Advancing Patient Safety Innovation in Rheumatology (ASPIRE)

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Purpose: The overarching aim of the Advancing Safety Process Innovation in Rheumatology (ASPIRE) project was to characterize ambulatory medication safety events related to high-risk immunosuppressive drugs and to use this data to develop electronic quality measures (eMeasures) to monitor and improve care.

Scope: In this project, an interdisciplinary team of rheumatologists, epidemiologists, clinical informaticists, and measurement experts studied ambulatory patient safety for people using high-risk drugs such as biologics and immunosuppressants. Data from epidemiologic investigations were then used to develop quality measurement tools to improve patient safety.

Methods: Using electronic health record (EHR) data from two large health systems in California as well as data from a national rheumatology registry, we analyzed the frequency and determinants of errors and adverse events for patients prescribed immunosuppressive drugs (Aim 1). For high-impact or high-frequency safety errors, we developed and validated eMeasures, or quality measures designed for the EHR (Aim 2). We submitted these measures for national endorsement and implemented them broadly through a national registry.

Results: The project generated new epidemiological evidence of patient safety risks and adverse events for drugs that are increasingly used by those with autoimmune diseases. Two eMeasures, related to screening for latent infections and hydroxychloroquine dosing, were developed and are now part of the Centers for Medicare and Medicaid Services Quality Payment Program. Additionally, these patient safety eMeasures were successfully implemented nationally in RISE, a Qualified Clinical Data Registry used for federal reporting and practice improvement by US rheumatologists.

Key Words: quality measures, immunomodulating drugs, patient safety

I. PURPOSE

The ASPIRE research program aimed to characterize ambulatory medication safety events and to use this data to develop prototype, health IT-enabled quality measures to monitor and improve care for people using high-risk drugs like biologics and immunosuppressants. We also sought to use epidemiological data to develop and implement "eMeasures" to monitor these risks. eMeasures use automatically extracted EHR information in order to track patient safety errors and to allow providers to benchmark their performance on specific patient safety issues. The proposed Aims were:

Aim 1: To analyze the frequency and determinants of errors and adverse events for patients prescribed high-risk medications and to characterize disparities in these across race/ethnicity, socioeconomic status, and medical complexity. Using data from two large health systems in California, as well as national data from a rheumatology registry, we studied how often clinical practice deviates from national patient safety guidelines for high-risk immunosuppressive medications and how often this results in harm to patients.

Aim 2: To develop and validate prototype eMeasures to monitor and address high-impact or high-frequency patient safety events related to medications. We used eMeasurement standards, including the Quality Data Model (QDM) and other structured coded terminologies, to develop, specify, and test prototype eMeasures.

II. SCOPE

Background

Patients using high-risk medications in the ambulatory settings face significant safety risks. A majority of US healthcare is delivered in the ambulatory setting, and most clinical adverse events originate in ambulatory care. Among adverse events, medication errors are of particular concern because they are common, costly, and potentially avoidable. Over 4.2 billion prescriptions were dispensed in the US in 2018, with almost half of Americans taking at least one prescription drug. Despite the frequency of ambulatory patient safety errors and adverse events, most efforts to study patient safety continue to focus on hospitalized patients. The ASPIRE reach program sought to address this gap by studying ambulatory patient safety errors for drugs commonly used to treat individuals with autoimmune diseases.

