ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

August 14, 2019 — New data from 2018 Q4 / 2019 Q1

NEW DRUGS FOR FLU, MIGRAINES

- Severe allergic reactions for a new flu treatment, baloxavir (XOFLUZA)
- Underestimated adverse effects of a new class of products for migraine prevention
- Manufacturer performance in reporting adverse effects of newly approved drugs

Executive Summary

In this issue we examine the emerging safety profiles of four newly approved drugs that address major medical needs: a new antiviral treatment for influenza symptoms and three biological products intended to reduce the number of migraine headaches per month with an entirely new mechanism of action. Postmarket surveillance is most important when drugs are new and when many questions are still unanswered. We also look at manufacturer performance in reporting adverse effects of these four new drugs launched in 2018-2019.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP). We analyze computer excerpts from the Food and Drug Administration Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

The FDA received 334,395 new case reports during 2019 Q1, including 87,119 cases that had a serious or fatal outcome and occurred in the U.S. This was little changed from the preceding quarter, 2018 Q4, when the agency received 327,308 new cases and 78,684 cases of death or serious injury.

in the U.S. Our analysis focuses on those cases most likely to reveal emerging drug risks. While we can identify 1,575 different drug products in the 2019 Q1 data, 390 (24.8%) of those drugs had five or fewer reports in this quarter, too few to help evaluate even a prominent adverse event. Another 160 drugs had 10 or fewer reports.

A New Treatment for the Flu

In October 2018 the FDA approved the first new antiviral treatment for influenza in nearly 20 years, baloxavir marboxil (XOFLUZA). When a single dose was taken within 48 hours of the first symptoms, the drug acted to slow further replication of the virus, leading to earlier alleviation of the classic flu symptoms of fever, cough, sore throat, nasal congestion, and muscle/joint pain. It is manufactured and was primarily developed in Japan by Shionogi, Inc.; it is marketed in the U.S. by Genentech.

The prescribing information and published clinical trial results reported that the flu symptoms were mostly alleviated approximately 26 hours earlier in those treated with baloxavir, in a median of 54 hours compared to 80 hours for those receiving an inactive placebo.

Given that potentially millions of people might be exposed to a new flu treatment, the limited clinical testing for FDA approval left questions unanswered about both benefits and risks. The FDA approved

baloxavir after only 710 patients had been exposed once to the recommended dose in clinical trials. Despite evidence of ethnic differences between the apparent benefits to Japanese and North American patients, the FDA accepted a single Phase 3 trial that enrolled only 113 patients treated with baloxavir in North America, including only 18 African Americans and 32 Hispanics. The sample size was too small to establish whether baloxavir was as beneficial in the North American subset or against the less common strain of influenza B.

Although no adverse effects warranting a warning or precaution were seen in clinical testing, we identified three signals of possible harms in the first quarter of FAERS data. Most important were 50 cases of potentially life-threatening allergic reactions—identified in our data as anaphylactic shock--including 7 deaths. Almost all these cases occurred in Japan. In addition, we observed gastrointestinal symptoms, including colitis (n = 9), blood in the stool (n = 17), vomiting (n = 22), and diarrhea (n = 22). Also seen were signals of serious adverse events in the central nervous system, including abnormal behavior (n = 17), altered consciousness (n = 9), and delirium (n = 5).

This first group of adverse event reports has limitations. The number of cases is relatively small (n = 382), and most are from health professionals in Japan. These reports do not provide information on how frequently these events might occur. The computer excerpts we use lack information about patient history and underlying illness needed for a full evaluation, especially of the cases of anaphylactic shock.

