▶ ISSUE 7 | ▶ VOLUME 7 | ▶ JULY/AUGUST 2017

MEDICATION SAFETYINSECONDS

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

ISMP REPORTS DRUGS WITH SIGNALS FOR WITHDRAWAL AND FREQUENTLY REPORTED SYMPTOMS

The Institute for Safe Medication Practices' (ISMP) latest Quarterly Report examined withdrawal symptoms reported by patients taking opioids, antidepressants, certain anticonvulsants/neuropathic pain medications, antianxiety drugs, and sedative hypnotics. Their assessment was prompted by concerns of underestimated injury rates due to a lack of evidence/data regarding withdrawal effects considering widespread exposure in large patient populations. Another matter of interest includes inadequate warnings and prescribing information regarding the severity, duration, and likelihood of withdrawal effects, as well as how to manage discontinuation of drugs that pose a risk.

Using adverse event data submitted to the FDA Adverse Event Reporting System (FAERS) in 2016, ISMP identified approximately 4000 cases of drug withdrawal effects associated with 42 agents (Table 1, page 2) that met the following requirements for a clear and credible signal of risk for withdrawal effects: at least 10 reported cases of withdrawal symptoms; at least twice as many cases as expected given the total number of adverse event reports for the drug; at least a 95% probability that the number of withdrawal effects could not have occurred by chance. ISMP notes that their lists may not be comprehensive due to the voluntary reporting nature of adverse events submitted to the FAERS. Other drugs may not have had enough reports to meet the study criteria. Another study limitation is the concomitant use of psychoactive agents for comorbid conditions such as antidepressants and benzodiazepines that could confound findings.

ISMP's review reinforces that certain drugs, when stopped abruptly without a gradual

(continued on page 2)

NEWSWORTHY...

from the pbm

- Hospira – 8.4% Sodium Bicarbonate Injection, USP, Neut™, Quelicin™, and Potassium Phosphate Injection, USP Recall Due To a Potential for Lack of Sterility Assurance - 06/26/2017 – PBM Patient Level Recall Communication; ****TARGETED to affected sites only****
- Becton Dickinson - #4406 – Insulin Syringes: Recall Due to Incorrect Product Labeling – 06/15/2017 - National PBM Patient Level Recall Communication

(continued on page 2)

IN THIS ISSUE:

VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

EDITOR-IN-CHIEF

Marie Sales, Pharm.D.
VA Pharmacy Benefits Management Services [PBM] & Center for Medication Safety [VA MedSAFE]; 1st Avenue—1 Block North of Cermak Road | Building 37; Room 139 | Hines, Illinois | 60141; www.pbm.va.gov

NEWSWORTHY...

from the fda

(continued from page 1)

PAIN MANAGEMENT

FDA Requests Removal of Opana ER for Risks Related to Abuse

06/08/2017

In March 2017, an FDA Advisory Committee convened and concluded that the benefits of reformulated Opana ER (oxymorphone hydrochloride) no longer outweighed the risks. Opana ER (oxymorphone hydrochloride) received approval in 2006 as a daily, around-the-clock, long-term opioid agonist to manage severe pain unrelieved by alternative treatment options. In 2012, the manufacturer introduced a new formulation with abuse deterrent characteristics in order to thwart crushing and snorting the controlled substance. However, users have discovered how to dissolve and inject the reformulated narcotic instead. Public health consequences associated with this current abuse by injection include a serious outbreak of HIV and hepatitis C, as well as cases of a serious blood disorder known as thrombotic microangiopathy. As such, in June 2017, the FDA has requested that Endo voluntarily remove reformulated Opana ER from the market and expressed that if the manufacturer does not comply, the agency will take steps to formally withdraw its approval.

REFERENCES

1. FDA News Release: FDA requests removal of Opana ER for risks related to abuse. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm . Accessed June 8, 2017.
2. OPANA® ER (Oxymorphone Hydrochloride) Extended-Release tablets CII [Prescribing Information]. Endo Pharmaceuticals Inc. December 2016.

