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Gaps in Ambulatory Patient Safety for Immunosuppressive Specialty Medications

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Abstract

Objectives: With new specialty drugs such as biologics available in record numbers, people with immune-mediated diseases face increasing safety risks. However, comprehensive assessments of patient safety for these new specialty drugs are lacking. We examined performance on key patient safety measures, such as screening for latent tuberculosis (LTBI), hepatitis B virus (HBV), and hepatitis C virus (HCV), for new users of a broad group of specialty medications.

Methods: Data were extracted via EHR data warehouses of a large, university health system using structured queries, and extensive chart review was performed to confirm measure elements. We included all new users of immunosuppressive specialty drugs between 2013– 2017. We assessed screening for LTBI, HBV, and HCV from 12 months before through 60 days after medication initiation, and calculated performance on a composite measure that required screening for all 3 infections. Multivariable logistic regression was used to assess differences in screening across specialties, adjusting for patient race, sex, age, and comorbidities.

Results: Among 2,027 patients, the most common drugs prescribed were adalimumab (32%), etanercept (24%), infliximab (19%), and ustekinumab (9%). Overall, 62% of patients were screened for LTBI, 42% for HBV, 33% for HCV. Only 26% of patients were screened appropriately for all 3 infections. Screening patterns differed significantly according to treating specialty.

Conclusions: We found gaps in ambulatory safety for patients treated with immunosuppressive specialty drugs for diverse inflammatory conditions across all relevant treating specialties. More robust safety protocols are urgently needed to prevent serious patient safety events in this high-risk population.

Specialty drugs such as biologic agents and tofacitinib are important new tools in the treatment of inflammatory conditions of the joint, skin, and gut, particularly for patients with disease refractory to conventional therapies.[1–4] While these medications are generally well tolerated, most confer an increased risk of preventable adverse events. Although specific screening procedures are recommended to prevent adverse events, including life-threatening infections, and to assist in appropriate patient selection prior to starting treatment,[5] few studies have examined adherence to these patient safety procedures for the rapidly growing number of individuals using these specialty drugs in the ambulatory setting.

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The primary safety concern with the use of biologic drugs is increased risk of life threatening infections, including tuberculosis and hepatitis. The estimated risk varies depending on the infection and the specific drug, host factors such as comorbidities, and concomitant use of other immunosuppressing medications.[6–12] For example, tumor necrosis factor inhibitor therapy increases the risk of conversion from latent to active tuberculosis (TB) infection.[8,11,13–15] Similarly, patients with prior exposure to hepatitis B are at increased risk of reactivation in the face of biologic therapy.[16–21] Though these risks are well established and have resulted in formal guidelines for screening prior to the initiation of particular drugs, estimates of gaps in patient safety across specialty ambulatory settings are largely lacking.

In this study we assessed performance on recommended safety screening tests for patients treated with immunosuppressive specialty drugs, including biologics and tofacitinib in the ambulatory setting. We also sought to determine whether safety practices varied across medical specialties.

METHODS

Data Sources

Data derive from the electronic health record (EHR) of a large health system serving almost 3.5 million patients with approximately 750,000 outpatient visits per year. The catchment area is large, and includes much of northern California. All EHR data were available for analysis, including demographics, diagnosis codes, problem lists, medications, laboratory studies, procedures, clinical encounter notes, and scanned documents. Variables were initially extracted electronically via EHR data warehouses using structured data queries. Following the automated data extraction, two physicians (SP and IA) and one clinical pharmacist (ZI) performed a comprehensive chart review, including review of clinical notes and scanned documents, to confirm the integrity of the data (see data checking procedures below).

