screenings
- Free to download

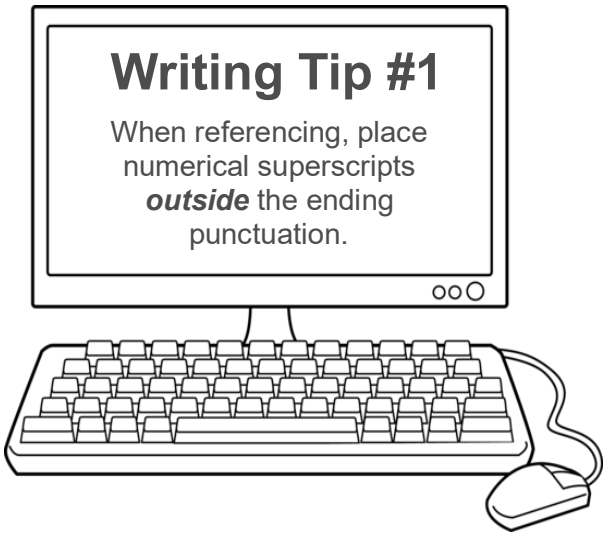
App Store rating: 3.4/5 stars

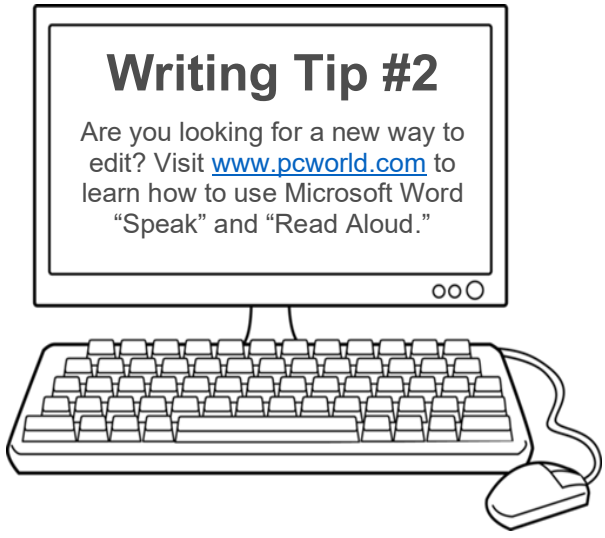
★★★★☆

IDSA Practice Guidelines

- Read all full-text “Infectious Disease Society of America (IDSA)” guidelines, both current and archived
- Create notes and highlight key sections for later viewing
- Search pharmacokinetic, pharmacodynamics, dosing, and monitoring for antibacterial and antiviral medications
- Free to download

App Store rating: 4.6/5 stars





Drug Information Questions of the Month

Question:

"As retail pharmacists, one of the questions we ask patients before giving the Shingrix vaccine is "are you immune compromised, or have you taken steroids in the past 3 months?" My question would be, what are the implications if they answer yes? Should we still vaccinate? For example, would you defer Shingrix for a patient who takes Humira?"

Response:

Per the CDC and Lexicomp, the Advisory Committee on Immunizations (ACIP) does recommend zoster vaccination in patients receiving low-dose immunosuppressants (eg. <20 mg/day of prednisone or equivalent steroid or inhaled or topical corticosteroids), and patients anticipating immunosuppression or who have recovered from an immunocompromising condition.[1] While immunosuppression is not listed as a contraindication in the prescribing information for Shingrix, per Lexicomp, the ACIP has not yet made recommendations for use of Shingrix in other immunocompromised populations.[2] According to Lexicomp, all age-appropriate vaccinations should be completed at least two weeks before initiation of an immunosuppressant. If a patient is vaccinated during or less than two weeks before starting immunosuppressive therapy, the patient may need revaccinated at least three months after the immunotherapy is discontinued if immune competence has restored.

In terms of post-marketing, the prescribing information for Shingrix does state that immunosuppressive therapies may reduce the effectiveness of Shingrix. In Reactions Weekly, a case series was identified that evaluated reports on Shingrinx within the Vaccine Adverse Event Reporting System (VAERS) between October 20, 2017 and June 30, 2018. Within the report, it was noted that two immunosuppressed patients died of septic shock after administration of Shingrix, but no comment was made on the relationship or likelihood of this event.[3]

Pertaining to patients on Humira, the prescribing information for Humira states that patients may receive concurrent vaccinations that are not live vaccines.[4] Furthermore, Lexicomp denotes that patients on Humira should be brought up to date with all immunizations before initiating therapy and that no data is available concerning the effects of therapy on vaccinations, such as Shingrix, or secondary transmission of live vaccines in patients currently receiving Humira therapy.