Helping to achieve safe medication use

ISMP REPORTS DRUGS WITH SIGNALS FOR WITHDRAWAL AND FREQUENTLY REPORTED SYMPTOMS

(continued from page 1)

taper, can have adverse effects (Table 1). According to ISMP's analysis, withdrawal symptoms ensue from neurotransmitter or receptor effects of certain drugs. When the drugs are discontinued, especially abruptly, symptoms may manifest as the cells make adjustments in neurotransmitter signal transmission, reuptake, or receptor expression. Effects vary with the individual patient, drug, dose, half-life, and duration of treatment. The neurotransmitters and receptors involved with the reported drugs and withdrawal effects associated with ISMP's findings include serotonin, gamma-aminobutyric acid (GABA), opioid, and dopamine.

Results suggest that some withdrawal effects may mimic the original condition (i.e., depression, insomnia), while others do not. Table 2 (page 4) catalogues the most frequently reported symptoms in patients that discontinued a psychoactive drug distinguished by ISMP's study criteria. Nausea, dizziness, skin sensations of electric shock, insomnia, and anxiety topped the list. However, ISMP's assessment does not link which drugs align with which symptoms.

(continued on page 4)

Table 1. Drugs identified by ISMP to have signals for withdrawal symptoms in 2016.

Effects on Serotonin	Effects on GABA	Effects on Opioid Receptors	Effects on Dopamine	Other Mechanisms
Duloxetine	Pregabalin	Buprenorphine/naloxone	Quetiapine	Baclofen
Paroxetine	Vigabatrin	Oxycodone	Olanzapine	Cetirizine
Venlafaxine	Gabapentin	Fentanyl	Methylphenidate	Ziconotide
Desvenlafaxine	Clonazepam	Buprenorphine		Omeprazole
Sertraline	Alprazolam	Naltrexone		Pramipexole
Mirtazapine	Clobazam	Naloxegol		Clonidine
Citalopram	Zolpidem	Morphine		
Bupropion	Lorazepam	Tramadol		
Escitalopram	Dexmedetomidine	Hydrocodone		
Fluoxetine	Diazepam	Hydrocodone/Acetaminophen		
		Naloxone		
		Morphine/Naltrexone		
		Methadone		

Getting the most from our safety surveillance

ATEZOLIZUMAB UTILIZATION IN UROTHELIAL CARCINOMA- A NATIONAL REVIEW

Submitted by: Katherine Kelly, PharmD, BCOP, Hematology/Oncology Clinical Pharmacist, VA North Texas Health Care System

Background

In May 2016, the FDA approved atezolizumab (Tecentriq®, Genentech, Inc.), a new, humanized monoclonal antibody targeting the programmed death-ligand 1 (PD-L1), for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have had disease progression during or following platinum-containing chemotherapy or have had disease progression within twelve months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.[1] This accelerated approval was based on data from a phase II study in 310 patients in which atezolizumab demonstrated a significant improved objective response rate of 15% compared to a historical control and a median duration of response that had not been reached.[2] A few safety concerns from this trial were brought to the attention of the national PBM during the formulary review for atezolizumab. In particular, providers were concerned about the response rate differences (25% versus 8%) between patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active) versus 1 (strenuous activity restricted), respectively.[2] A national chart review was designed to investigate atezolizumab safety concerns in the VA population.

Methods

The objectives of the chart review were to assess (1) whether the facility prior authorization process was utilized, (2) provider adherence to the national atezolizumab criteria for use (CFU, see Table 1), (3) reasons for drug discontinuation and causes of death during and after atezolizumab therapy, and (4) potential relationships between failure to follow the CFU and discontinuations/deaths. A total of 105 charts were reviewed across 59 different VA facilities utilizing the CAPRI software. Data was collected by one clinical oncology pharmacist.