A New Class of Drugs for Migraine Prevention

The 18% of women and 8% of men who are regularly afflicted with migraine headaches were the target patient population for a new class of biological products. The three drugs in this new class were first approved in 2018 with evidence they could reduce the number of migraine headache days per month in many patients. These drugs block the effects of a signaling molecule in the body that, among its many functions, seems to play a role in migraine headaches. The new drugs are:

- Erenumab-aooe (AIMOVIG, Amgen), approved in May 2018. It had 277,400 outpatient prescriptions in 2019 Q1.
- Fremanezumab-vfrm (AJOVY, Teva), approved in September 2018. It had 79,700 prescriptions in the latest quarterly data.
- Galcanezumab-gnlm (EMGALITY, Eli Lilly) and also approved in September 2018. It had 65,300 prescriptions in 2019 Q1.

Although the three drugs have many similarities, our primary analysis focused on erenumab-aooe. It was the first in this new drug class to be approved and had the largest patient population and the most adverse drug event reports. In terms of benefits, all three new drugs reduced the number of migraine headache days by a median of 1-2 days per month compared to placebo in a group of episodic migraine patients then experiencing 8-9 headache days per month. One striking feature of these new products was large variability in their effects. The results ranged from no effect in some patients in reducing migraine days, to others who reported treatment eliminated–or nearly eliminated–migraine headaches. Also, trials showed a substantial placebo effect in patients who did not receive the active drug.

The early adverse event data showed that erenumab-aooe also had adverse effects, some apparently underestimated in its clinical studies. We identified clear signals for constipation, which ranged from cases managed effectively with laxatives to serious events requiring hospitalization and/or discontinuation of treatment. There was also a signal for alopecia (hair loss) and cases of hypersensitivity that ranged from many reports of injection site reactions to less frequently reported cases anaphylactic shock. Muscle and joint pain were also seen both in clinical trials and in the early adverse drug event data.

FDA Adverse Event Reporting System

In evaluating the adverse events for the four new drugs in this report, we observed large differences in the completeness of the reports from the different manufacturers. Given that all four sets of reports came from major drug manufacturers and all were for newly approved brand name drugs, the differences seemed mostly attributable to the companies' postmarket surveillance programs. Our elementary standard of minimally complete was defined as a report with at least age, gender, and one valid adverse event term. Our results:

Table 1. Completeness of FAERS reports for 4 new drugs*

Drug name	Brand	Source	Report total	Pct complete**
Migraine preventives (manufacturer)				
Erenumab	AIMOVIG	Amgen	9,938	59%
Galcanezumab	EMGALITY	Eli Lilly	1,020	20%
Fremanezumab	AJOVY	Teva	457	41%
Migraine preventives (direct to FDA)				
All three		FDA	639	94%
Flu treatment				
Baloxavir	XOFLUZA	Genentech	382	74%

*For 12 months ending March 31, 2019

**Pct (minimally) complete = at least age, gender, 1 adverse event term

Given that more than 90% of all reports to FAERS were prepared by manufacturers in the 12 months ending 2019 Q1, company performance in submitting at least minimally complete reports is central to effective postmarket surveillance. In addition, during the early months of product launch the company interactions with health professionals and consumers should be predictable, allowing for standard protocols to capture essential data.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. While the sheer numbers of case reports have scientific weight, because of variation in reporting rates they reveal little about how frequently the events occur in the broader patient population. While reporting rates vary among drugs, only a small fraction of the adverse events occurring are reported. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

The most basic conclusion about the new flu antiviral baloxavir is that we need to know more about the benefits and risks of this new drug, especially in western or non-Asian ethnic groups. Given a treatment for a disease that affects tens of millions of people every season, it is not clear why the FDA accepted such a small clinical trial data set. The recommended dose had been given to 910 patients and a small number of U.S. minorities, despite evidence of substantial ethnic differences in drug effect. It is now clear that in some patients baloxavir can cause life-threatening allergic reactions. But neither the prescribing information for physicians nor patient information makes any mention of this risk. It also does not provide instructions for

detecting and managing this adverse effect. More needs to be known about possible gastrointestinal and psychiatric side effects.