Over the past two decades, as chronic disease management has become more complex due to the increased number of medications available and fractured care across multiple providers, safety risks have grown, particularly for the millions of Americans requiring immunosuppression. Use of new immunosuppressive medications has expanded at an unprecedented pace; this class of medications now accounts for over a third of drug spending in the United States.[1] Currently, there are over 300 biologic drugs on the market, with new agents, including biosimilars, becoming available in record numbers each year. People with immune-mediated diseases, such as rheumatoid arthritis, psoriatic arthritis, lupus, and inflammatory bowel disease, therefore face increasing safety risks. Unfortunately, health system innovations to ensure safe prescribing, monitoring, and use of these medications have not kept pace, and reports of preventable adverse events are increasing.[2,3] Examples include fulminant hepatic failure from hepatitis B in patients taking B-cell--depleting therapies without appropriate preventive measures,[4,5] reactivation of latent tuberculosis in those taking anti-TNF therapies,[6,7] serious zoster infections among many biologic drugs users,[8,9] and birth defects from teratogenic

immunosuppressive medications in women not receiving appropriate counseling or contraception.[10-13] Despite these reports, carefully done, well-powered epidemiologic studies to quantify these risks across the population are sparse.

Context

The rapid pace of drug development and quickly expanding indications for immunosuppressive medications necessitate ongoing investment in monitoring and addressing patient safety risks. Administrative claims data are sometimes less well suited to the task of monitoring patient safety, given lags in data availability and lack of clinical detail to allow for adjudication of safety errors or adverse events. Manual chart review studies remain important but are resource intensive and costly. Therefore, investment in the use of electronic health record (EHR) data to supplement these other types of data used to monitor patient safety is important. Adequately utilized, EHR data has the potential to permit detection of new classes of errors and to simultaneously determine which patients are at greatest risk. Moreover, because patient safety process errors such as (1) failure to institute preventive practices that reduce adverse medication events, (2) lack of safety monitoring for patients using high-risk immunosuppressive medications, or (3) absence of systems to manage abnormal results from medication toxicity monitoring are all potentially measurable through an EHR, each patient receiving a class of medication associated with any of these processes can be assessed for receipt of recommended care.

The ASPIRE project was designed to study the epidemiology of patient safety errors using a systematic, EHR-based approach. In turn, this approach served as the foundation for the development of quality measures based on EHR data, or eMeasures.

Settings

The epidemiologic investigations of patient safety were conducted at the University of California, San Francisco (UCSF) by an interdisciplinary team of rheumatologists, epidemiologists, clinical informaticists, and measurement experts. We used data from two large health systems associated with the university as well as data from a national rheumatology registry called RISE. The UCSF Health system is a tertiary referral center for Northern California. San Francisco General Hospital is the safety net hospital for the city and serves publicly insured, uninsured, or underinsured individuals. RISE is national registry that collects complete EHR data from approximately one third of the US rheumatology workforce. These local and national data were the primary sources of information for the analyses performed.

Quality measures were developed by the study team at UCSF and tested in collaboration with staff and leaders at the American College of Rheumatology (ACR) using the RISE registry. This partnership was critical to the success of the project, as ACR was in a position to ensure that the measures had maximal impact through implementation in rheumatology practices around the country through the RISE registry.

Participants

Because ASPIRE used secondary data generated from EHRs, no individual patient participation was required. Patient data were derived from San Francisco General Hospital, which has almost 600,000 outpatient visits and uses eClinicalWorks as its ambulatory EHR vendor, and from UCSF Medical Center, which has almost one million outpatient visits per year and uses Epic as its EHR vendor.

Data from these EHRs were queried to generate the specific populations used to study patient safety errors and adverse events.

For the RISE registry, we analyzed de-identified EHR records from over 300 US rheumatology practices, which included two million individual patients around the United States. The procedures for using data from the local health systems and for the RISE registry were approved by the Institutional Review Board at UCSF.

Incidence/Prevalence

Generating population-based estimates of incidence and prevalence was not part of this study. However, in the results section below we outline the proportions of patients found to have safety errors or adverse events associated with specific immunosuppressive drugs in the data sources we examined.

III. METHODS

Study Design

For Aim 1, we used EHR-based data for all patients receiving high-risk immunosuppressive medications. Eligibility criteria included having at least two face-to-face ambulatory encounters within 365 days before or after the index prescription (in order to collect information on covariates) and evidence of a prescription of at least one high-risk immunosuppressive medication. Evidence of a prescription could include addition of ≥30-day supply to a medication list with an included start date or evidence of at least one ambulatory administration of an infusible medication.