Study Population

The study population included all patients in the EHR who were new users of a biologic drug (abatacept, adalimumab, anakinra, belimumab, canakinumab, certolizumab, etanercept, golimumab, infliximab, rituximab, secukinumab, tociluzimab, or ustekinumab) or tofacitinib (a synthetic small molecule JAK inhibitor) between July 2013 and October 2017. New users were defined as those with a new prescription and no treatment with any of the listed medications during the 12 months before the prescription index date (date of the new biologic or tofacitinib prescription). We also required at least 30 days of follow-up after the index date, as evidenced by an encounter, lab, medication order, or note. If a patient was started on more than one biologic drug or tofacitinib over the course of the study, only data about screening prior to the first drug was included.

The study was approved by our Committee on Human Research.

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Outcomes

Based on consensus and FDA recommended screening for the medications included in the analysis (supplementary appendix Table A2), we examined four primary outcomes. First, we calculated the proportion of eligible patients who received pre-treatment screening for tuberculosis (TB). The denominator for this measure included new users of any biologic drug or tofacitinib with the exception of rituximab and belimumab, as these B cell therapies have not been shown to increase risk of TB re-activation.[11,22,23] Adequate screening was defined according to the American College of Rheumatology (ACR) guidelines as completion of a purified protein derivative (PPD) skin test or interferon gamma release assay (IGRA) in the 12 months preceding biologic prescription, or prior treatment for latent or active TB at any point before the index date.[2] We allowed a 60-day grace period for screening after the index date, since it is common in practice to perform pre-treatment screening in parallel with the first order for a medication (often medications require insurance pre-authorization and there is a delay between drug ordering and drug dispensation). Patients met criteria for prior treatment for TB if they had a prescription for a first or second-line antimicrobial for the treatment of TB (rifampin, rifapentine, isoniazid, pyrazinamide, and ethambutol) for at least six months, or documentation of prior treatment for TB in a clinical encounter note. Patients could have multiple TB screening tests performed if they were screened by both IGRA and PPD. They could also meet screening criteria if there was documentation of screening in the provider note without specification of the screening method (these cases were labeled as “screened by unknown procedure”).

Second, we calculated the proportion of new users of biologics or tofacitinib who were screened for HBV (by hepatitis B surface antigen (HBsAg)) and HCV (by hepatitis C antibody) during the 12 months before, or 60 days after, the medication index date.

Third, we created a composite outcome variable to determine the proportion of patients who received all recommend screening for indolent infections (TB, HBV, and HCV) prior to receiving a biologic DMARD or tofacitinib. Patients were given a “pass” if they had documentation of screening for TB, hepatitis B, and hepatitis C during the pre-treatment window (12 months prior to, or 60 days after, the index date).

Finally, we assessed adherence with recommended medication-specific laboratory screening. Four of the medications included in this study—rituximab, anakinra, tocilizumab, and tofacitinib—require laboratory testing in addition to screening for indolent infections based on drug manufacturer and FDA recommendations.[24–27] All four medications require monitoring of CBC with differential, while tocilizumab and tofacitinib also require liver enzymes and lipid levels.[28–36] Rituximab can cause hypogammaglobulinemia in a subset of patients, and therefore warrants assessment of quantitative immunoglobulin levels (IgG).[28] For this subset of medications, we calculated the proportion of patients who completed each of the recommended laboratory tests during the period 12 months before or 60 days after the index date.

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Sensitivity analyses

We performed a sensitivity analysis in which we liberalized the screening window for TB and viral hepatitis such that patients met criteria for completing screening if testing was performed at any point prior the index date or, as with the primary analysis, up to 60 days after the index date. This liberalized screening window was motivated in part to capture patients who may have undergone hepatitis screening in preparation for conventional synthetic DMARD treatment prior to advancing to a biologic DMARD, in which case the screening tests would not necessarily be repeated. We conducted an additional sensitivity analysis for the composite screening measure to determine the proportion of at-risk patients screened for both TB and HBV, but not HCV, given prior literature suggesting that the risk of re-activated HCV with immunosuppressive therapy is lower[37–41].

