ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

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FOCUS ON NEWLY APPROVED DRUGS

Safety profile of a new generation of cholesterol-lowering drugs
Complaints that a new psoriasis treatment could aggravate the condition
Eye inflammation linked to a novel immunosuppressant for atopic dermatitis

Executive Summary

This issue focuses on key findings from the adverse drug event reports for 97 drugs and biological products first approved by the U.S. Food and Drug Administration (FDA) from 2015 to 2017. We examine the emerging safety profile of a new generation of cholesterol-lowering drugs, called PCSK9 inhibitors, that reduce low-density lipoprotein (LDL) by 45%-60%. Signals are examined for the two newest treatments for psoriasis that target forms of interleukin-17A, a component of the complex immune response. Another immunosuppressant–targeting a different form of interleukin–was approved to treat atopic dermatitis but is linked to conjunctivitis and other eye disorders.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP). We analyze computer excerpts from the FDA 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 safety profiles of the most recently approved drugs are of increased importance in an era in which U.S. policy and law emphasize rapid approval of new drugs and defer many studies until later. To get a close look at the newest drugs we examined the most recent 12 months of adverse drug event reports for the new therapeutic drugs and biological products approved in calendar years 2015, 2016, and 2017. For the 12 months ending June 30, 2018, we identified 130,028 adverse event reports for the newly approved drugs, or 9.6% of all reports for all drug products. Among these reports, 49,976 (38%) described events with a serious or fatal outcome. Compared to all other drugs, the newly approved drugs had a smaller share of serious events (38% vs. 56%), with greater numbers of non-serious events, likely reflecting more contact with consumers and health professionals because of the educational and marketing activities attending the introduction of new products.

Signals for Key New Products

The five new products that are examined in depth in this issue share common features. Unlike a majority of therapeutic drugs, they are biological products–genetically engineered monoclonal antibodies administered through periodic self-injections. Three of the five (and numerous others not reviewed here) are immunosuppressant drugs. And like many of the newest drugs, their costs (and out-of-pocket costs) are much higher than for older generic drugs, which account for 90% of outpatient prescriptions.

Another feature is that the five drugs target widely prevalent diseases, according to estimates from disease advocacy groups and epidemiologic studies. Each of these conditions–serious cardiovascular disease, psoriasis, and atopic dermatitis–affect 6 to 8 million U.S. adults.

Drugs That Lower LDL Cholesterol

Evolocumab (Repatha). This biological product provides a new adjunctive or alternative treatment for one of the most widely used preventive therapies in all of medicine: cholesterol-lowering statins to prevent new and recurrent heart attacks and other cardiovascular events. Evolocumab achieves larger reductions in LDL than statins–about 45%-60%–by inhibiting a lipid regulatory enzyme called PCSK9 (proprotein convertase subtilisin/kexin type 9**)**. Despite these substantial effects on LDL, evolocumab lowered the risk of cardiovascular events by only 15% in its only large clinical trial in selected patients with a history of serious cardiovascular disease.

We identified more adverse drug event reports for evolocumab than for any other drug in our sample, a total of 24,551 cases, including 3,699 cases with a serious or fatal outcome. The most frequently reported adverse events–accounting for thousands of reports–were muscle and joint pain, a symptom also reported for the statins and thought to result from damage to skeletal muscle. The reports were also distinctive in that they described pain or other problems involving the self-injectors, which are used once or twice a month. However, this group of reports did not include any cases of the most severe form of muscle harm, called rhabdomyolysis, which occurs when compromised muscle cells release proteins that overwhelm the kidneys.

Alirocumab (Praluent). This was the first approved PCSK9 inhibitor, and it initially received a restrictive indication for use only in a smaller patient population with genetic abnormalities that lead to exceptionally elevated cholesterol levels. A new clinical trial just published in November 2018 reported benefits in a broader patient population with cardiovascular disease.

Partly because of a much smaller patient population, alirocumab accounted for only 2,930 case reports in our sample, with 493 indicating a serious or fatal outcome. Most prominent were reports of muscle and skeletal pain. Compared to evolocumab, it had a smaller share of reports of complications or pain with the injection.