Results

This chart review was conducted on national data for 105 urothelial carcinoma patients started on atezolizumab between June 1, 2016 to February 28, 2017. The first study objective was to evaluate usage of the prior authorization process. The national CFU was published in August of 2016.[3] A total of 92/105 (87.6%) of patients initiating on atezolizumab received approval for atezolizumab through the prior authorization process, whereas the remaining 12.4% utilized atezolizumab without any drug approval process. Of the 32 patients started prior to CFU publication, 87.5% initiating on atezolizumab received approval for atezolizumab through the prior authorization process, whereas of the 73 patients started after CFU publication, 87.6% had prior authorization approval. Of all patients started on atezolizumab, only 17% of patients met all CFU parameters. Table 2 (page 4) presents the various CFU failures. It is important to note that patients could have failed more than one CFU parameter. Nineteen percent of patients did not meet the FDA indication for the drug. Most of these patients had not received platinum therapy for metastatic disease or could not tolerate platinum therapy after a few prior cycles. Not including the FDA indication failures, 70.4% of patients did not meet at least one of the inclusion criteria. Lack of documentation of an ECOG status and/or "goals of care" discussion comprised the majority of the inclusion failures. However, inadequate laboratory values and lack of baseline TSH were also common. Ninety-five percent of laboratory failures were due to inadequate hemoglobin levels (median Hgb 8.4 g/dL, range 7.1-8.9) or inadequate platelet levels (median platelet 70.5 K/µL, range 41-95). There were only 7 patients that met one of the exclusion criterion (5 with histories of chronic hepatitis B or C and 2 patients had corticosteroid use during atezolizumab utilization).

(continued on page 4)

Table 1. Inclusion & Exclusion Criteria from Atezolizumab CFU[3, 4]

EXCLUSION CRITERIA	INCLUSION CRITERIA
◊ Care not provided by a VA or VA purchased care provider ◊ Active, corticosteroid dependent or untreated brain metastases ◊ History of autoimmune disease or other conditions requiring immunosuppressive therapy ◊ Any corticosteroid use ◊ Acute or chronic Hepatitis B or C ◊ HIV positive ◊ Received a live, attenuated vaccine within the past 28 days ◊ Pregnant/Breastfeeding	◊ Meets FDA indication ◊ ECOG 0-2 ◊ Goals of Care/Palliative Care Consult discussed & documented ◊ Adequate Laboratory Values • Hgb ≥ 9 g/dL • WBC > 2500/mm^3 • ANC ≥ 1500/mm^3 • Platelet count ≥ 100,000/mm^3 • Total bilirubin ≤ 1.5x ULN • ALT & AST ≤ 2.5x ULN • Baseline TSH test

ECOG: Eastern Cooperative Oncology Group Performance Status; Hgb: hemoglobin; WBC: white blood cell count; ANC: absolute neutrophil count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TSH: thyroid-stimulating hormone

Helping to achieve safe medication use

ISMP REPORTS DRUGS WITH SIGNALS FOR WITHDRAWAL AND FREQUENTLY REPORTED SYMPTOMS

(continued from page 2)

Although more may be known about withdrawal effects of certain drug classes (i.e., opioids and benzodiazepines), the warnings and patient information for others (i.e., antidepressants, synthetic GABA agents, and antipsychotic agents) are limited. Because clinicians may not recognize effects upon discontinuation as "withdrawal" symptoms, it could mislead them to reinitiate therapy on the same or related drugs. Alternatively it may lead to unnecessary evaluation, and possible use of other pharmaceuticals.

As such, ISMP's findings may prove useful when considering discontinuation of agents of interest. Providers should taper, rather than abruptly stop, medications including (but not limited to) those listed in Table 1 (page 2). In addition, providers should caution patients that they may experience symptoms such as those frequently reported in Table 2 as they stop taking certain at-risk medications, and that patients should inform their health care provider in the event any symptoms become intolerable.