Data Validation

After extracting structured EHR data, several additional steps were taken to ensure the data accuracy. Because screening for TB is not consistently recorded in structured data fields, keyword searches of unstructured data (i.e. clinical notes) were used to identify text strings including “PPD”, “quantiferon,” “tuberculosis”, and “TB” from clinical encounter notes. Two physicians reviewed the extracted clinical notes to determine whether they provided sufficient information to meet criteria for completion of TB screening. We also performed manual chart review on patients without evidence of TB screening by the aforementioned methods to confirm absence of screening, including review of scanned documents that represent care at outside facilities. A similar process that included chart review of cases with absent testing was undertaken for the other safety measures.

Covariates

Demographic information including age, sex, and race/ethnicity was extracted from the EHR. Number of outpatient visits in the 6 months before the index date was computed as a measure of healthcare utilization. Treating specialty was defined based on the ordering supervising physician for the medication. In cases where the treating specialty could not be determined by structured data extraction, chart review was performed to ensure accurate treating specialty categorization. A modified Charlson score was calculated according to the Deyo protocol.[42]

Statistical analysis

We used Chi-squared tests to compare performance on pre-treatment screening across different treating specialties. Multiple logistic regression was used to calculate odds ratios for completing all recommended pre-treatment screening for indolent infections within the pre-treatment window as a function of treating specialty adjusted for race, sex, age, and Charlson score. Several procedures were used to ensure the integrity of the adjusted model: restricted cubic splines were used to check linearity of age; collinearity was assessed by calculating a variance inflation factor (VIF) for each covariate (there were no collinear variables with VIF $\geq$ 10); and goodness of fit tests were used to assess calibration performance. We then calculated adjusted proportions of at-risk patients who completed the

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composite screening measure across treating clinics based on the multivariable regression. All analyses were performed using Stata (version 14, College Station, TX).

RESULTS

There were 2,027 patients with a new prescription for a biologic drug or tofacitinib during the study period, and 1,029 patients in the sub-group that required TB screening. Fifty three percent were women and the mean age was 44 (SD 20). Sixty percent of patients were white, 15% Hispanic, 13% Asian, and 6% African American. Overall the most common treating subspecialty was oncology (20%). When we excluded patients treated with rituximab, the most common prescribing subspecialties were rheumatology (25%), dermatology (22%), and gastroenterology (19%). Additional information regarding patient characteristics is presented in Table 1; the sample size for each individual drug is in supplementary appendix A1.

Among the 1,029 patients who required screening for TB, 62% had documentation of screening within the screening window (Table 2). The mechanisms by which patients completed TB screening were: 30% PPD, 20% IGRA, 4% both, 6% unknown (provider documentation of screening without specification of method), and 3% had documentation of prior treatment. Overall performance by treating specialty ranged from 55–72%, although this difference was not statistically significant (p=0.051).

Table 3 summarizes performance on screening for HBV and HCV prior to immunosuppressive therapy across all treated patients and by treating specialty. Fifty two percent and 42% of patients started on a biologic or tofacitinib completed screening for HBV and HCV, respectively, during the screening window. HBV screening ranged from 32–76% (p<0.001) and HCV screening ranged from 18–70% (p<0.001) across different treating specialties. Only 26% of all at-risk patients successfully completed all pre-treatment infection screening (TB, HBV, and HCV; see Table 4). In the assessment of safety screening using the modified composite measure, which excluded the requirement for HCV screening, 36% of at-risk patients had screening for both TB and HBV. Performance was highest in the sub-group treated by dermatology (35%) and lowest among patients treated in pediatric specialties (1%). Even after adjusting for race, sex, age, and comorbidities, there was a large difference in performance across specialties (p<0.0001).

In the sensitivity analysis in which we liberalized the time frame for completion of screening to anytime prior to new drug initiation through 60 days after the index date, we saw only modest increases in proportion of screened patients. TB screening increased from 62% to 68%; HBV screening increased from 52 to 65% percent; HCV screening increased from 42 to 58%. The overall proportion of patients who were screened for all three infections increased to 36%.