Immunosuppressants for Psoriasis

Secukinumab (Cosentyx). This injectable biological product joined an already crowded field of newer treatments for psoriasis. It is a genetically engineered monoclonal antibody that inhibits interleukin-17A, a chemical messenger of the immune system. In 12-week clinical trials, 51%-68% of secukinumab-treated patients were judged to be clear or almost clear of psoriasis, compared to 2%-3% of those on placebo.

This product was the primary suspect in 15,500 adverse event reports, second only to evolocumab among the newer drug products. Despite these clinical trial results, we identified an unexpectedly large number of reports that the treatment was ineffective or aggravated the psoriasis. The signal was seen by several measures: a large number of cases, a greater percentage of cases than for most other drugs, and a strong statistical association.

Ixekizumab (Taltz). This is another interleukin-17A inhibitor with clinical trial results showing 81%-82% clear or almost clear of symptoms at 12 weeks. It had many fewer reports overall, 2,339 cases, with the largest number describing injection site reactions. There were also reports confirming clinical trial signals that, while it made one autoimmune disorder better, in some cases it made another worse. We identified 50 reported cases of various forms of colitis, including inflammatory bowel disease and Crohn's disease.

Atopic Dermatitis Treatment

Dupilumab (Dupixent). This is another monoclonal antibody targeting a different chemical messenger in the immune system, interleukin-4. Its clinical trial results showed that at 16 weeks, 36%-39% of treated patients were clear or almost clear of atopic dermatitis, compared to 9%-12% of placebo patients.

The adverse event reports were notable for the number and variety of reports indicating eye-related adverse effects. Reported events include conjunctivitis, eye swelling, irritation, and discharges; inflammation of the eyelids, and tear-duct disorders. An FDA analysis of the safety data from the clinical trials indicated that eye issues might affect 35.7% of patients over one year's treatment.

Prescription Volume Growth

Dispensed prescription volume data in Table 1 show that despite target populations numbering in many millions, the market uptake of these new products has been relatively modest. These data suggest that by the second quarter of 2018 around 135,000-150,000 patients were using one of these new products. Uptake likely was limited by the requirement for self-injection and high costs. List prices ranged from approximately $124,000 per year for ixekizumab to $7,000 per year for evolocumab (following a 50% price cut in November 2018). Actual costs are usually negotiated with providers, and out-of-pocket costs may vary widely.

Table 1. Dispensed prescriptions for five new biological products*

	----Total Rx per Quarter----					
Product	17Q3	17Q4	18Q1	18Q2		Total
LDL-cholesterol						
Evolocumab	77,935	90,198	99,287	122,670		390,090
Alirocumab	53,933	60,663	59,599	70,164		244,359
Psoriasis						
Secukinumab	72,986	86,555	90,628	105,320		355,489
Ixekizumab	29,556	33,194	35,777	46,087		144,614
Atopic dermatitis						
Dulipumab	25,046	39,201	49,124	62,476		175,847

*Data from IQVIA National Prescription Audit.

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 those 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 newest biological products that are reviewed in this issue illustrate an important truth about many new drugs: While the investigators are interested in only the main effect of the drug on a disease target, drugs have many effects throughout the body. This unfortunate dimension of pharmaceutical reality is demonstrated with several of the drugs analyzed for this issue. Notably, dupilumab had a positive effect on the disease target of atopic dermatitis, but a substantial negative effect on the eyes. Ixekizumab produced substantial benefit in the autoimmune disorder of psoriasis but was also linked to harmful effects on autoimmune disorders of the digestive tract such as colitis or inflammatory bowel disease.

A second important perspective on these new drug treatments is simply missing from these data and prior clinical testing. The long-term risks of these potent immunosuppressants are not yet known. Several potential harms from immunosuppression–such as serious infection and cancer risk–have not been adequately studied beyond 52 weeks.

For dupilumab, we believe that the FDA and manufacturer should review and strengthen the warnings for eye disorders. Current warnings in prescribing information not only understate the findings in these new adverse event data, but also risks seen in the clinical trials. The information for patients briefly mentions eye problems.

