DUR Capsules
News and Information for West Virginia Providers from the West Virginia Bureau for Medical Services (WVBMS)

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2nd Quarter 2018
Published Quarterly by Health Information Designs, LLC

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Topics Covered in This Issue

Overview of Retrospective Drug Utilization Review (RDUR) Programs

Introduction

- Many people receive complicated drug regimens with different dosing schedules and/or receive their medications from different prescribers, increasing their risk for therapeutic duplication and drug interactions. In order to help reduce this risk, federal legislation mandates that all state Medicaid agencies must have a Retrospective Drug Utilization Review (RDUR) Program.
- As the name suggests, RDUR is a review of a members' drug utilization and health history after a medication has been dispensed by a pharmacy. During this review, the member's profile is evaluated for prescribing practices and/or member utilization issues that are considered unsafe, ineffective, or otherwise inconsistent with evidence-based standards of care. If any of these

potential issues are found during review, they are identified and the prescriber of the medication is notified.

West Virginia Medicaid's RDUR Program

- The WV Medicaid RDUR Committee is comprised of 5 actively practicing healthcare professions (currently 4 pharmacists and an MD). Committee members meet monthly to review selected patient prescription and medical profiles which have been identified as having potential drug utilization issues through a combination of targeted interventions and general RetroDUR principles. Providers are notified by letter when potential problems are identified. A pharmacy lock-in program, aimed at reducing the inappropriate use of controlled substances, is also overseen by the RDUR Committee and maintained by the Bureau for Medical Services.
- RDUR review typically focuses on 5 general areas, but may include targeted monthly interventions:
    - **Drug/Drug Interactions**: Drug-drug interactions occur when patients receive two or more drugs that, when taken together, may interact to produce adverse effects.
    - **Drug/Disease Conflicts**: includes drug therapies that could precipitate or worsen existing medical conditions.
    - **Underutilization**: defined as recipients taking medications for the treatment of chronic conditions at levels below the acceptable minimum dose or dosing interval.
    - **Overutilization**: occurs when recipients take medications in high doses or for lengths of time exceeding label recommendations. Drugs used in high quantities or for unduly prolonged periods of time place recipients at unnecessary risk of adverse effects.
    - **Therapeutic Appropriateness:** monitors recipients to ensure the right medication is being used based on parameters such as standard of care for certain medical conditions or disease states.
- In instances where the RDUR criteria is not met, prescribers are sent notifications that identify the specific patient and potential intervention needed. The notification also asks for a prescriber response indicating whether a therapy change will be made or why no change is necessary, as well as asking for feedback on the program itself.
- Through these notifications, the RDUR program aims to aid prescribers in improving patient care both directly and indirectly.
    - Patient care can directly be improved by highlighting specific instances of abuse and inappropriate drug therapy (e.g., therapy duplication, drug-drug and drug-disease interactions, inappropriate drug dosing, medication underutilization and overutilization, etc.).
    - These notifications may also aid prescribers indirectly by allowing them to compare their approach to treating certain diseases with their peers, which can improve the care of their patients, both individually and within entire patient populations.
- The RDUR program is informational in nature and allows prescribers to incorporate the information provided into their continuing assessment of the patient's drug therapy requirements.
- RDUR programs create an opportunity for wide-ranging improvements in health outcomes, however being only education in nature, it is critical that prescribers receiving these notifications to both respond to the letters and make the necessary interventions in order to attain these benefits. Because of this, we ask all prescribers to please continue to respond and provide feedback on this program in order for it to be as effective and useful as possible.

OVERVIEW OF CGRP AND MIGRAINE

Migraine Epidemiology and Symptomology

- Migraines are a headache disorder characterized by recurrent headaches that typically last from 2-72 hours. The headaches produce an intense pulsing or throbbing pain in one area of the head, often resulting in secondary symptoms of nausea, vomiting, and sensitivity to light and sound.
- Due to the severity and duration of these symptoms, migraine headaches are often disabling. It is estimated that ~6% of men and ~18% of women experience a migraine in the United States annually.
- Patients suffering from migraine will commonly experience recurring migraine headaches, brought on by a number of different environmental and physiological "triggers", often including stress, hormonal changes, lighting, diet, and/or fatigue.