The results for performance of medication-specific laboratory testing for rituximab, anakinra, tocilizumab, and tofacitinib are presented in Table 5. Most patients requiring a CBC with differential or LFT testing had documentation of appropriate testing. In contrast, only 19% and 45% of patients had lipid testing prior to treatment with tocilizumab and

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tofacitinib, respectively. Monitoring for hypogammaglobulinemia among patients treated with rituximab was also limited: 39% were tested before starting treatment, and 52% had a documented IgG level between 3 and 12 months after the first infusion.

DISCUSSION

This study is the first comprehensive examination of ambulatory patient safety for immunosuppressive specialty drugs, a class of medications that accounted for 38% of US drug spending in 2015 and 70% of drug spending growth between 2010 and 2015.[43] We found widespread gaps in safety screening procedures for patients treated for diverse inflammatory conditions across all relevant treating specialties. Pre-immunosuppression screening for indolent infections was low, with only 62% of patients screened for TB and approximately half screened for viral hepatitis. Perhaps most concerning, only 26% of patients treated with medications that confer risk of re-activation TB and hepatitis B and C had documentation of screening for all three infections. The proportion of at-risk patients with pre-immunosuppression screening remained low even after excluding the requirement for HCV screening and liberalizing the screening window to any time prior to medication initiation. Performance on medication-specific laboratory testing was slightly higher but variable by laboratory test. Overall, our findings suggest that despite the widespread and increasing use of these specialty drugs in the ambulatory setting, relatively large gaps in patient safety procedures exist.

Over the past two decades, as chronic disease management has become progressively more complex due to the increased number of drugs available and fractured care across multiple providers, safety risks have grown, particularly for the millions of Americans requiring immunosuppressive medications. Use of new immunosuppressive medications has grown at an unprecedented pace, and this class of medications now accounts for over a third of total drug spending in the United States.[44] With new biologic agents and biosimilars reaching the market in record numbers each year, people with immune-mediated diseases such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease face increasing safety risks. Unfortunately, reports of preventable adverse events are increasing, including fulminant hepatic failure from hepatitis B in patients taking B-cell depleting therapies without appropriate preventive measures[45,46], a complication of therapy we have observed within our own health system[47]. There are also multiple reports of reactivation of latent tuberculosis in patients taking anti-TNF therapies[48,49]. Despite these reports, carefully done, well-powered studies to quantify patient safety errors across health systems are lacking. Our study suggests health systems innovations to ensure safe prescribing, monitoring and use of these medications have not kept pace, putting patients at risk for avoidable adverse events.

Tuberculosis reactivation can be fatal in patients using biologic therapies or tofacitinib, and the gaps in TB screening in our study are therefore concerning. Relative to the other safety measures examined in our study, there are a relatively larger number of prior studies examining TB screening in different health care system. For example, a study of rheumatoid arthritis electronic clinical quality measures performed by the American College of Rheumatology found relatively higher rates of TB screening over time in the health systems examined with an increase from 74% to 91% from 2011 to 2013.[50] More recent data from

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the American College of Rheumatology's RISE registry examining 95 practices across the country suggest wide variations in TB screening, with an overall screening rate of 56%.[51] A retrospective study of patients with Crohn's disease initiating TNF inhibitor therapy found that 75% of patients received pre-treatment TB screening.[50,52] In contrast, in a study of RA patients using large claims databases, only 30% were screened for TB before initiating a biologic.[53] Overall, all of the above studies found significant gaps in TB screening, and differences in the magnitude of these gaps between studies likely reflects both methodological differences (eg EHR versus claims data) as well as differences in healthcare delivery across healthcare systems.