Evolocumab and alirocumab without question have dramatic effects in lowering LDL. But despite these large effects on a biomarker and substantial alteration of normal lipid metabolism, the harms from the PCSK9 drugs appeared similar to those already known for the statins. The clinical trials also revealed smaller than expected benefits in reducing cardiovascular risks, and no measurable benefits for cardiovascular deaths. However, these trials were conducted in a highly select patient population already tolerant of statins and involved achieving low LDL levels not previously studied.

The primary safety concerns about the new psoriasis treatments–secukinumab and ixekizumab–involve better measurement of the long-term extent to which these treatments increase the risks of serious infection, other autoimmune disorders, and cancer. With two new members of a generation of potent new treatments for psoriasis, comparisons between their safety profiles are needed.

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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 describe adverse events in clinical studies and post-marketing reports.[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), which also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 27 categories. The QuarterWatch database was updated in November 2017 to MedDRA version 20.1.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the most recent version of the case report. The drug 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 of drugs used 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 and other formulations.

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 hypotension occurred in 12% of all cases of the suspect drug but occurred in only 3% of the cases for the comparison drugs, it would produce a PRR of 4. We also calculate the Yates X^2 value for the comparison and estimate the probability that the difference might have occurred by chance.

To help interpret the adverse events reported, we assess the patient exposure to drugs based on dispensed outpatient prescription data provided by IQVIA. 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 2018 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IQVIA or any of its affiliated or subsidiary entities."

In this issue we selected the most recent revision all new adverse drug event reports that identified as primary suspect drug one of the new therapeutic drugs approved in 2015, 2016, or 2017. We excluded diagnostic and imaging agents as well as eight drugs for rare diseases with no reports in our 12-month study period ending June 30, 2018.

Results

Reports Overview

For the 12 months ending June 30, 2018, the FDA received 130,028 adverse event reports identifying drugs approved for the first time in 2015, 2016, or 2017. The new drug case reports amounted to 9.6% of the 1,361,116 reports for all drugs received in the 12-month period. The new drug reports included 9,638 (7%) patient deaths and 17,085 cases (13%) requiring hospitalization, but the majority of cases (80,052, 62%) described events that were coded as non-serious. Adverse events classified as non-serious included fatigue, nausea, drug ineffective, and headache.

We identified reports in widely varying numbers for 97 of the 105 new drugs approved in the three-year period. Just two of the drugs examined in this report–evolocumab and secukinumab–accounted for 30.8% of all the reports for the 97 new drugs with reports. The number of reports is typically influenced by three factors: 1) The number of patients exposed; 2) Toxic properties of the drug; 3) The event reporting rate, which can be influenced by publicity and manufacturer marketing. Drugs with these disproportionately large report totals typically combine all three factors.

At the lower extreme lies a group of drugs with few or no adverse event reports. This included 16 drugs each with fewer than 50 case reports and 8 drugs without any adverse event cases yet reported. The unusual distribution of case reports is shown in Table 2.

Table 2. Adverse event reports for recently approved drugs

Total reports	Number of drugs
0	8
1-49	16
50- 499	37
500-4999	40
5000 +	4
Total approved	105

*For year ending June 30, 2018

Drugs That Lower LDL Cholesterol

The FDA approval of two new biological products that reduce low-density lipoprotein (LDL) cholesterol by 45%-60% opened a new chapter in treatments to lower the risk of heart attack and stroke. The first to win approval was Regeneron/Sanofi-Aventis's alirocumab (Praluent), approved in July 2015. It was followed a month later by evolocumab (Repatha) from Amgen. Their ability to lower LDL cholesterol was substantially greater than the familiar statins; however, they were a genetically engineered product that required monthly or bimonthly self-injections; list price costs were vastly higher–now at least $7,000 a year compared to approximately $120 a year for generic statins. However, recently published large trials in high-risk patients produced much weaker results than seen in earlier trials of statins. Although conducted in highly selected patient populations, they reduced cardiovascular events by only 14%-15% and had no effect on cardiovascular deaths.[7] [8]

A Massively Used Intervention

The lowering of LDL cholesterol to prevent heart attack and stroke is one of the largest therapeutic undertakings in the U.S. In 2016, more than 42 million adults reported filling 218 million prescriptions for one of the statins.* The treated population was older: 45% of all adults age 65 and older and 20% of those age 45-64 reported they were taking a stain. An estimated 80% of those taking statins said they had not previously had coronary heart disease. This is the primary prevention group with a lower risk of a heart attack or stroke.