The Role of Calcitonin Gene-Related Peptide (CGRP) in Migraine

- While the precise etiology of migraine remains unknown, it has long been recognized that migraine headaches occurrences are accompanied by dilation of cranial blood vessels, as well as elevations of plasma levels of calcitonin gene-related peptide (CGRP).
- CGRP is a neuropeptide that is synthesized and released by neurons throughout the central and peripheral nervous system. Because it is a very potent microvascular vasodilator (~10 times more potent than the most potent prostaglandins) and is primarily contained in nerve fibers associated with pain processes, the primary functions of CGRP are related to pain perception and inflammatory processes around nerves.
- Based on the growing understanding of the role of CGRP in migraine and other research, many current hypotheses regarding migraine pathophysiology theorize a system of self-perpetuating vasodilation that is mediated in part by CGRP.
- In these hypotheses, the pathophysiology of a migraine is generally explained as follows:
    1. Migraine triggers lead to dysfunction within the brain, causing dilation of cranial blood vessels
    2. The dilated vessels activate sensory fibers of the trigeminal nerve which conveys a pain response to the brain
    3. Pain responses in the brain evoke a release of CGRP and other mediators from trigeminal nerve fibers
    4. CGMP & other mediators cause further vasodilation, further activating trigeminal sensory fibers, causing a repeat of the pain response cycle
- Because of the growing understanding of the potential role of CGRP in migraine, drugs targeting CGRP activity have been in development for a number of years, the first of which received FDA approval earlier this year.

Review of Aimovig

- On May 17, 2018, the FDA approved Amgen's Aimovig (erenumab-aooe) for the preventive treatment of migraine in adults.
- It is a human monoclonal antibody that achieves its therapeutic effect by blocking the activity of CGRP at the receptor level, thus reducing the effects of endogenous CGRP.

- **<u>Clinical Trial Experience</u>**
    - The effectiveness of Aimovig for the preventive treatment of migraine was demonstrated in three placebo-controlled clinical trials, evaluating the average reduction in monthly migraine days at the end of the trial. The table below describes the size, duration, migraine type treated, and average effect of Aimovig vs. placebo of each trial.

	Number of Patients	Migraine Type	Trial Duration	Average Effect of Aimovig vs. Placebo*
Study 1	955	Episodic Migraine	6	1-2
Study 2	577	Episodic Migraine	3	1
Study 3	667	Chronic Migraine	3	2.5
**Reported as Average Reduction in Number of Monthly Migraine Days on Aimovig Compared to Placebo*				

    - During the trials, the most commonly reported (≥5%) adverse effects to therapy with Aimovig were:
        - Constipation (3%)
        - Antibody development (3% to 6%)
        - Injection site reaction (5% to 6%)
        - Muscle cramps or spasms (≤2%)
- **<u>Safety Profile of Aimovig</u>**
    - There are no contraindications to therapy listed in the manufacturer's labeling.
    - The label does contain a warning that the product packaging may contain latex.
    - The only other drug known to interact with Aimovig at this time is belimumab, which may have its toxic effects enhanced when treated with Aimovig.
- Aimovig is recommended to be administered subcutaneously, at a dose of 70 mg or 140 mg once monthly.
- While the approval of Aimovig signals the arrival of a new drug class indicated for the prevention of migraine, it is just one option for therapy as there are multiple other medications that carry similar indications to Aimovig (e.g. propranolol, topiramate, and divalproex), and there is no available data evaluating the efficacy of Aimovig vs. these other migraine prophylaxis agents. As always, patient care should be personalized based on multiple factors including current medications, comorbid conditions, and past medical history.

OVERVIEW OF CAR T-CELL IMMUNOTHERAPIES

Introduction

- Recently, the FDA granted approval to Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), the first and second cancer therapies that use genetically engineered immune cells collected from patients to elicit their therapeutic response. These immunotherapies, called chimeric antigen receptor (CAR) T-cell therapies, are unique to other chemotherapy agents in that the active product is actually genetically modified versions of a patient's own T-cells, representing a promising new wave of bioengineered cancer treatments.
    - Yescarta is indicated for the treatment of relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy. This includes diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
    - Kymriah is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in patients up to 25 years of age.

