Magellan Rx MANAGEMENT

Clinical Alert

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ICER Review of Rheumatoid Arthritis (RA) Immune Modulators

An estimated 1.5 million Americans are affected by RA, which can have periods of symptom flares and remission. New immunotherapy agents have been introduced to the market in recent years. The Institute for Clinical and Economic Review (ICER), an independent non-profit research organization, performed a meta-analysis that included 67 randomized controlled trials and 17 observational studies to assess the clinical effectiveness, potential harms, and economic value of targeted immune modulator (TIMs) drugs to treat moderate to severe RA. They compared the use of TIMs, as monotherapy or in combination with conventional disease modifying antirheumatic drugs (DMARDs), to conventional DMARDs alone and to the market leader, adalimumab (Humira®). The review included the following TIMs: tumor necrosis factor (TNF) inhibitors adalimumab, certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®/Simponi Aria®), and infliximab (Remicade®); the CD20-directed cytolytic antibody rituximab (Rituxan®); the T cell inhibitor abatacept (Orencia®); interleukin-6 (IL-6) inhibitors sarilumab (investigational) and tocilizumab (Actemra®); and the Janus kinase (JAK) inhibitors baricitinib (investigational) and tofacitinib (Xeljanz®).

ICER reported that all TIMs (monotherapy and combination therapy) offer significant clinical improvement over conventional DMARDs regarding symptom response, disease activity, and radiographic progression. In head-to-head trials when used either alone or in combination therapy, abatacept, certolizumab pegol, etanercept, and tofacitinib had similar effects on clinical outcomes compared to adalimumab (monotherapy or combination therapy); while baricitinib, sarilumab, and tocilizumab were reported to be superior to adalimumab. The overall incidence of serious adverse events were similar between treatments, including conventional DMARD therapy.

ICER conveyed disease burden as quality-adjusted life year (QALY), which captures both the quality and the quantity of life lived; 1 QALY is equal to 1 year in perfect health. The cost of adding any TIM to conventional DMARDs exceeded the commonly-cited cost-effectiveness thresholds (between $50,000 and $150,000 per QALY); ranging from about $170,000/QALY for subcutaneous (SC) tocilizumab to $270,000/QALY for tofacitinib. In addition, most of the Food and Drug Administration (FDA)-approved TIMs were more effective and cost less than adalimumab; exceptions to this were abatacept SC, etanercept, and tofacitinib. ICER estimated that prices for the currently available TIMs would need to be discounted between 29% and 69%, depending on the product, to meet the commonly-cited cost-effectiveness thresholds. Cost-effectiveness of the 2 investigational products, baricitinib and sarilumab, remain to be seen.

ICER recognizes that, in clinical practice, treatment choice is often based on individual patient characteristics and risk factors. Patients may try various agents before finding one that is effective and tolerable. In addition, the overall incidence of serious adverse events, serious infections, and deaths were comparable between treatments, including conventional DMARDs.

The ICER findings were reviewed at the New England Comparative Effectiveness Public Advisory Council (CPAC) on March 24, 2017. The full report is available at https://icer-review.org/materials/.