* Exposures were calculated from the publicly-available Medical Expenditure Panel Survey for 2016.

The benefits of statins have been studied in some of the largest, longest clinical trials conducted in human subjects, lasting many years and enrolling tens of thousands of patients. One of the largest trials in primary prevention illustrates both the strengths and limitations of this intervention. A 2003 European study measured cardiovascular outcomes in 10,305 patients treated with atorvastatin (Lipitor) or placebo for 3.3 years.[9] None had a history of heart attack or stroke, but all had hypertension. The treatment reduced LDL cholesterol by 35% and reduced selected cardiovascular events by 36%. However, the absolute patient benefit was small because 95% of an untreated comparison group did not experience a cardiovascular event either. Each year an event was likely prevented in 4 out of every 1,000 patients treated (0.3%). Over the 3.3-year trial, cardiovascular events were likely prevented in 1.1% of treated patients. The trial reported no significant benefit on total mortality, in those with diabetes, or among women.

Despite consistently positive results in clinical trials, controversies have arisen over safety. The evidence is substantial that statin treatment can damage or destroy skeletal muscle cells. According to less systematic estimates, myopathy and other forms of muscle and joint damage occur in an estimated 5%-10% in clinical practice,[10] [11] especially in higher-dose patients.[12] Some of those who studied the issue note that both trials and physicians underestimate the problems.[13] In an often-cited study, 207 patients experiencing muscle problems they thought were related to statin treatment reported this to their physician. Only 29% of physicians acknowledged that statins might be a possible cause and 47% denied that the drugs could even have this adverse effect.[14] Also, some later clinical trials with enhanced monitoring of blood sugar reported an increased risk of diabetes.[15] Other dissenters have published elaborate re-analyses of clinical trials to advance the proposition that the statins' beneficial effects are likely to accrue from some other mechanism beside reducing LDL.[16] Finally, the advent of alternative treatments has redefined "adverse events" into "statin intolerance", a category that included additional patients where statin cholesterol-lowering was substantially smaller than expected. In some estimates 25% of patients were described as having "statin intolerance."[17]

Enter a New Kind of LDL-Lowering Product

A natural human enzyme called PCSK9 (proprotein convertase subtilisin/kexin type 9) operates as a braking system that limits the ability of liver and other cells to absorb needed LDL from the circulating blood. Cells use LDL to obtain cholesterol for cell membranes and have receptors to trigger the process of absorbing the circulating LDL. The two new biological products target the PCSK9 braking system, freeing liver cells to absorb much greater quantities of LDL. These Y-shaped monoclonal antibodies bind to the PCSK9 enzymes, disabling them. The effects on circulating levels of LDL are larger than any previously available agent—lowering LDL cholesterol levels by 45% to 60%.[18] [19] There is a crude similarity in mechanism between the PCSK9 inhibitors and the statins in that both lower LDL primarily through inducing the liver to absorb more circulating lipid particles.