Based on the evaluated literature, select immunocompromised patients, as listed above, may receive Shingrix, but caution and monitoring should be performed before and after administration. At this time, the ACIP has not released information definitively stating whether Shingrix can be used in other immunocompromised patients. ACIP does state that they will be reviewing evidence for Shingrix in immunocompromised patients as soon as it becomes available and will modify the vaccine policy as necessary.[1] In reference to patients on Humira, there is also insufficient evidence on whether Shingrix should be administered or not. In conclusion, extreme caution and clinical judgment should be used before administration of Shingrix in the immunocompromised population.

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3. Hesse EM, et al. Postlicensure Safety Surveillance of Recombinant Zoster Vaccine (Shingrix) - United States, October 2017-June 2018. Morbidity and Mortality Weekly Report 68: 91-94, No. 4, Feb 2019. Available from: http://doi.org/10.15585/mmwr.mm6804a4
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Drug Information Questions of the Month

Question:

"Is it appropriate to initiate a known QTc prolonging medication in a patient with a pacemaker?"

Response:

Cardiovascular implantable electronic devices (CIED) include permanent pacemakers (PPM), implantable cardioverter defibrillators (ICD), and cardiac resynchronization therapy devices (CRT). Over 200,000 CIED insertions are performed each year in America. Specifically, PPMs prevent or treat symptomatic bradyarrhythmias (sick sinus syndrome, AV block etc.) using atrial and/or ventricular pacing to maintain adequate heart rate, stimulate contractility as needed, and improve hemodynamic stability.[1,2] Other indications for a PPM include cardiac transplantation or prevention/termination ventricular tachycardias.[2] Observational studies support the use of cardiac pacing for patients with symptomatic congenital long QT syndrome, but long-term survival benefits are not yet proven.[3]

Though the incidence of acquired long QT syndrome is challenging to assess, a 2004 review article states that marked QT-prolongation is reported in 1 – 10% of patients taking QT-prolonging antiarrhythmic medications, but occurs in less than 1% of patients taking other medications with QT-prolonging potential. A prolonged heart rate-corrected QT interval, or QTc, is defined as > 450 msec for men and > 460 - 470 msec for females.[4] QTc prolongation is an indicator of prolonged ventricular repolarization, which is associated with increased risk for fatal cardiac arrhythmias.[5] Torsades de Pointes (TdP) is a dangerous form of ventricular tachycardia with long QTc associated with syncope and sudden cardiac death. On an EKG, TdP present as a characteristic twisting of QRS complex peaks around the isoelectric line. Again, the incidence is difficult to estimate, though approximately 12,000 TdP cases are presumed to occur each year in the US with an estimated mortality and morbidity of up to 31 percent. As QTc increasingly prolongs, the risk of TdP also increases. A clinical review of published case reports found that about 90% of TdP cases occurred when QTc > 500 msec.[1]

Most patients have at least one identifiable risk factor for prolonged QTc, many of which are medication-associated (high concentration or rapid infusion rate of causative agent, use of $\geq$ 2 QT-prolonging agents, concomitant therapy with potassium-wasting diuretics or P450 inhibitors that block the metabolism of the causative agent). Cardiovascular conditions such as ventricular arrhythmia, bradycardia, recent conversion from atrial fibrillation, left ventricular hypertrophy, myocardial ischemia, hypertension, and heart failure with reduced ejection fraction increase risk of QTc prolongation. Electrolyte abnormalities (low serum potassium, magnesium, and/or calcium), female sex (2 – 3 times greater risk), elevated BMI, elevated serum cholesterol, hyper- and hypothyroidism, hypothermia, diabetes, and renal/hepatic failure are also risk factors for acquired long QT syndrome. Additionally, older age, reduced left ventricular ejection fraction, and bradyarrhythmias place patients at greater risk of TdP.[4] Notably, some of the cardiac comorbidities listed as risk factors are also potential indications for CIED placement.