Clinical Trial Experience with Current CAR T-Cell Immunotherapies

- Kymriah and Yescarta both demonstrated their efficacy in open-label, multicenter trials.
    - Yescarta was established in an open-label trial of 101 adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Of these patients, 51% achieved complete remission (CR) and 21% achieved partial remission, with a median duration of response (DOR) of 9.2 months and a median time to response of 0.9 months.
    - Kymriah's was studied in a trial including 63 pediatric and young adult patients with B-cell precursor ALL. Of these patients, 63% and 19% achieved CR or complete remission with incomplete blood count recovery (CRi) respectively. The median DOR was not reached and the median time to onset of CR/CRi was 29 days.

How CAR T-Cell Immunotherapies Work

- A simple explanation of how CAR T-cell therapies is that the therapies encode a new gene on a patient's own T-cells, reprograming them to produce a surface CAR that allows it to target a specified antigen.
- For Kymriah and Yescarta, the CAR is an antibody fragment which recognizes and binds to an antigen present on malignant and normal B-cells, becoming activated.
    - CAR activation of both Kymriah and Yescarta results in the same basic downstream effects: the CAR transmits a signal that promotes T-cell proliferation, activation, secretion of inflammatory mediators, causing the destruction of CD19-expressing cells.
- Because CAR T-cell immunotherapies are genetically enhanced versions of a patient's own T-cells, a multi-step process must take place prior to actual treatment with either Yescarta or Kymriah. This process can be broken down into 4 broad steps outlined below:
    1. Patient's T-cells are removed from their blood using a process called leukapheresis
    2. T-cells are sent to a lab where they are genetically engineered to produce CD19 directed CARs
    3. The number of modified CAR T-cells is augmented by growing cells in the laboratory, which are then frozen
    4. The patient's modified CAR T-cells are transfused into the patient's blood stream

Safety Profiles and Product Comparison of Available Products

- Both medications carry box warnings regarding the existence of a REMS program for each product as well as on the risk of potentially fatal or life-threatening cytokine release syndrome (CRS) and neurological toxicities associated with the products.
- Beyond the boxed warning, these products carry several serious warnings and precautions patient should be monitored for, including an increased risk of the following:
    - Serious viral, bacterial, and other infections (should not be given to patients with clinically significant active systemic infections)
    - Prolonged cytopenias (neutropenia, thrombocytopenia, and anemia)
    - Hypogammaglobulinemia
    - Hepatitis B virus (HBV) reactivation
    - Development of secondary malignancies or leukemia recurrence during treatment
- Patients receiving these therapies are at risk for a host of other common (>10%) adverse reactions, including blood pressure changes, tachycardia, headache, fatigue, delirium, hypophosphatemia, GI upset, acute renal failure, hypoxia, cough, myalgia and fever.
- The table below provides a brief summary of other important information from each medication's prescribing information:

Drug	**Yescarta™**	**Kymriah™**
Disease State	Relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy.	B-cell precursor ALL that is refractory or in 2nd or later relapse

Dosing and Administration	• Maximum Dose
	  ○ 2x 10^8 CAR-positive viable T cells IV
	• Target Dose
	  ○ 2 x 10^6 CAR-positive viable T cells per kg body weight IV
		• Patients > 50 kg
		  ○ 0.1 to 2.5 x 10^8 CAR-positive viable T cells IV
		• Patients ≤50 kg
		  ○ 0.2-5 x 10^6 CAR-positive viable T cells per kg body weight IV

Dosage Form	• IV suspension	• IV suspension
Pregnancy	Treatment is not recommended during pregnancy. Pregnancy testing is recommended prior to therapy in sexually active women of reproductive potential	
Pediatric Use	Safety and efficacy have not been established	Only for patients ≤ 25 years of age
Renal Impairment	No dose adjustments provided in labeling (has not been studied)	
Hepatic Impairment	No dose adjustments provided in labeling (has not been studied)	
Drug Interactions	Consider avoiding corticosteroids and live vaccines	Consider avoiding corticosteroids and live vaccines Avoid with Granulocyte CSFs and Sargramostim
Limitations	Not indicated for the treatment of patients with primary CNS lymphoma.	

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