Limited Effects on Cardiovascular Events

The unanswered question at the time of FDA approval in 2015 was whether this massive lowering of LDL would translate into the clinical benefit of fewer cardiovascular deaths, heart attacks, and strokes, and if so by how much. The primary FDA-authorized initial medical use was limited to special populations with genetic or other defects that resulted in abnormally high LDL levels. But optimists predicted that the PCSK9s would substantially outperform statins and reduce cardiovascular events by 50%.[14]

The first large clinical trial to assess cardiovascular benefit (rather than lipid levels) was published in March 2017 and compared evolocumab when added to statins in 27,564 selected high risk-patients.[7] Despite a 59% drop in LDL, the PCSK9 reduced the risk of a cardiovascular event by only 15%. More disappointing yet, the PCSK9 had no measurable effect on cardiovascular or total mortality. Treatment prevented non-fatal heart attacks and strokes in 1.4% of the patients treated for 3.3 years. Another suggestion that clinical benefits were small came from a 52-week trial of evolocumab with only 900 patients. It did not detect any clinical benefit and had an unfavorable trend.[20] As this report was being prepared, the

results of a similar large trial of alirocumab were published and showed very similar results: a 15% reduction in cardiovascular endpoint benefiting 1.6% of 9,462 treated for 2.2 years.[19].

Interpreting these results was challenging because of the design features of both trials. All the patients were also treated with statins, and most were taking several other effective cardiovascular drugs. Patients who had not tolerated or responded to statins were excluded. LDL had already been lowered substantially below levels achieved previous statin treatment, and the effects of this additional LDL lowering had not been previously studied in large at-risk patient populations.[21] This limited the trials' ability to assess either the benefits or the harms.

The safety data in the evolocumab cardiovascular trial were particularly difficult to interpret. Both treated and comparison group patients were taking high doses of statins, which are active in similar LDL pathways in the liver. The PCSK9 inhibitor group had muscle-related events in 5% patients, compared to 4.8% of the mostly high-intensity statin patients. Another evolocumab trial used a run-in period that would have eliminated patients with early problems taking statins.[20] The results of the largest evolocumab trial showed that 5% experienced a muscle-related event, and 0.7% had laboratory evidence of muscle damage or loss. In addition, 3% reported an allergic reaction and 2.1% an injection site reaction.

The FAERS Adverse Event Profiles

Adverse drug events provide an additional perspective on safety. Key features of the safety profile of the two PCSK9 inhibitors are shown in Table 3. As the table indicates, for both drugs the most frequently reported adverse event was musculoskeletal pains (21% to 24%), most often myalgia, similar to what is reported for statins. Another large category was injection site reactions. There were some reports of memory loss.

The most notable difference between the two new products is in the overall number of reports: Evolocumab reports totaled 24,551 vs. just 2,930 for alirocumab, an 8-fold difference. Part of the difference is accounted for by prescription volume – evolocumab had nearly twice as many prescriptions as alirocumab. However, even after adjusting for exposure, more than a 4-fold difference in report volume remains. Limiting the analysis to the most serious events does not change the difference.

Evolocumab accrued an unexpectedly large number of reports by almost any measure. It had so many adverse event reports that it ranked No. 1 among all newly approved drugs in our sample and by itself accounted for 19% of the entire report total. This was more than 50 times higher than the typical drug in our group of 97 new products–which accounted for a median of 393 reports. A third influence on report totals could be aggressive direct-to-patient and physician promotion. The evolocumab web site (https://www.repatha.com/) offers six different kinds of patient support programs. We could not assess the manufacturer's interactions with prescribing physicians–who need to train patients to use the injectors.

Nevertheless, this leads to the conclusion that patients did not like taking this expensive injectable drug for a medical condition that had no symptoms and when the alternative was an inexpensive once-a-day tablet. The injections were sometimes painful. Patients experienced muscle pains similar to but possibly worse than those seen in many patients starting on higher-dose statins.

Table 3. Adverse event reports for two new PCSK9 inhibitors				
	Evolocumab		Alirocumab	
	Number	(%)	Number	(%)
Total reports*	24,551		2,930	
Serious/fatal outcome	**3,699**	**(15)**	**493**	**(17)**
Musculoskeletal (SOC)	**5,162**	**(21)**	**689**	**(24)**
Arthralgia	935	(4)	132	(5)
Back pain	1,523	(6)	65	(2)
Muscle spasms	843	(3)	150	(5)
Muscular weakness	269	(1)	45	(2)
Myalgia	1,305	(5)	257	(9)
Other terms	287	(1)	40	(1)
Memory loss (HLT)	**393**	**(2)**	**48**	**(2)**
Medication error (SMQ)	**4,602**	**(19)**	**442**	**(15)**
Injection site reactions (HLT)	**4,629**	**(19)**	**396**	**(14)**
Bruising	1,249	(5)	106	(4)
Hemorrhage	619	(3)	59	(2)
Pain	2,404	(10)	115	(4)
Other terms	357	(1)	116	(4)
Unique cases for 12 months ending June 30, 2018. One case can include several terms.				
SOC = System Organ Class; HLT = High Level Term; SMQ = Standardized MedDRA Query.				