We followed subjects until death, until the end of the study period, or until 90 days after the high-risk medication was stopped, as indicated by its discontinuation from the medication list, whichever came first. If patients were prescribed more than one high-risk immunosuppressive medication concurrently or at different times during the study period, they contributed more than one observation to the analysis. We accounted for repeated measures of the same patient in our statistical analysis.

For Aim 2, we assessed the validity, reliability, and feasibility of prototype eMeasures. eMeasure concepts were specified using the Quality Data Model and standard coding terminologies. These procedures are outlined in more detail below.

Data Sources/Collection

In order to identify medication-related errors and adverse events among ambulatory patients on high-risk immunosuppressive medications, we examined three sources of data:

- Electronic health records from an urban safety net health system (San Francisco General Hospital and Community Health Network). San Francisco General Hospital has almost 600,000 outpatient visits and used eClinicalWorks as its ambulatory EHR vendor during the study period. All EHR data fields were available for analysis, including demographics, diagnosis grouper codes, problem lists, medications, laboratory studies, procedures, and clinical encounter notes.
- Electronic health record from a university center (UCSF Health System). UCSF Medical Center has almost one million outpatient visits per year and uses Epic as its EHR vendor. All

EHR data fields were available for analysis, including demographics, diagnosis grouper codes, problem lists, medications, laboratory studies, procedures, and clinical encounter notes.

- National RISE registry. The RISE registry draws information from the EHRs of over 300 US rheumatology practices and >1,000 clinicians. Since its inception in 2014, RISE has collected information on more than two million patients. EHR data from rheumatology practices continuously flow into RISE. All EHR data fields were available for analysis, including demographics, diagnosis codes, problem lists, medications, laboratory studies, procedures, and clinical encounter notes.

Interventions

There were no interventions.

Measures

For Aim 1, in which we examined the epidemiology of patient safety errors and adverse events, we used Reason's classic framework to identify and classify both latent and active errors,[14] examining errors such as failures in preventive practices that reduce adverse medication events and failures in safety monitoring for patients using high-risk immunosuppressive medications. Failures in preventive practices that are known to reduce adverse events included failures to determine, document, or follow up on results of tests prior to medication initiation and failure to adequately implement prophylactic measures. For example, post-marketing surveillance data have suggested that rituximab can result in fulminant liver failure among patients with active or subclinical hepatitis B infection.[4,5,15] As a result, guidelines recommend universal screening for hepatitis B for patients who plan to begin CD20-depleting therapies such as rituximab.[16] Thus, we examined process failures in which patients did not have hepatitis B status determined, or, if status was determined to be positive, the provider did not act on this information (by not giving prophylactic hepatitis B treatment prior to rituximab).

For Aim 2, we used a multi-step approach to develop quality measures designed for EHR use in areas with high-severity or high-frequency patient safety errors. eMeasure concepts were chosen because they reflected scientific evidence and had clear safety gaps, had auditable actions, were under the control of providers and health systems, and were feasible and meaningful in practice. eMeasure concepts developed by our team were submitted to the ACR's Quality Measures subcommittee to ensure that they had face validity with rheumatologists.

Two eMeasures were electronically specified using standard procedures, including using the Quality Data Model (QDM). We specified all possible code sets linked to QDM elements, including ICD9, ICD10, LOINC, SNOMED-CT, CPT, HCPCS, and RxNorm. With the full list of possible codes, our investigators worked independently in pairs to review the codes associated with each QDM element, assessing their clinical appropriateness for inclusion; differences were adjudicated through discussion. eMeasures were then assessed for feasibility, accurate data capture, and validity of individual data elements. Testing occurred using the RISE registry's data infrastructure.