Though the performance in this study of viral hepatitis screening was surprisingly low, it is consistent with prior reports. Previous studies evaluating hepatitis B screening have found that 14 to 62 percent of patients initiating immunosuppressive therapy were screened, and similar to our findings, most reported percentages between 40 and 50 percent.[52,54–57] We considered whether the low rate of hepatitis B screening may have been due to prior HBV vaccination, especially among pediatric patients, and therefore assessed whether patients without HBV screening had documentation of prior vaccination. Only 6.6% of patients without documented HBV screening had evidence of vaccination. This number may be deceptively low because many patients may have received hepatitis B screening outside our institution. If indeed patient reported prior vaccination to their provider, it would seem prudent that those patient would be tested for anti-Hepatitis B surface antibody to confirm immunity prior to immunosuppression. However, among patients with no testing for HBsAg, only 2.4% had Hepatitis B surface antibody testing. Therefore, we conclude that prior HBV vaccination does not account for the absence of screening observed in most cases, documentation to confirm immunity among those who have been vaccinated is lacking, and current practice does not align with FDA guidance.

The risk of progressive liver injury from hepatitis C among patients treated with immunosuppression is controversial. Though rituximab associates with worse outcomes in those with active hepatitis C infection, there is limited data regarding the impact of TNFα-inhibitors (TNFi) and risk of HCV reactivation. A trial of 29 patients with rheumatoid arthritis and hepatitis C treated with methotrexate or etanercept did not show an increase in viral load [39]. However, etanercept has a lower risk of infectious complications relative to other TNF antagonists in prior studies[40], and other TNF agents such as infliximab and adalimumab may therefore pose a greater risk among patients with HCV. Though existing data which derive mostly from case reports[37,38,41] suggest that biologic therapy may not have a detrimental effect on HCV infection, given the limitations with prior studies, current guidelines continue to recommend screening for HCV in advance of therapy to allow for shared decision making and cautious use of biologic DMARDs among patients who screen positive [2,58].

Although we found gaps in patient safety procedures across all medical specialties examined, we also observed some interesting differences. For example, screening for hepatitis B varied significantly, with solid organ transplant specialists performing screening more consistently than other specialists. At least one prior study has reported that hepatitis B screening was higher among patients undergoing organ transplantation,[56] suggesting that

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these specialists may have more standardized screening procedures to reduce the risk of adverse events in this high risk population.

This is the first study to look at specialty drug-specific laboratory testing, such as examinations for critical cytopenias, liver dysfunction, and hyperlipidemia, and a number of gaps in screening were identified. More than 85% of patients started on medications requiring blood count and liver function testing had documentation of those labs, but less than half of patients who needed testing for lipids or quantitative immunoglobulins were screened appropriately. This discrepancy may be explained by the common ordering of complete blood counts and liver function tests for a variety of clinical indications outside medication safety monitoring among patients with inflammatory conditions. Additionally, because the risk of hyperlipidemia is specific to tocilizumab and tofacitinib, and the risk of hypogammaglobulinemia is specific to rituximab, treating physicians may be less likely to remember these toxicities and monitor for them with appropriate testing. It is unclear at this point whether lipid testing for this patient population should occur in the primary care setting or the prescribing sub-specialty clinic, and perhaps attention to this issue within relevant guidelines would improve performance on pre-treatment lipid testing. Regardless of who orders lipid testing, it would be helpful for the treatment team prescribing medications that confer increased risk of hyperlipidemia to ensure that appropriate pre-treatment screening is documented in the EHR. Furthermore, systems to decrease the cognitive load of physicians who are currently faced with having to recall specific safety screening procedures across the growing and diverse number of specialty drugs are needed to effectively reduce patient safety risks.

Although our study provides important insights into ambulatory patient safety risks for patients using immunosuppressive specialty drugs, we acknowledge that there are limitations to consider. Because data were extracted from our health system's EHR, screening performed in other facilities may have been missed. However, multiple steps were taken to mitigate this limitation, including text string searches of clinical notes augmented with manual chart review of notes and scanned documents for patients with absent screening. We are therefore confident that if screening procedures were performed at an outside facility, they were not noted anywhere in the EHR by the physician initiating therapy in our health system, which suggests a lack of standardized screening and documentation protocols. In addition, our data derives from an academic institution and may not be generalizable to other healthcare systems. However, the studies cited above have found similar gaps in patient safety for several of the drugs examined here, suggesting that gaps in ambulatory patient safety for immunosuppressive specialty drugs are likely pervasive across health settings. Finally, we did not have access to pharmacy data, posing a risk that some patients with an order for a relevant medication never filled the prescription. We mitigated the risk of the latter during our chart reviews, which included a search for explanations to account for absent screening and dropping patients from the denominator (reducing the overall N from 2,493 to 2,027) who were prescribed, but did not actually initiate, treatment.