Other than report volume, the two PCSK9 inhibitors show a similar safety profile in Table 3. (Note similar percentages for the different types of adverse events.) However, the safety profile of both drugs was also notable for the absence of signals of more severe safety problems. We could identify no cases of rhabdomyolysis, which is the result of the most severe form of muscle damage, and no signal for kidney disorders that might be caused by destruction of muscle cells. Given that the liver was the target organ for this intervention, it was also notable that there were few cases indicating harm and many fewer than expected given the volume of adverse drug event reports.

Conclusions

With both substantial adverse event reporting and the results of two large cardiovascular trials now available, the data show the clinical benefits were modest and harms difficult to assess because comparison groups were also taking high-dose statins. With a benefit rate of 4 per thousand per year in high-risk patients, and a list price cost of around $7,000 annually, the cost per event prevented will be high.

Immunosuppressants for Psoriasis

Plaque psoriasis was the primary target disorder for two new immunosuppressant biological products, secukinumab (Cosentyx) from Novartis and ixekizumab (Taltz) from Eli Lilly. Both are genetically engineered monoclonal antibodies that inhibit the same chemical messenger in the immune system, interleukin 17A (IL-17A). Both products are administered by injection every four weeks after a more intensive series of loading doses. In clinical trials of secukinumab, 51%-68% of treated patients were clear or almost clear of psoriasis plaques at 12 weeks; for ixekizumab 81%-83% were clear or almost clear.[22] [23] The early adverse drug event data produced signals that both products might make another autoimmune disorder worse, namely colitis or irritable bowel syndrome. In addition, secukinumab accounted for more than the expected number of reports that the treatment was ineffective or aggravated the condition.

A New Immune Target

These two new products join an already substantial group of immunosuppressant biological products for psoriasis that target different elements of the immune system. Five other biologics block tumor-necrosis factor (TNF) alpha; another product targets IL-12/23; two other products target only IL-23. Still another drug inhibits an enzyme involved in regulating cellular energy production. These drugs are variously approved for other auto-immune disorders, notably rheumatoid arthritis, Crohn's disease, and ulcerative colitis. While this group of drugs has demonstrated substantial benefits for these auto-immune disorders that can seriously impair the quality of life, they also have substantial toxicity. Variously, the immunosuppressants increase the risk of invasive fungal and serious bacterial infections and cancer. They also have been linked to heart failure, neurological reaction, hypersensitivity, and abnormalities in blood cells. Most of these adverse effects occur because the treatments disable a major component of a complex, interacting immune system.

The Skin Condition

Psoriasis involves development of reddened patches or plaques of skin that can itch, scale off, or bleed. It is caused by an immune disorder that leads to abnormal growth of skin cells. If the process occurs in joints, it is called psoriatic arthritis, and most of the drugs are approved for both forms. The condition waxes and wanes over time, and the affected areas range from a few patches of skin to 10% or more of the body surface area. An estimated 7.5 million persons in the US may have this disorder.[24]

The Adverse Event Profiles

We identified four substantial differences in the adverse drug event profiles of the two agents, even though the therapeutic target, IL-17A, was similar for the two products. Notable was the large difference in the volume of reports over 12 months ending June 30, 2018: secukinumab with 15,500 reports compared to just 2,339 for ixekizumab. The difference also extended to serious reports (4,337 for secukinumab vs. 403 for ixekizumab). This difference is partly explained by the 2.4-fold greater patient exposure, based on dispensed prescription data in Table 1. Additional differences in overall report totals may be explained by how these expensive treatments are marketed to physicians and consumers—who need insurance authorization and training in using the self-injectors. However, we observed specific adverse reactions where notable differences between the two products persist even after adjusting for differences in reporting rates and report volume.