The new class of drugs for migraine prevention provides its own set of unanswered questions. Here are the first drugs that inhibit calcitonin gene-related peptide (CGRP), a signaling molecule that performs many functions in the circulatory system and elsewhere in the body. It means this drug has many biological effects, only one of which is an effect on migraines. Although the drugs are intended for long-term use, there are no multi-year studies of either long-term benefits or long-term adverse effects. There are at least theoretical risks that these new treatments could cause other health problems. The adverse event data and an early independent study suggest that the likelihood of constipation was underestimated in clinical trials. Reports of hair loss were seen for all three drugs, but this adverse effect was not identified in the prescribing information.

The widely varied performance of drug manufacturers in preparing adverse event reports about newly approved drugs provides still another reason why the FDA should strengthen and modernize its adverse event reporting system. The key guidance and other requirements date back to 2001, before the extensive online transactions of the internet era and other large-scale changes in the practice of medicine and the marketing of drugs. Better performance is clearly feasible: Note that 74% of the reports for baloxavir (mostly from Japan) and 59% of the reports prepared by Amgen for erenumab-aooe were at least minimally complete. And direct reports to the FDA from health professionals and consumers were 94% complete. Problems can be found at both extremes of severity of injury: very low-quality non-serious reports from limited interaction with many consumers, and poor-quality reports of patient deaths where manufacturers report any death whether or not the drug was suspected of contributing to the event. The starting point for an update of the FAERS system should be improving reporting during the critical first years after product launch.

In conclusion, we are concerned about the limited information about adverse drug events that was available prior to FDA approval for two novel kinds of drugs to which large populations may be exposed. The price of making new drugs available as quickly as possible is that millions may be exposed to new drugs about which we don’t know enough to use them wisely and to prevent injury.

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Methods Summary

QuarterWatch monitors the safety of therapeutic drugs and biological products through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (https://www.ismp.org/quarterwatch/methods)

The severity of the reported adverse event is classified as serious under FDA regulations if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life-threatening, or had other medically serious consequences.[2] Cases without these outcomes are classified as non-serious, Only cases reported for the first time in the reporting period were included in this analysis.

In these data, the adverse events reported are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to standardize adverse event reporting in clinical studies and postmarket surveillance.[3] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[4] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. Also, High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine all the terms into 27 categories. The QuarterWatch database was updated in December 2018 to MedDRA version 21.1.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the most recent version of the case report. Product names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology.[5] When cited in the text, tables, or charts, the brand name used for a drug is normally the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release or other formulations. Reports are submitted to the FDA via two basic routes: directly to the FDA through its online portal (6% of reports) and through drug manufacturers (94% of reports), which are required to investigate and report adverse events that they hear about from consumers and health professionals. In QuarterWatch we describe as the *initial reporter* the type of individual (consumer, MD, pharmacist) who was the primary information source for either a direct report, or through a manufacturer.

To identify signals for various adverse events, we also utilize the disproportionality method of Evans[6] to calculate a Proportional Reporting Ratio (PRR). The PRR is similar to the concept of relative risk of the specific adverse event being reported and permits comparison among drugs with notably different total numbers of reports. In this statistical technique, we compare the fraction of a specific kind of adverse event for the suspect drug to the fraction of such events occurring among other comparison drugs in our study period. For example, if reports of vomiting occurred in 12% of all cases of the suspect drug but occurred in only 3% of the cases for the comparison drugs combined, it would produce a PRR of 4. We also calculate the Yates X^2 value for the strength of association and estimate the probability that the difference might have occurred by chance.

The number of outpatient prescriptions in this report was provided by IQVIA, a healthcare information company. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IQVIA includes the following disclaimer:

"The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IQVIA information service called the National Prescription Audit™ for 2019 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IQVIA or any of its affiliated or subsidiary entities."

Results

Reports Overview

The new data for this report consisted of 334,395 new adverse drug events received by the FDA in 2019 Q1 and 327,308 new case reports from 2018 Q4. Two quarters are combined for this report because the FDA made excerpts available more promptly and we chose not to defer analysis of the latest group of quarterly data. We focus most closely on the cases that report serious or fatal adverse events in the U.S. The quarterly totals were 87,119 new cases in 2019 Q1 and 78,684 cases in 2018 Q 4.