Limitations

The main limitation of the studies performed relate to the use of EHR data. Methods in using EHR data for epidemiologic research and for quality measurement are still evolving. For

example, clinicians may not perform medication reconciliation regularly, so medication lists may be inaccurate or out of date. Second, rare adverse events are challenging to accurately identify. For several aspects of this project, we therefore used manual chart review to supplement information that was extracted from the EHR. Third, some important patient safety errors are not amenable to EHR-based quality measurement. We therefore focused on areas for which reliable information from EHRs could be obtained to construct meaningful and actionable eMeasures.

IV. RESULTS

Principal Findings for Aim 1

In a series of studies, we examined safety errors related to screening for active or latent infections prior to immunosuppression.

- Hepatitis B virus (HBV) reactivation in the setting of rituximab use is a potentially fatal but preventable adverse event. We were able to complete and publish a comprehensive study that examined the epidemiology of process errors and adverse events across two large health systems related to HBV screening (*Schmajuk G, Tonner C, Trupin L, Li J, Sarkar U, Ludwig D, Shiboski S, Sirota M, Dudley RA, Murray S, Yazdany J. Using health-system-wide data to understand hepatitis B virus prophylaxis and reactivation outcomes in patients receiving rituximab. Medicine (Baltimore). 2017 Mar;96(13):e6528*). The study found significant gaps in patient safety, with frequent process errors, as well as several serious adverse events. We included 926 patients from a university and 132 patients from a safety net health system. Sixty-one percent of patients from the university had adequate screening for HBV compared with 90% from the safety net. Among patients at risk for reactivation based on results of HBV testing, 66% and 92% received antiviral prophylaxis at the university and safety net, respectively.

- Hydroxychloroquine is an immunomodulating medication that is commonly used to treat a variety of rheumatic diseases. Recent studies demonstrate that ocular toxicity from the medication is more common than previously thought. Because ocular toxicity increases if patients receive higher than recommended doses, we examined medical errors related to dosing using EHR data. We constructed a longitudinal, retrospective cohort of patients with hydroxychloroquine prescriptions (1,681 patients with 3,490 prescribing events) between 2012-2016. We measured drug dosing patterns relative to American Academy of Ophthalmology guidelines (<6.5 mg/kg and <5.0 mg/kg) over time and examined sociodemographic, clinical, and health system factors associated with receiving higher than recommended doses of hydroxychloroquine. We found that almost one third of patients are dosed above guideline recommendations and that those with low body weight were at highest risk for inappropriate dosing (*Gianfrancesco MA, Schmajuk G, Haserodt S, Trupin L, Izadi Z, Jafri K, Shiboski S, Sirota M, Dudley RA, Yazdany J. Hydroxychloroquine dosing in immune-mediated diseases: implications for patient safety. Rheumatol Int. 2017 Oct;37(10):1611-1618*).

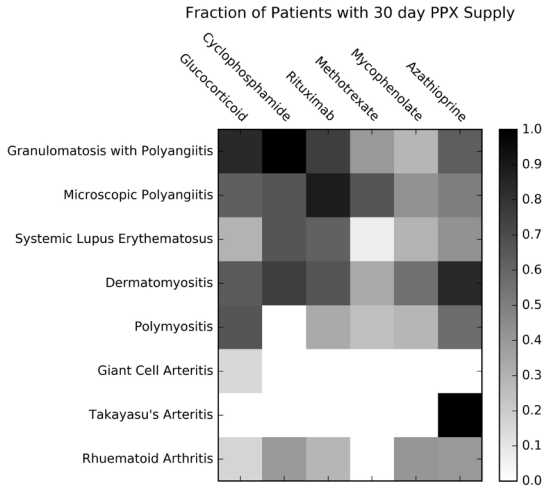
- Using local health system data, we examined performance on patient safety measures such as screening for hepatitis B virus (HBV), hepatitis C virus (HCV), and latent tuberculosis infections (LTBI) for new users of a broad group of immunosuppressive medications. Among 2027 new users of high-risk drugs, only 42% of patients were screened for HBV; 33%, for HCV; and 62%, for LTBI. These gaps in care were observed across all specialties examined, including rheumatology, gastroenterology, and dermatology (*Patterson S, Schmajuk G,*

Evans M, Aggarwal I, Izadi Z, Gianfrancesco M, Yazdany J. Gaps in Ambulatory Patient Safety for Immunosuppressive Specialty Medications. Jt Comm J Qual Patient Saf. 2019 May;45(5):348-357).