REFERENCE:
Institute for Safe Medication Practices (ISMP). QuarterWatch™ (2016 Annual Report). Part 1: Consumers at risk from drug withdrawal symptoms. *ISMP Medication Safety Alert! Acute Care* July 2017; 22 (14): 1-5.

Table 2. Most frequent withdrawal symptoms according to ISMP during 2016.

RANK	PREFERRED TERM	NUMBER OF CASES (one case could have multiple symptoms)	PERCENT
1	Nausea	955	2.8
2	Dizziness	939	2.8
3	Parasthesia	935	2.8
4	Insomnia	831	2.5
5	Anxiety	812	2.4
6	Suicidal Ideation	719	2.1
7	Headache	713	2.1
8	Agitation	694	2.0
9	Fatigue	686	2.0
10	Irritability	682	2.0
11	Hyperhydrosis	651	1.9
12	Vertigo	547	1.6
13	Confusional State	483	1.4
14	Tremor	470	1.4
15	Vomiting	448	1.3
16	Nightmare	414	1.2
17	Mood Swings	408	1.2
18	Diarrhea	406	1.2
19	Sleep Disorder	379	1.1
20	Pain	337	1.0

Getting the most from our safety surveillance

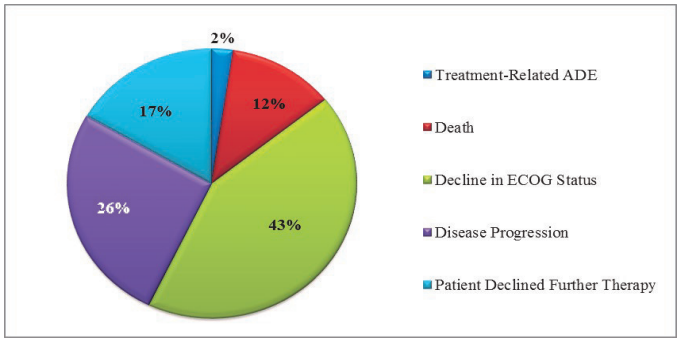
ATEZOLIZUMAB UTILIZATION IN UROTHELIAL CARCINOMA- A NATIONAL REVIEW

(continued from page 3)

Table 2. CFU Failures

CFU Failures	% of Patients (N=105)
Failure to Meet FDA Indication	19
Failure to Meet at Least One Inclusion Criterion$^{\Delta}$	70.4
ECOG Performance Status >2	8.5
No Documented ECOG Performance Status	20
Goals of Care Not Documented	24.8
Inadequate Laboratory Values	21.9
Baseline TSH Not Completed	14.3
Met an Exclusion Criteria	6.6
Patients could have failed more than one criterion $^{\Delta}$Excluding FDA indication	

Figure 1. Reasons for Drug Discontinuation



When examining the discontinuation and death rates of patients receiving atezolizumab, 40% of patients had discontinued therapy at the time of chart review. Figure 1 illustrates the reasons for discontinuing therapy. It is important to note that the chart review was still being conducted as new patients were initiated on therapy; therefore, some had not received multiple doses of atezolizumab prior to chart review. Of the 40% that discontinued, a notable 67% discontinued after one or two doses of atezolizumab. Discontinuing therapy after only one or two doses would fall before the median time to response seen in the atezolizumab clinical trial, which was 2.1 months.[2] Thus, these patients discontinued treatment before benefit was expected. The majority

(continued on page 5)

Getting the most from our safety surveillance

ATEZOLIZUMAB UTILIZATION IN UROTHELIAL CARCINOMA- A NATIONAL REVIEW

(continued from page 4)

of treatments were discontinued due to declining functional status and/or disease progression. Most of the deaths during the review were considered unrelated to treatment and appeared attributable to disease progression and disease-related complications. Only one patient discontinued for a therapy-related adverse event (atezolizumab-induced colitis).