For 2019 Q1 we monitored a total 1,575 drugs for this report but found 1,121 drugs with 100 or fewer reports. This large group of drugs accounted for just 3.2% of the drug reports that the FDA received during the quarter. At the other extreme, a small group of the 81 drugs that each accounted for 1,000 or more reports accounted for 55.9% of reports. The unbalanced results are shown in Table 2. The number of reports for a drug are affected by two principal factors: The toxicity of the drug and the extent of drug manufacturer direct contacts with health professionals and consumers. Drug manufacturers are required to report only those adverse events they learn about through these interactions, or when contacted by a patient or provider who complains.

Table 2. Reports per drug, 2019 Q1

Size Group	Drugs	Reports	Pct
1-5 reports	390	915	0.3%
6-10	160	1,202	0.4%
11-50	422	10,571	3.2%
51-100	149	10,699	3.2%
101-500	294	68,327	20.7%
501-1000	79	54,152	16.4%
> 1000	81	184,963	55.9%
Total*	1,575	330,829	

*Excludes 3,566 cases without verified drug names

A New Treatment for the Flu

Our first look at baloxavir marboxil (XOFLUZA), a new antiviral treatment for influenza, identified new serious adverse drug events and raised questions about its limited clinical testing before approval.

Influenza is the most aggressive and successful viral predator of the human species. It combines effective transmission with the ability to mutate rapidly to evade immune, vaccine, and antiviral defenses. In the 2018-2019 season, influenza infected an estimated 37-43 million people in the U.S., or more than 1 out of 10 adults and children.[7] The severity of a flu infection varies by the viral strain, year, and patient. It typically ranges from a moderate fever and cough to a potentially life-threatening infection requiring hospitalization. In the past season about 1 in 1,000 infected with flu died.

The nation's primary defense against influenza is vaccination. In the past season, approximately 45% of the population got a flu shot.[8] Vaccine effectiveness varies by age and the circulating flu strain.[9] In the last season, an estimated 43% of those with the flu had also gotten a vaccination.[9] The best result was 61% effectiveness in children 17 and younger. The poorest result was 8% effectiveness in adults 50 years age and older with the most common circulating strain of influenza A (H1N1).

Antiviral drugs are a major treatment. Oseltamivir (TAMIFLU) is the most widely used. An analysis of 20 clinical trials showed it alleviated symptoms about 17 hours earlier in adults and 29 hours faster in children.[10] But given oseltamivir's modest benefit, a new antiviral for the flu with a new mechanism of action could provide a valuable approach to combating our most prevalent viral adversary.

Enter a New Antiviral

Baloxavir marboxil (XOFLUZA), approved in October 2018, was the first new FDA-approved antiviral treatment for the flu in nearly 20 years.[11] It was developed in Japan by Shionogi, Inc. and is marketed in

the U.S. by Genentech (a Roche subsidiary). It had one immediate advantage over oseltamivir – it is taken in tablet form as a single dose just once within 48 hours of flu onset rather than twice a day for five days. It was potentially useful in having a different mechanism of action, blocking a different step in viral replication. In terms of benefits, the FDA affirmed a claim that treatment with baloxavir shorted the duration of the flu from a median of 80 hours to 54 hours (a difference of 26 hours).[12]

Both the benefits and risks of baloxavir are challenging to assess because of the limited pre-approval testing that the FDA accepted:

- Physicians in clinical practice may not see as good results as those reported in the trials and prescribing information. Unlike most clinical practice, in the trial the patients with flu symptoms were tested before treatment to confirm they had the flu and not some other respiratory infection.[13] [14]

- The trials excluded those over age 65—a population group with a greatly reduced response to flu vaccines.[13] (Note the 8% vaccine effectiveness reported above for those over 50.)