- To extend this work to a national dataset, we used data from the American College of Rheumatology's RISE registry to examine a range of immunosuppressant drugs that increase the risk of HBV, HCV, and TB reactivation. We developed quality measures to identify pretreatment safety screening labs in new users of biologic or targeted synthetic immunosuppressive drugs in the registry. We included 26,802 patients across 213 rheumatology practices. Overall, only 45% and 41% of patients had documented HBV or HCV screening, respectively, and 30% had TB screening in the year prior to drug start. This study suggests that there are significant gaps in documentation of key safety measures across rheumatology practices nationwide.

In additional studies, we examined specific adverse events related to immunosuppressive drug use. In ambulatory care, clinical decisions that affect patient safety are often complex, and understanding gaps in care requires a detailed examination of practice patterns.

- Prescribing antimicrobial prophylaxis for pneumocystis pneumonia to appropriate patients is important, given that this infection can be fatal in immunocompromised individuals. To understand patient safety events and errors related to this area, we used EHR data to examine antimicrobial prescribing patterns for patients receiving immunosuppression as well as adverse events (e.g., allergies and serious side effects) related to the antimicrobial prophylaxis. In this analysis, we followed 316 patients for approximately 23 months. Overall, 124 (39%) of patients received prophylactic antibiotics for pneumocystis. At least 25% of patients with the highest-risk conditions (e.g., vasculitis) or highest-risk immunosuppressants (e.g., cyclophosphamide) did not receive pneumocystis prophylaxis. We found no cases of pneumocystis infection over 640 patient-years of follow up, including among those not receiving prophylaxis, and an overall incidence rate of ADEs of 2.2% per patient-year. These surprising results suggested that the adverse event rate from antimicrobial prophylaxis was far greater than the infection the prophylaxis is used to protect against. Although we had initially embarked on this project to identify patient safety errors in antimicrobial prophylaxis for immunosuppressing drugs, we instead concluded that there is inadequate evidence to pursue quality measures in this area (*Schmajuk G, Jafri K, Evans M, Shiboski S, Gianfrancesco M, Izadi Z, Patterson SL, Aggarwal I, Sarkar U, Dudley RA, Yazdany J. Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Semin Arthritis Rheum. 2019 Jun;48(6):1087-1092*).



- This was further confirmed in our analysis of national hospitalization data, which showed that pneumocystis infections have fallen considerably among patients with systemic lupus over time (*Murray SG, Schmajuk G, Trupin L, Gensler L, Katz PP, Yelin EH, Gansky SA, Yazdany J. National Lupus Hospitalization Trends Reveal Rising Rates of Herpes Zoster and Declines in Pneumocystis Pneumonia. PLoS One. 2016 Jan 5;11(1):e0144918*).

Together, these studies allowed us to identify and prioritize patient safety errors related to immunosuppressive drugs identified through EHR data. This work laid the foundation for developing new EHR-based quality measures to monitor and address these gaps in patient safety.

Principal Findings for Aim 2

In partnership with the American College of Rheumatology, we led the development of national infrastructure to create EHR-based ambulatory patient safety quality measures (*Yazdany J, Myslinski R, Miller A, Francisco M, Desai S, Schmajuk G, Lacaille D, Barber CE, Orozco C, Bunyard M, Bergman MJ, Passo M, Matteson EL, Olson R, Silverman S, Warren R, Nola K, Robbins M. Methods for Developing the American College of Rheumatology's Electronic Clinical Quality Measures. Arthritis Care Res (Hoboken). 2016 Oct;68(10):1402-9*). Through the ASPIRE research program, we developed two patient safety EHR-based quality measures, or eMeasures.