Drug Information Highlights

- GlaxoSmithKline voluntarily recalled 3 lots of Ventolin® HFA (albuterol) inhalers due to a leakage of the inhalers' propellant that may lead to fewer doses delivered than indicated on the dose counter. Affected lots involve nearly 600,000 inhalers. No shortage of supply is anticipated. Consumers should not be affected by this class 2 recall.
- Upsher-Smith and Supernus have received new indications for their respective oral extended-release topiramate capsules, Qudexy® XR and Trokendi® XR, for the prophylaxis of migraine headache in adults and children ≥ 12 years of age. The recommended starting dose for both products for migraine is 25 mg once daily, which may be titrated to a maximum of 100 mg once daily. These products are also indicated to treat various seizure disorders; Qudexy XR is approved for use in patients ≥ 2 years of age, while Trokendi XR is approved for patients ≥ 6 years.
- The FDA removed the conditional approval status for Pfizer's cyclin dependent kinase 4/6 (CDK 4/6) inhibitor, palbociclib (Ibrance®), for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer when used in combination with an aromatase inhibitor (AI) in postmenopausal women, or with fulvestrant in women with disease progression after endocrine therapy. Palbociclib's full approval is based on results of the confirmatory PALOMA-2 trial. This approval also expands the use of palbociclib with any AI, rather than only letrozole.
- The tyrosine kinase inhibitor (TKI) osimertinib (Tagrisso™) by AstraZeneca was granted full FDA approval for the treatment of metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, in patients whose disease has progressed during or after EGFR TKI therapy. It is the first agent in the United States (U.S.) indicated for use in patients with NSCLC and this specific tumor mutation.
- The Drug Enforcement Agency (DEA) has issued an interim final rule designating dronabinol 5 mg/mL oral solution (Syndros®) and other oral solutions containing dronabinol as Schedule II controlled substances. Insys is anticipated to begin marketing Syndros in the second half of 2017, after the DEA final ruling has been made. Syndros was FDA approved in July, 2016, to treat adults with AIDS-associated anorexia or chemotherapy induced nausea and vomiting.

Expanded Indications for Hepatitis C Antivirals

Recently, the FDA expanded the indications for 3 direct-acting antivirals (DAA) used to treat chronic hepatitis C virus (HCV) infections. In April, Gilead's sofosbuvir (Sovaldi®) and sofosbuvir/ledipasvir (Harvoni®) gained approval for use in children ≥ 12 years old or weighing ≥ 35 kg without cirrhosis or with compensated cirrhosis. Harvoni is indicated in children with HCV genotypes (GT) 1, 4, 5, and 6; Sovaldi is indicated in combination with ribavirin (RBV) in children with GT 2 or 3. For both products, the recommended dosing in pediatric patients is the same as adults, including patients who are HCV/HIV-1 coinfected. In March, the indication to treat HCV GT4 for Abbvie's fixed-dose combination of ombitasvir/paritaprevir/ritonavir (Technivie™) was expanded to include patients with compensated cirrhosis; it was previously only approved in patients without cirrhosis. The 12-week dosing regimen in combination with RBV is the same regardless of presence of compensated cirrhosis.

ADA Releases Updated Diabetic Retinopathy Guidelines

Diabetic retinopathy is the most frequent cause of new cases of blindness among adults in developed countries. The American Diabetes Association's (ADA) updated diabetic retinopathy position statement was published in the March 2017 edition of *Diabetes Care* and includes significant changes to the treatment options and diagnostic assessment since it was last released in 2002. In order to decrease the risk of developing diabetic retinopathy or slow its progression, the guidelines recommend optimizing control of blood glucose, cholesterol, and hypertension. All diabetic patients should have a comprehensive dilated eye exam performed within 5 years of diagnosis for type 1 diabetic adults and at the time of diagnosis for type 2 diabetic patients.

Regarding treatment, the ADA recommends that patients with any level of macular edema, severe nonproliferative diabetic retinopathy, or any proliferative diabetic retinopathy, should be referred to an ophthalmologist who is experienced in the management of diabetic retinopathy. Laser photocoagulation therapy reduces the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. Intravitreous injections of anti-vascular endothelial growth factor (VEGF) products are indicated for central-involved diabetic macular edema (DME). Finally, the guidelines state that aspirin does not increase the risk of retinal hemorrhage; therefore, retinopathy is not a contraindication to cardioprotective doses of aspirin. The complete guidelines may be viewed at http://care.diabetesjournals.org.

AGA Guidance on Long-term Use of Proton Pump Inhibitors (PPIs)

The long-term use of PPIs doubled in the U.S. from 1999 to 2012, resulting in an increase in adverse events by the same magnitude. The American Gastroenterological Association (AGA) states that, when PPIs are used appropriately, their benefits exceed their risks. Based on expert opinion and a review of the most recent data on the risks and benefits of PPIs, the AGA developed best practice advice on the long-term use of PPIs, focusing on the management of gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis.