The key findings are shown in Table 4, and the most revealing columns are labeled "PRR" or proportional reporting ratio–a measure of disproportionality, which compares the number of adverse events reported for the target drug with those expected based on all other drugs in the 12-month period. For injection site reactions, it shows that secukinumab had 1.8 times the number expected and ixekizumab had 15.6 times the number expected.

Table 4. Selected adverse event reports for two new IL-17A inhibitors					
	Secukinumab			Ixekizumab	
	Number	PRR*		Number	PRR*
Total reports**	15,500			2,339	
Serious/fatal outcome	4,337			403	
Injection site reactions (HLT)	603	1.8		630	15.6
Colitis (HLT)	198	2.5		50	5.1
Drug efficacy issues	2,908	2.0		137	0.6
Drug ineffective (PT)	2,321	2.6		115	0.7
Condition aggravated (PT)	338	2.1		21	0.6
Drug effect incomplete (PT)	313	2.7		3	NA
* PRR = proportional reporting ratio. PRR < 1 = fewer than expected.					
** Unique cases for year ending June 30, 2018. Case can include 1 or more terms.					

Colitis: A Signal for Both Products

We observed an unexpectedly large number of reports indicating various form of colitis—inflammation of the digestive system. The signal was stronger for ixekizumab with 5.1 times the number of reports expected, compared to 2.5 times the number of expected reports for secukinumab. Colitis is primarily an autoimmune disorder, and these data illustrate that these immunosuppressant treatments make one condition better (i.e. psoriasis) but, apparently, make another worse.

Secukinumab and Efficacy

The leading complaints about secukinumab was that the product either was ineffective against psoriasis or aggravated the condition. The signal was a strong one by several measures: A large number of reports; more reports than expected, even after adjusting for the large report volume; a strong statistical association unlikely to have occurred by chance, and a difference with a comparator drug used in a similar population. That said, it is likely that patients starting a treatment for a visible skin condition, using an expensive new drug administered by injection, might well be more critical and more carefully scrutinize results than, for example, those taking an oral pain or arthritis medication. Further, in the systematic evaluations of clinical trials, approximately 2 out of 3 patients improved substantially.

Ixekizumab and Injection Site Reactions

The most frequent adverse events for ixekizumab were 630 cases of injection site reactions. The reactions included one or more of these terms: redness (n = 232), pain (n = 275), swelling (n = 157), as well as injection site hypersensitivity reactions, including urticaria (hives), rash, or injection site mass. We observed a numerically similar number of injection site reactions (n = 603) for secukinumab but it was a much smaller share of total adverse reactions.

Conclusions

While we detected differences between the two new IL-17A inhibitor products, we did not compare their safety profiles to the other approved agents. Given the notable toxicities of many of these other treatments, further systematic comparisons might reveal a favorable safety profile for one or both of these new agents. For example, in these early short-term data we did not detect a signal for increased cancer risk, as we have previously reported for ustekinumab (Stelara).[25]

Atopic Dermatitis Treatment

The FDA approved dupilumab (Dupixent) for moderate-to-severe atopic dermatitis in adults in March of 2017. After 16 weeks of bi-weekly injections, the adults with an itchy rash and/or oozing skin blisters were rated as clear or almost clear in 36%-39% of treated patients compared with 9%-12% of those receiving an inactive placebo.[26] However, in clinical trials and new adverse drug event reports, treatment also resulted in unexpectedly large number of reports of eye inflammation and other ocular adverse effects.

A Novel Pathway for Intervention

The effects of this new biological product are also a classic illustration of the central features of drug development and approval: Drugs have many effects even though the sponsors are usually interested in only one–in this case, a specific benefit in reducing the symptoms of atopic dermatitis. But to achieve these benefits, the product targets a chemical messenger in a complex, interacting immune system with many effects.