A 2016 retrospective cohort study aimed to determine whether QTc prolongation in patients with pacemakers is associated with an increased risk of fatal cardiac complications, as well as if these patients can safely receive known QT-prolonging medications. Seventy-six patients with baseline narrow QRS complexes and QTc < 500 msec were included, all of whom had baseline ischemic heart disease and permanent dual-chamber ventricular pacemakers implanted due to bradyarrythmias. At baseline (prior to device implantation) and annually within the 5-year follow-up period, EKG, ECHO, and 24-hour Holter monitoring were performed. QTc intervals increased in all patients during the study duration. However, only 59 patients met the study's criteria for QTc prolongation (QTc > 500 msec), which differs from the widely accepted male and female clinical definitions of long QTc syndrome. Patients were classified into either Group I (n=17, QTc < 500 msec), Group II (n=24, QTc > 500 msec), or Group III (n=35, QTc > 500 msec plus at least one concomitant QTc-prolonging drug therapy). At the five-year follow-up, one patient (5.8%) from Group I, two patients (8.3%) from Group II, and four patients (11.4%) from Group III died, but this was not a statistically significant finding (p-value > 0.9). However, a statistically significant increase in risk of cardiovascular hospitalization in patients with QTc > 500 msec was noted (17.7%, 45.8%, and 48.6% respectively; p-value < 0.001). A statistically significant association with increased risk of newly diagnosed heart failure, as well as worsening of heart failure, was also seen for patients with QTc > 500 msec (Groups II and III). Based on the presented data, study authors concluded that use of QTc-prolonging agents in patients with QTc > 500 msec posed no additional clinically significant risk.[5] Additional trials with larger sample sizes and longer follow-up periods are warranted to elaborate on these findings.

A 2013 clinical review concluded that present literature demonstrates patients living with CIEDs have an elevated associated risk of TdP, meaning prescribers must be able to identify additional risk factors for acquired QT-prolongation, recognize the type and pacing setting of the specific patient's CIED, and perform baseline EKG and electrolyte monitoring before considering initiation of a known QT-prolonging pharmacotherapy. Should a patient be at elevated risk, but the QT-prolonging agent in question cannot be reasonably avoided, minimize other concomitant QT-prolonging or interacting agents, consider dose reduction if QTc > 500 msec, maintain serum potassium between 4.5 and 5 mmol/L and serum magnesium $\geq$ 2 mg/dL, repeat EKG after initiation and dose titrations, and consider cardiology consult. While this review was specifically aimed at psychiatrists prescribing QT-prolong psychotropics, the fundamental recommendations remain applicable to all practitioners.[1]

An evidence-based clinical decision-making tool, available with free registration, is available at https://medsafetyscan.org for additional support when choosing whether to initiate a QTc-prolonging agent in your future patients. Additionally, https://www.crediblemeds.org/drugsearch is another renowned source for risk of drug-induced QT prolongation. Search the brand or generic medication name and risk category with explanation will be provided.

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The Basics of Biosimilars

- **Biologics** are products used to diagnose, prevent, treat and cure diseases and medical conditions. This diverse body of products (which includes therapeutic proteins and monoclonal antibodies) is produced using biotechnology in a living system, for example, a plant or animal cell.

- A proposed biosimilar is compared to an FDA-approved biologic agent, called the **reference product**.

- A **biosimilar** must be "highly similar to" and have "no clinically meaningfully differences from" the reference product.

- **The 2009 Biologics Price Competition and Innovation Act** created an abbreviated approval process with the goal to increase consumer access and decrease health care costs through safe and effective biologic products.

- To gain biosimilar approval, the manufacturer must amass a wealth of comparative data to the reference product to prove biosimilarity.
  1. Collect structural and functional analytical data.
  2. Conduct non-clinical animal testing to evaluate safety and toxicity of the proposed biosimilar.
  3. Evaluate clinical comparative studies of pharmacokinetics, pharmacodynamics, and immunogenicity.
  4. If warranted to ensure no clinically meaningful differences, additional human clinical trials must be conducted.

- To apply to be an **interchangeable** product, manufacturers must demonstrate the ability of the biosimilar to produce the same clinical result with no increase in safety risk or decrease in effectiveness as the reference product in any given patient population. As of the date of this publication, there are no FDA-approved interchangeable biologic products.

- **The Purple Book**, a searchable online database containing information on all FDA-approved biologics, can be found at https://purplebooksearch.fda.gov/results?query=adalimumab&title=Humira.

Go beyond the basics!

Click on this link to check out the FDA's five-part YouTube video series on biologics and biosimilars:
https://www.youtube.com/playlist?list=PLey4Qe-UxcxbFinyBSntx188r2lvxqxak

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