The AGA instructs that PPIs be prescribed for short-term healing, maintenance of healing, and long-term symptom control in patients with GERD and acid-related complications (e.g., erosive esophagitis or peptic stricture). Therapy discontinuation or dose reduction should be attempted in patients with uncomplicated GERD who respond to short-term PPIs. For patients who cannot reduce their dose, ambulatory esophageal pH/impedance monitoring should be considered to identify if a functional syndrome is present. This is particularly useful in patients who experience mostly atypical symptoms or who do not have a clear predisposition for GERD (e.g., central obesity, large hiatal hernia).

Long-term use of a PPI should be prescribed in patients with BE and symptomatic GERD and may be considered in those with asymptomatic BE. Patients who are at high risk for ulcer-related bleeding from NSAID therapy should take a PPI as long as NSAIDs are required.

AGA recommends that patients be evaluated periodically and managed with the lowest effective PPI dose. Patients on long-term PPIs should not routinely use probiotics or increase their intake of calcium, vitamin B12, or magnesium beyond the recommended dietary allowance. In addition, routine monitoring of bone mineral density, and serum creatinine, magnesium, or vitamin B12 is not required. Lastly, AGA advises prescribers against choosing a PPI based on its potential risks since evidence is lacking to compare the agents based on this factor.

The full guidance was published in the March 2017 edition of *Gastroenterology* and may be viewed at http://www.gastrojournal.org.

- Gilead is voluntarily withdrawing Vitekta® (elvitegravir) tablets from the market due to low utilization of the product (< 50 patients in the U.S.). Fixed-dose combinations that contain elvitegravir will remain on the market.
- Genentech's VEGF inhibitor, ranibizumab (Lucentis®), received an expanded indication under an FDA priority review to treat all forms of diabetic retinopathy. It is administered by a monthly intravitreal injection and is the only agent approved to treat diabetic retinopathy in patients with or without DME. Additional indications include wet age-related macular degeneration, macular edema post retinal vein occlusion, DME, and myopic choroidal neovascularization.