Dupilumab was another example of a generation of biological products where development has proceeded backwards from what an outsider might expect. Rather than a breakthrough in understanding atopic dermatitis, the breakthrough was a genetically engineered product that targeted a specific component of the immune system–then tested to see if it would work in various autoimmune disorders. The human immune system has 26 related chemical messengers–numbered interleukin 1 to 26–with a role in the immune response. Other products have other immune system targets, including interleukins 6, 7, 12, and 23. Other biological products inhibit TNF-alfa and various interferons.

Dupilumab inhibits interleukin-4 (IL-4), which also inhibits another messenger, interleukin-13. The sponsor, Regeneron Pharmaceuticals, was also testing or planning to test the drug for asthma, nasal polyps, pulmonary disease, and food allergies.[27] (In October 2018 it won approval for use in certain forms of asthma.)

These facts also illustrate the importance of clinical trials not only to prove that a new product has the benefits the sponsors hope for, but also to obtain information about its many other effects, some harmful. In the case of dupilumab, clinical trials exposed one notable but unexpected safety issue. Inhibiting IL-4 had positive effects on atopic dermatitis but apparently opened the door to other disorders.

The Skin Disorder

Atopic dermatitis is a skin disorder with symptoms of itchy, reddened skin and oozing blisters. It is estimated that 10% of children and 3% of adults have the condition.[28] The FDA required clinical testing in adults before launching studies in children; as a result, approval was based on adult studies and initially limited to that population.

A Safety Issue Emerges

In clinical trials, at 16 weeks of treatment, 11% of patients reported possible symptoms of an eye inflammation or infection called conjunctivitis, an event that was broadly defined.[29] Another 3% had possible inflammation of the cornea. The limited longer-term data shows that at one year of treatment 35.7% would experience treatment-emergent conjunctivitis, compared to 12.7% taking placebo.[29]

The FAERS data

The first year of post-market surveillance confirmed and extended the safety signal already identified in pre-market testing. Overall, we identified 3,778 adverse event reports for dupilumab, far more than the median of 393 cases for newly approved drugs. However, only 10% of dupilumab reports were coded as having a serious or fatal outcome. The reports were of higher-than-average quality, with 62% including age, gender, and at least one specific adverse event term.

However, 1,131 (30%) of the adverse event reports identified eye problems, or 7.2 times the number expected compared to all other drugs.

Eye Symptoms

The most frequently reported adverse drug event for dupilumab was conjunctivitis (n = 383). Also frequent were various forms of eye inflammation or redness (n = 217), and itching eyes (n = 244) and irritation (n = 138). Case reports described both dry eye (n = 165) and excessive tears (n = 104). However, the manufacturer or direct reporter coded only 10% of the eye reports as medically serious, about the same as for all adverse event reports for this product. Our data lacked sufficient detail to assess the severity and persistence of the adverse effects on the eye.

Other Adverse Events

Other reported events included urticaria (n = 90) and oral herpes (n = 76). In addition, case reports described various symptoms related to the injection, notably pain (n = 147) and swelling (n = 58).

Prescribing and Patient Information

The prescribing information for dupilumab includes a warning section that, in our view, does not adequately describe the extent of the risk of eye problems that can be expected to occur in approximately 1 in 3 patients over a year's treatment. The prescribing information states that conjunctivitis and keratitis occurred "more frequently" in treated patients but does not communicate the large numbers. The only incidence numbers provided were for the rarest event, keratitis, with less than 1% at 16 weeks and 4% at 52 weeks. The patient package insert [26] also provides only a limited mention of eye problems as the second-listed "common" side effects.

Conclusion

The signal for eye problems linked to dupilumab was strong by several measures. The sheer number of reports–more than 1,000–was large. The MedDRA broad category of reported ocular infections (n = 593) occurred 24 times more frequently than would be expected when adjusted for the number of reports. The statistical association was strong and had a less than 0.01 probability of occurring by chance. And while we could not assess severity, the percentage of patients expected to experience eye problems (around 38%) over one year's time is roughly similar to the percentage of those expected to show the most improvement in atopic dermatitis.

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