We have identified an important opportunity to improve safety among a high-risk patient group; the next step will include interventions to narrow the gap between recommended and observed pre-treatment screening. There are two ways patients access specialty medications:

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through a prescription drug benefit in the case of injectable biologics and tofacitinib, and through a medical benefit in the case of intravenous medications. Therefore, safety protocols should be established for both of these pathways, including engagement of payers, pharmacies, and infusion centers to ensure a streamlined approach to patient safety. After reviewing the workflow in subspecialty clinics at our institution in detail, we have identified several specific measures that can be taken to address this problem. First, there should be a designated field in the EHR, such as a problem within the problem list titled “need for screening before immunosuppressive therapy”, that can serve as an electronic checklist where documentation of recommended testing is easily recorded and referenced by all members of the multidisciplinary treatment team. This structured field within the EHR will allow for quick identification of patients in need of outstanding testing and prevent unnecessary duplication of testing already performed. Working with interprofessional teams, including nursing to ensure screening tests are up to date before drug administration is also important. Second, retrievable structured data in the EHR will allow the generation of reports to track performance over time and assess the impact of improvement activities. Finally, the prior authorization step will serve as a “checkpoint” after the treating provider has placed the medication order, and this will require that members of the team (eg medical assistant, clinical pharmacist) are adequately trained to perform an accurate chart review to ensure completion of appropriate pre-treatment testing and associated documentation in the aforementioned structured field.

In addition to improving medication safety within our own institution, we are developing quality improvement (QI) tools that can be shared across a broad system of diverse clinics and health systems. For example, we are testing electronic clinical quality measures (eCQMs) that can be shared, and constructing a publically available quality improvement toolkit to disseminate among practices participating in the Rheumatology Informatics System for Effectiveness (RISE) Learning Collaborative (risepro.ucsf.edu). The learning collaborative will include detailed measurement specifications and QI workflows to facilitate improvement in patient safety across the health system for populations using immunosuppressive drugs

In conclusion, we found widespread gaps in patient safety procedures for individuals initiating biologic drugs and tofacitinib across all specialties examined. Performance of TB and hepatitis screening among patients initiating these specialty drugs was poor, despite relatively generous screening windows. These findings suggest missed opportunities to prevent re-activation of life-threatening infections, and indicate a need for systems-wide solutions to prevent avoidable adverse events among the growing number of patients receiving these drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of patients initiated on specialty drugs (biologics or tofacitinib).

Characteristics	All Patients* (N = 2,027)	Patients Requiring TB Screening** (N = 1,029)
Female, N (%)	1078 (53.2)	544 (52.9)
Age, mean (SD)	44.1 (20.2)	39.5 (19.5)
Age Categories, N (%)		
<18	246 (12.1)	170 (16.5)
18–50	954 (47.1)	542 (52.7)
51–75	699 (34.5)	278 (27.0)
>75	128 (6.3)	39 (4.8)
Race, N (%)		
White	1214 (59.9)	656 (63.8)
African American	118 (5.8)	42 (4.1)
Asian	258 (12.7)	125 (12.1)
Hispanic	300 (14.8)	131 (12.7)
Other	483 (23.8)	231 (22.4)
Charlson score, mean (SD)	1.9 (2.6)	1.1 (2.1)
No. Outpt Visits in 6 months, median (IQR)	4 (1, 8)	3 (1,6)
Year of index date		
2013	186 (9.2)	103 (10.0)
2014	380 (18.7)	202 (19.6)
2015	421 (20.8)	191 (18.6)
2016	548 (27.0)	283 (27.5)
2017	492 (24.3)	250 (24.3)
Medication ordering provider specialty		
Hematology/oncology	402 (19.8)	19 (1.8)
Rheumatology	333 (16.4)	261 (25.4)
Dermatology	264 (13.0)	223 (21.7)
Gastroenterology	209 (10.3)	190 (18.5)
Neurology	204 (10.1)	5 (0.5)
Pediatric rheumatology	121 (6.0)	107 (10.4)
Solid organ transplant	81 (4.0)	6 (0.6)
Pediatric gastroenterology	38 (1.9)	36 (3.5)
Other	375 (18.5)	182 (17.7)