Pipeline News: Upcoming Prescription Drug User Fee Act (PDUFA) Dates

- **Quarter 2, 2017:** edaravone; intravenous (IV) neuroprotective agent; amyotrophic lateral sclerosis; Jiangsu Simcere/Mitsubishi Tanabe.
- **Quarter 2, 2017:** nonacog beta pegol; IV long-acting recombinant factor IX; Hemophilia B; Novo Nordisk.
- **Quarter 2, 2017:** ozenoxacin; topical quinolone antibiotic; impetigo; Ferrer/Medimetriks.
- **May 7, 2017:** Yuvvexy; bio-identical 17-beta-estradiol; vaginal estrogen; moderate to severe dyspareunia; Therapeutics MD.
- **May 10, 2017:** Keytruda®; pembrolizumab; IV programmed cell death 1 (PD-1) inhibitor; NSCLC (first-line regardless of PD-1 expression and EGFR and ALK tumor mutation negative); Merck.
- **May 29, 2017:** glycopyrronium bromide; inhaled long-acting muscarinic antagonist; chronic obstructive pulmonary disease; Sumitomo Dainippon/Sunovion.
- **June, 2017:** Retacrit; epoetin zeta, biosimilar to Amgen's Epogen® and Janssen's Procrit®; IV/SC erythropoietin stimulating protein; anemia due to chronic kidney disease, zidovudine therapy, or effects of myelosuppressive chemotherapy, and also for the reduction of allogeneic red blood cell transfusions in select patients undergoing surgery; Hospira/Pfizer.
- **June, 2017:** Grastofil; filgrastim, biosimilar to Amgen's Neupogen®; IV/SC colony stimulating factor; cancer patients receiving bone marrow transplant or myelosuppressive chemotherapy, severe chronic neutropenia; Accord/Apotex/Intas.
- **June, 2017:** Lapelga; pegfilgrastim, biosimilar to Amgen's Neulasta®; SC colony stimulating factor; cancer patients receiving myelosuppressive chemotherapy; Accord/Apotex/Intas.
- **June 9, 2017:** CHS-1701; pegfilgrastim, biosimilar to Amgen's Neulasta®; SC colony stimulating factor; cancer patients receiving myelosuppressive chemotherapy; Coherus.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
niraparib	Zejula™	The FDA approved niraparib (Zejula), a poly (ADP-ribose) polymerase (PARP) inhibitor, indicated for the maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. The recommended dose is 300 mg orally once daily with or without food until disease progression or unacceptable toxicity occurs. Niraparib is approved as 100 mg capsules. Developed under a fast track designation, niraparib is the first PARP inhibitor approved by the FDA that does not require BRCA mutation or other biomarker testing. It was granted orphan drug status for the treatment of ovarian cancer.	Tesaro	FDA NDA priority approval 03/27/2017
dupilumab	Dupixent®	Dupilumab (Dupixent), an interleukin (IL)-4 receptor alpha antagonist that inhibits IL-4 and IL-13 signaling, was FDA approved for the treatment of adults with moderate to severe atopic dermatitis (eczema) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The FDA granted dupilumab breakthrough therapy and fast track designations. The recommended initial dose is 600 mg, administered as two 300 mg SC injections at separate injection sites, followed by 300 mg administered every other week. It may be used with or without topical corticosteroids. Dupilumab is approved as a 300 mg/2 mL solution in a single-dose prefilled syringe.	Regeneron	FDA BLA priority approval 03/28/2017
abatacept	Orencia	The T cell inhibitor, abatacept (Orencia) SC formulation, was approved to treat moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients ≥ 2 years of age. It may be used alone or in combination with methotrexate. To accommodate the weight-based dosing in this patient population, the FDA approved 2 new strengths of abatacept SC, 50 mg/0.4 mL and 87.5 mg/0.7 mL, in prefilled syringes. It is also available as a 125 mg/mL prefilled syringe for SC use. Intravenous administration of abatacept has not been studied in patients < 6 years old. Abatacept (IV and SC administered) is also indicated in adults with RA.	Bristol-Myers Squibb	FDA sBLA priority approval 03/30/2017
deutetrabenazine	Austedo®	The FDA approved the orphan drug deutetrabenazine (Austedo), a vesicular monoamine transporter 2 (VMAT2) inhibitor, for the treatment of chorea associated with Huntington's disease. The recommended initial dose is 6 mg once daily. The dose may be titrated at weekly intervals by 6 mg per day with total daily doses of 12 mg or more given in 2 divided doses. The maximum daily dose is 48 mg; however, in patients who are also taking a strong CYP2D6 inhibitor or who are poor CYP2D6 metabolizers, the maximum daily dose is 36 mg. Deutetrabenazine is approved as 6 mg, 9 mg, and 12 mg tablets, which should be taken with food and swallowed whole. When switching from tetrabenazine (Xenazine®), initiate deutetrabenazine 1 day following the last dose of tetrabenazine. Contraindications include suicidality, untreated or inadequately treated depression, hepatic impairment, and concurrent use of a monoamine oxidase inhibitor (MAOI), reserpine, or tetrabenazine. Deutetrabenazine carries a boxed warning regarding the risk for depression and suicidality.	Teva	FDA NDA approval 04/03/2017
valbenazine	Ingrezza™	The VMAT2 inhibitor valbenazine (Ingrezza) is the first product indicated for the treatment of adults with tardive dyskinesia. The FDA granted valbenazine breakthrough therapy status. It is initially dosed as 40 mg once daily with or without food; the dose is increased to the recommended 80 mg once daily after 1 week. Dose reductions are advised in patients with moderate to severe hepatic impairment and in patients with poor CYP2D6 metabolism. It is FDA approved as a 40 mg capsule.	Neurocrine Biosciences	FDA NDA priority approval 04/11/2017
atezolizumab	Tecentriq®	The FDA expanded the indication for atezolizumab (Tecentriq), a programmed death-ligand 1 (PD-L1) blocking antibody, to include treatment of locally advanced or metastatic urothelial carcinoma (UC) in patients who are not eligible for cisplatin chemotherapy. It was previously approved for locally advanced or metastatic UC in patients who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of receiving chemotherapy before or after surgery. Its use for UC is approved under an accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Atezolizumab is also indicated to treat select patients with metastatic NSCLC. The recommended dose for all indications is 1,200 mg IV over 60 minutes every 3 weeks.	Genentech	FDA sBLA priority approval 04/17/2017

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application

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