The last objective of the review was to examine those who discontinued or died and evaluate if there was any relationship with failure to meet the CFU. Table 3 examines the percentages of patients that discontinued therapy and if a CFU criterion was failed. A comparison to those still receiving therapy was also included in this table, however this column is slightly inflated due to patients who recently initiated therapy. Of those who discontinued or died, 30-40% of patients had an ECOG performance status of 2 or greater or did not meet one of the CFU laboratory parameters.

Discussion

There were a few limitations with this chart review. The most notable being that it was an on-going review and patients who recently started therapy have not yet had enough time on the medication to determine adverse effects or discontinuation. This review also examined all urothelial patients on atezolizumab since FDA approval was obtained (including those patients started on therapy before CFU were established in August 2016), so the 32 patients initiated prior to CFU publication may have been started inappropriately upfront due to the lack of CFU. Also, the chart review was performed by one pharmacist, which could introduce potential bias.

Overall, it appears that most VA facilities are enforcing the prior authorization process to evaluate clinical use. However, few are strictly following the CFU or documenting enough information to support the fulfillment of the CFU. Documentation of a "goals of care" discussion was the most common CFU failure, and ideally, this discussion should be done at initiation of 2nd-line therapy with atezolizumab, as this drug only provides modest improvements in response rate and survival is still poor.[2] If available, palliative care teams can be helpful in assisting with these discussions and managing many of the comorbidities that metastatic bladder cancer patients encounter. A baseline TSH was the only laboratory value often neglected by providers despite this recommendation being in the CFU and the prescribing information.[1,3] Thyroid dysfunction can be managed with drug therapy during treatment; therefore, it should be a standard laboratory value that providers monitor to ensure prompt detection and management of thyroid-related adverse effects. One interesting result of this review was the observation that ECOG performance status is not consistently being documented within the medical record. Performance status also appears to be an important factor for consideration when initiating atezolizumab, as those with ECOG of 1 had a decreased response rate in the clinical trial and those who discontinued therapy in this review had high rates of ECOG of 2 or greater.[2] Therefore, based on this finding, the national PBM has changed the CFU to require an ECOG of 0 or 1 for initiation of atezolizumab. Lastly, the CFU laboratory parameters coincide with the requirements in the atezolizumab clinical trial and appear to be appropriate limits. Lack of adherence to these laboratory parameters may be associated with higher rates of discontinuation, as shown in this chart review.

REFERENCES:

1. Tecentriq [package insert]. Genentech Inc., South San Francisco, CA. April 2017. https://www.gene.com/download/pdf/tecentriq_prescribing.pdf. Accessed April 28, 2017.
2. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016. 387(10031):1909-20. https://doi.org/10.1016/S0140-6736(16)00561-4.
3. Atezolizumab (TECENTRIQ) Prior Authorization-Facility (PA-F) Criteria for Use. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs; August 2016. https://www.pbm.va.gov/
4. Atezolizumab (TECENTRIQ) National Drug Monograph. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs; August 2016. https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs/Atezolizumab_TECENTRIQ_Monograph.pdf

Table 3. Comparison of Discontinuation/Death & Failures to Meet CFU

CFU Criteria	No (%) of Patients Who Discontinued Therapy or Died on Therapy (n=42)	No (%) of Patients Who Discontinued Therapy or Died on Therapy after 1 or 2 doses (n=28)	No (%) of Patients Who are Still Receiving Therapy (n=63)*
Failed to Meet FDA Indication	7 (16.6%)	4 (14.3%)	13 (20.6%)
Documented ECOG ≥ 2	15 (35.7%)	9 (32%)	11 (17.5%)
Inadequate Laboratory Values	13 (30.9%)	12 (42.8%)	11 (17.5%)
Met an Exclusion Criterion	1 (2.3%)	1 (3.57%)	6 (9.5%)
Overall Failed to Meet at least 1 CFU Requirement	35 (83.3%)	24 (85.7%)	52 (82.5%)

*Due to ongoing nature of the review, many of these patients may have just started therapy and only received a few doses
Patients could have failed more than one criterion