- The FDA told the Japanese sponsor it was not necessary to do the customary two Phase 3 trials, even though the single Phase 3 trial included only 113 patients who were North Americans and received the active drug. Both U.S. and Japanese regulators observed ethnic differences in response to treatment, with better results in Japanese people.

- Trials were so small that no benefits could be measured in important subgroups, including the North Americans (non-Asians) and those with influenza B. Gauging the extent of baloxavir's benefit in those subgroups would take a larger clinical study. No treatment benefit was established on two other measures: the quality of life and time to return to work.[13,14]

- Identification of less common side effects was limited because only 710 patients were exposed to the recommended dose in phase 2-3 clinical studies. This is a small safety database to support a drug to which millions could be exposed.

On the other hand, there was substantial evidence that baloxavir had potentially useful antiviral activity. The results were better in those proven to have the flu, excluding those with some other respiratory illnesses. Its inhibiting effect on viral replication could be seen in both human and laboratory studies. In a comparative trial, the results looked approximately similar to the effects of oseltamivir, which has been studied for many years.

Baloxavir Safety Profile

The reports for baloxavir shared several characteristics. For the 12-month period, we identified 382 case reports naming baloxavir as the primary suspect drug, all but 14 with a serious or fatal outcome. Although our reporting period spans 12 months, 94% of the cases were reported in the three months of 2019—the first complete quarter after approval of baloxavir in October 2018. Two other features were notable: 92% of the cases originated from Japan, where the drug was approved in early 2018, and 96% of the reports were from health professionals, mainly physicians. Patient exposure was vastly greater in Japan, where approximately 6 million patients were exposed during the 2018-2019 flu season, according to the company. In the U.S. an estimated 93,000 prescriptions were dispensed in the first quarter of 2019, according to IQVIA. Selected adverse drug events from the U.S. and Japan are shown in Table 3.

Table 3. Baloxavir selected reported adverse drug events, 12 months ending 2019 Q1		
Adverse event	Cases	PRR*
Hypersensitivity		
Anaphylactic shock (SMQ)	50	3.3
Severe cutaneous (SMQ)	14	1.7
Central nervous system		
Abnormal behavior (PT)	17	39.1
Altered consciousness (PT)	9	38.2
Delirium (PT)	5	15.0
Loss of consciousness (PT)	15	12.2
Seizure (PT)	13	8.6
Gastrointestinal		
Melena (PT)	17	62.2
Colitis ischemic (PT)	9	158.2
Vomiting (PT)	22	4.8
Diarrhea (PT)	22	3.2
*PRR= Proportional Reporting Ratio compared to all other drugs		
MedDRA: SMQ = Standardized MedDRA Query; PT = Preferred Term		

Of particular concern were the 50 reported cases of a life-threatening allergic reaction, anaphylactic shock. Typical symptoms include rapidly dropping blood pressure, flushing, swollen airways that may block breathing, and swelling elsewhere, called angioedema. Without prompt intervention with an injection of epinephrine, anaphylactic shock can be fatal. Seven of these reported cases were fatal; however, the computer excerpts lacked the detail needed for systematic evaluation of the possible causal role of the drug. However, all of the anaphylactic shock cases were reported by medical professionals, with 74% from MDs. Further investigation is needed to better characterize the cases, identify high-risk patients, and understand when first symptoms occur.

The central nervous system adverse drug events resemble those described in FDA-required warnings for oseltamivir: delirium and abnormal behavior, primarily among pediatric patients and with rapid onset.

In addition, we saw a few cases indicating possible harm to the kidneys, including rhabdomyolysis (n = 17), or acute kidney injury (n = 6), or renal impairment (n = 4).

We gave less weight to adverse events often associated with or complications of influenza itself, including pneumonia (n = 41), pyrexia (n = 4), influenza (n = 6), or headache (n = 4).

A Company Perspective

We shared our preliminary data with Genentech, the company licensed to market baloxavir in the U.S. in partnership with the Japanese manufacturer, Shionogi. Genentech also maintained a global safety database. The company told us it had also seen a safety signal for hypersensitivity, including anaphylactic reactions, and were “closely monitoring these events.” However, with regard to both GI tract and CNS events, the company said, “To date we have not identified these events as safety signals.” It also noted that some other serious events were likely complications of influenza in vulnerable patients or else a result of secondary bacterial infections.