First, quantifying process errors and significant variations in performance in Aim 1 allowed us to develop an eMeasure to address HBV screening. We specified the measure using the Quality Data Model, worked with clinical informaticists to develop code sets for the measure, assessed face validity through a consensus process administered by the American College of Rheumatology's Quality Measures subcommittee, and tested the measure's validity and reliability. This testing was used as the basis for a submission to CMS to include this measure in the Quality Payment Program. CMS approved the measure for inclusion in the 2020 and 2021 Merit-based Incentive Payment System (MIPS).[17] We have also worked with the American College of Rheumatology to implement the measure in the RISE registry since 2019. Over 300 rheumatology practices participating in RISE are now able to benchmark their performance on this measure through the registry's web-based dashboard.

Second, using these same procedures, we developed an eMeasure related to appropriate hydroxychloroquine dosing, which aims to reduce visual loss from this drug. CMS approved the measure for inclusion in the 2020 and 2021 MIPS program.[17] We have also implemented this measure in the RISE registry since 2019.

Finally, our research group worked with the American College of Rheumatology to develop an updated version of a measure related to screening for latent tuberculosis prior to starting biologic immunosuppressive therapies. The new measure builds on a previous measure that was limited to just rheumatoid arthritis; we revised the measure to include *all* biologic users, regardless of indication. We also updated the measure to include new synthetic and biologic drugs with safety signals regarding TB reactivation. The updated measure has been implemented in the RISE registry as well as in the MIPS program. This work illustrates the need for continued patient safety surveillance to update measures, harmonize them across specialties, and ensure their clinical applicability.

Outcomes

The ASPIRE project has highlighted major gaps in patient safety for those with immune-mediated diseases in the United States. Key outcomes of the project include quantifying gaps in patient safety, using this data to develop and test patient safety eMeasures, and, importantly, implementing these measures in the US healthcare system by deployment in a national registry and introduction into CMS payment programs.

Discussion

Biologic and novel immunomodulating therapies have reached the market in record numbers in recent years, but systems to safely deliver and monitor these drugs in the ambulatory setting were underdeveloped. Biologic drugs account for 37% of total prescription drug spending in the US, representing $125 billion in spending in 2018.[18] Given that millions of Americans currently take biologic and other immunosuppressive drugs, research to identify areas with the greatest patient safety risks is an important public health investment. The ASPIRE project has generated epidemiologic evidence regarding patient safety for immune-mediated diseases. Moreover, the project team has developed validated, scalable eMeasures to drive quality improvement.

A unique aspect of the ASPIRE research program has been moving ambulatory safety research beyond evidence generation to creating novel infrastructure for national improvements in patient safety. For example, the research program generated data on gaps in screening for latent infections prior to the initiation of immunosuppressive drugs; developed eMeasures to allow for broad, EHR-based tracking of this patient safety error; achieved national endorsement for relevant measures on this topic through CMS payment programs; and then, importantly, implemented these measures broadly across rheumatology practices through an EHR-based national registry. Practices around the country now have real-time access to their performance on quality measures and to national benchmarks, filling key information needs to drive local quality improvement.

Conclusions, Significance and Implications

The use of biologic and novel synthetic immunosuppressive drugs will continue to rapidly expand in the coming years. Looking ahead, it will be important to develop and maintain systems that can monitor and address gaps in ambulatory patient safety, particularly for new high-risk medications for which clinical workflows to avoid adverse events are underdeveloped. The ASPIRE research program has created a framework for generating data on patient safety related to these drugs using EHR data and for developing eMeasures to track patient safety in clinical practice. Moreover, the research program was successful in national dissemination of patient safety eMeasures to frontline clinicians through implementation in a national registry that provides regular audit and feedback.

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