Conclusions

The first full calendar quarter of adverse event data following the approval of baloxavir provides clear signals for potentially important adverse drug events that were not detected in the limited pre-approval testing. It is of particular importance to learn more about the life-threatening and possibly fatal hypersensitivity reactions that were reported after a single exposure. In addition, the benefits of baloxavir remain unproven in North Americans and against influenza B. Potential adverse effects in the GI tract and CNS require further study.

A New Class of Drugs for Migraine Prevention

Migraine headache impairs the quality of life of millions of adults for decades on end. The symptoms include a throbbing headache that can trigger nausea, vomiting, and sensitivity to light and sound and typically last from 4 to 72 hours. It afflicts approximately 18% of women and 8% of men. Clinically, migraines are categorized as episodic (fewer than 15 days a month) or chronic (15 days or more), with approximately 8% of the group with the more severe chronic variant.[15]

Medications to prevent migraines have modest effects in most patients. Onabotulinumtoxina (BOTOX) reduces the frequency of chronic migraines by an average of less than 2 days a month.[16] Topiramate reduced the frequency of episodic migraines from approximately 5 days a month to 4 days, after adjusting for placebo effect.[17] Such is the impact of migraines on the quality of life that a survey would likely produce a large majority saying more effective prevention is an important unmet medical need.

A New Approach

A new class of drugs for migraine prevention was born with the idea to target a highly prevalent signaling molecule called calcitonin gene-related peptide (CGRP), which has many different biological roles, notably in the vascular system. A lengthy technical review noted that despite being known for 30 years, “the role of CGRP remains unclear.”[18] It became a molecular drug target because CGRP was found to be released during migraine headaches, and infusion of CGRP was found to trigger some migraines.[19] Starting in 2018, the FDA began approving the first migraine preventive biological products that blocked CGRP or its receptors. They are erenumab-aooe (AIMOVIG),[20] galcanezumab-gnlm (EMGALITY),[21] and fremanezumab-vfrm (AJOVY).[22] All three are genetically engineered monoclonal antibodies injected monthly.

Erenumab-aooe, the first CGRP inhibitor to win FDA approval, is the primary focus of this profile. Its effects in preventing migraines were, for many patients, similar to previously approved treatments.[23] In the largest pivotal trial in episodic migraines, the number of migraine days each month was reduced from 8 days to 5 days at the recommended 70 mg dose. But behind these summary results were two other instructive details. The placebo effect was substantial, with migraines reduced from 8 days to 6 in the untreated placebo patients. Thus, compared to placebo, treatment reduced the number of headache days by approximately one day per month. By another measure–cumulative headache hours–small differences with placebo (65 hours vs 55 hours) were not statistically significant.[23]

In addition, the results varied substantially among patients. Approximately 15% of treated patients experienced no reduction at the recommended dose. At the other extreme, approximately 20% of treated patients and 7% of placebo patients experienced a 75%-100% reduction. Variable effects in different patients was also a feature of other migraine preventive treatments. Similar benefits were reported for erenumab-aooe in episodic migraine patients who had failed 2-4 previous treatments.[24] Given a clinical trial patient population that had lived with migraines an average of 20 years, those experiencing the larger changes would surely welcome the results. But those with only one or fewer episodes per month might seek alternative treatments.

The Safety Profile

The central safety question about CGRP inhibitors was similar to that asked of many new drugs that introduce a novel mechanism of action. This molecular target might play a role in migraines, but it has numerous other roles in the body. It is also a major vasodilator in the coronary arteries, [25] has an effect on GI motility, and a likely role in wound healing. And as noted above, all the roles that CGRP might play in the body were simply not understood. One headache specialist listed 10 other possible effects of CGRP inhibition, both positive and negative.[26] However, the clinical trials of erenumab-aooe revealed only a few frequent adverse drug events. Three adverse events occurred 2% more frequently in the treatment group compared to placebo: constipation, cramps/muscle spasms, and injection site reactions.[23]

The Adverse Event Results

The most striking feature of the erenumab-aooe adverse event data was the sheer number of case reports in our totals for the 12 months ending with 2019 Q1. We identified 10,508 case reports, including 1,458 with a serious outcome. The drug ranked first in number of reports for 33 new drugs approved in 2018 and accounted for more than twice as many cases as the other 32 new drugs combined. Part but not all of the large report total might be explained by a successful product launch. By the first quarter of 2019, erenumab-aooe (a monthly injection) was used by approximately 93,000 patients a month, according to dispensed outpatient prescription data from IQVIA. As might be expected from the gender imbalance for migraines, 85% of the reports were about women. The initial reporters were divided between consumers (43%) and health professionals (57%), mostly physicians. Such large numbers of reports carry the scientific weight of sheer numbers, but because they are voluntary, they are not useful in estimating how often these events might be occurring. Nevertheless, the volume of reports still implies that large numbers of patients were experiencing adverse drug events–mostly non-serious–and were reporting them both directly to the FDA and to Amgen. These are the safety issues raised in this first large group of FAERS reports:

Gastrointestinal Effects

Constipation was the most frequent adverse effect reported (n = 1,169 PRR = 16.7, $p < 0.01$). It was the also the most frequently identified in the subset of cases with a serious outcome (n = 187). This is a plausible effect of inhibiting CGRP, which affects GI motility. It was seen in the clinical trials, but in these studies the apparent incidence rate was very low: 1% at the 70 mg dose. It is well known, however, that the incidence of drug adverse events can be underestimated unless they are specifically asked about during patient visits.[27] When most patients were specifically asked about constipation in a small retrospective study (n = 220), 20% reported this problem.[28] The large number of adverse event reports of constipation is more consistent with the 20% incidence rate when most patients were asked about it, than the 1% in the clinical trials setting. The severity of the constipation varied in the clinical trials, the adverse event data, and the retrospective study. Many were managed with laxatives, while others led to hospitalization or treatment discontinuation.

Hair Loss

We observed a clear signal for alopecia (n = 376 PRR = 2.56, $p < 0.01$) in the adverse event reports, even though it was seen in only 2 patients in the clinical trials and not identified in the retrospective study. In addition, 64 (17%) of the alopecia adverse event cases were classified as serious. We suspect that hair loss was underestimated in the other two studies because patients were not asked about it. Alopecia was also prominent in the subset of cases (n = 107) that were directly reported to the FDA rather than through the manufacturer.

Cramps/Muscle Spasms

Muscle disorders were seen prominently in the adverse event data, also reported in the clinical trials and in the retrospective study. The specific events reported were muscle spasms (n = 263), arthralgia (n = 173), and myalgia or muscle pain (n = 121). Unless these symptoms were specifically queried in a clinical

study, they also could have been underestimated. Muscle disorders were reported in approximately 1% in clinical trials and 3% in the retrospective study.

Hypersensitivity

The adverse event data confirm mostly injection site reactions seen in clinical studies, notably injection site erythema (n = 139), swelling (109), rash (123), and pruritus (107). However, both the manufacturer prescribing information and the QuarterWatch data also identified potentially life-threatening cases of anaphylactic shock (n = 35).

Other Adverse Events

We also observed psychiatric side effects, most notably depression (n = 309). Given a disorder prevalent in the middle-aged female population, depression warrants additional study and information to assess a possible relationship. There were large numbers complaints that the drug was ineffective (n = 2,086). This was expected, given the clinical trial results showing that erenumab-aooe had limited or no benefit in 15% of preselected patients and only modest reductions in headache days in many others.

Cardiac Risk

Possible adverse effects in the cardiovascular system were a concern when FDA reviewers were evaluating erenumab-aooe for approval.[23] This occurred because the CGRP molecular target of erenumab-aooe was found in the coronary arteries and was a potent vasodilator. However, no warnings were required based on the clinical studies. We identified a possible signal for cardiac arrhythmia (n = 225), notably palpitations (86), heart rate increase (60), and loss of consciousness (27), but also cardiac arrest (5) and sudden death (1).

Two Other CGRP drugs

In September 2018 the FDA approved two more migraine preventives with a similar mechanism of action, fremanezumab-vfrm (492 adverse event reports), and galcanezumab-gnlm (1,054 reports). With a later launch and smaller patient population, there were insufficient data to compare the safety profiles of this new class of drugs. However, the two new drugs also shared reports of hypersensitivity, constipation, and alopecia.

Conclusion

The emerging safety profile of erenumab-aooe shows that it is likely that adverse effects of this migraine preventive were underestimated in the clinical trials. Early data show many of these specific adverse events are also being reported for the other two new CGRP products but could be more or less severe and frequent. With a new mechanism of action for these drugs, the long-term effects of blocking all the functions of a highly prevalent signaling molecule remain undetermined.

FDA Adverse Event Reporting System

The first few years after the launch of a new therapeutic drug are regarded as a critical period for postmarket surveillance through adverse drug event reporting and other methods. Some regulators (notably in Japan and the United Kingdom) require various forms of enhanced surveillance during the early period after approval. However, the FDA does not have such requirements unless specified individually in a Risk Evaluation and Mitigation Strategy (REMS) plan.

The reason early postmarket surveillance is most likely to identify new, more frequent, or more severe adverse effects is linked to the weaknesses in clinical trials in identifying adverse effects: 1) Trials are too small or too short to capture less frequent effects; 2) Vulnerable patient populations are excluded; 3) Unlike

treatment benefits, treatment adverse effects are not systematically collected with a checklist or other instrument; 4) Duration and severity of adverse drug events are rarely captured.

For this reason we evaluated the completeness of the adverse event reports for the four newly approved drugs that were the focus of this QuarterWatch report. Our findings, reprinted from the Executive Summary:

Table 1. Completeness of FAERS reports for 4 new drugs*

Drug name	Brand	Source	Report total	Pct complete**
Migraine preventives (manufacturer)				
Erenumab	AIMOVIG	Amgen	9,938	59%
Galcanezumab	EMGALITY	Eli Lilly	1,020	20%
Fremanezumab	AJOVY	Teva	457	41%
Migraine preventives (direct to FDA)				
All three		FDA	639	94%
Flu treatment				
Baloxavir	XOFLUZA	Genentech	382	74%

*For 12 months ending March 31, 2019

**Pct (minimally) complete = at least age, gender, 1 adverse event term

Our standard of minimally complete is elementary: The ability to evaluate a suspected adverse drug event is limited without knowing the age, gender, and at least some description of the adverse event. (Simply reporting “hospitalization” or “death” doesn’t provide useful information for managing a drug risk.)

The data for the four drugs in this report support several conclusions: The problem lies with drug manufacturers, since 94% of reports submitted directly to the FDA from health professionals and consumers were minimally complete. The best results were for baloxavir (74% minimally complete) but almost all came from Japan rather than the U.S. The stronger performance of Amgen reporting on erenumab-aooe (59% minimally complete) shows that better accuracy and completeness is feasible and realistic. Not only was Amgen’s reporting the best, the company submitted far more reports than for the other three drugs, indicating the company had a system capable of collecting a large report volume without loss of quality.

Conclusion

These data identify a useful and manageable place for the FDA to start in updating its adverse event reporting system requirements for manufacturers: It should develop requirements and protocols for the first few years after a drug is launched, when high-quality data collection is most important and relevant. In addition, product launch is a large and complex organizational effort, but with elaborately planned and largely predictable interactions with both health professionals and consumers. There is no reason why those product launch plans should not include enhanced and accurate postmarket surveillance such as occurs in Japan.

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