TB = tuberculosis, SD = standard deviation

* Patients initiated on treatment with a biologic drug (abatacept, adalimumab, anakinra, belimumab, canakinumab, certolizumab, etanercept, golimumab, infliximab, rituximab, secukinumab, tocilizumab, ustekinumab) or tofacitinib between June 2013 and October 2017 and with at least 60 days of follow-up after the index date.

** Patients initiated on any drug listed above except for rituximab and belimumab, as they do not require TB screening.

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Table 2.

Proportion of at-risk patients receiving pre-treatment screening for tuberculosis

Treating Specialty	All Clinics N(%)	GI N(%)	Rheum N(%)	Dermatology N(%)	Pediatric Rheum N(%)	Pediatric GI N(%)	Other N(%)
Total	**1029 (100)**	**190 (18.5)**	**261 (25.4)**	**223 (21.7)**	**107 (10.4)**	**36 (3.5)**	**212 (20.1)**
Screening in window from 12 months preceding through 60 days after medication initiation	639 (62.1)	115 (60.5)	165 (63.2)	123 (55.2)	62 (57.9)	26 (72.2)	148 (69.8)
IFGRA	201 (19.5)	23 (12.1)	59 (22.6)	15 (6.7)	42 (39.3)	13 (36.1)	49 (23.1)
PPD	304 (29.5)	76 (40.0)	69 (26.4)	78 (35.0)	16 (15.0)	8 (22.2)	57 (26.9)
IFGRA & PPD	42 (4.1)	5 (2.6)	7 (2.7)	3 (1.3)	0 (0.0)	3 (8.3)	24 (11.3)
Unknown	65 (6.3)	6 (3.2)	22 (8.4)	24 (10.8)	1 (0.9)	1 (2.8)	11 (5.2)
Treated for TB	27 (2.6)	5 (2.6)	8 (3.1)	3 (1.3)	3 (2.8)	1 (2.8)	7 (3.3)
Not screened	390 (37.9)	75 (39.5)	96 (36.8)	100 (44.8)	45 (42.1)	10 (27.8)	64 (30.2)
Screening at anytime preceding through 60 days after medication initiation	696 (67.6)	121 (63.7)	191 (73.2)	130 (58.3)	67 (62.6)	29 (80.6)	158 (74.5)
IFGRA	211 (20.5)	23 (12.1)	67 (25.7)	15 (6.7)	46 (43.0)	14 (38.9)	46 (21.7)
PPD	322 (31.3)	75 (39.5)	80 (30.7)	80 (35.9)	17 (15.9)	8 (22.2)	62 (29.2)
IFGRA & PPD	70 (6.8)	12 (6.3)	15 (5.7)	6 (2.7)	1 (0.9)	4 (11.1)	32 (15.1)
Unknown	65 (6.3)	6 (3.2)	22 (8.4)	24 (10.8)	1 (0.9)	1 (2.8)	11 (5.2)
Treated for TB	28 (2.7)	5 (2.6)	7 (2.7)	5 (2.2)	2 (1.9)	2 (5.6)	7 (3.3)
Not screened	333 (32.4)	69 (36.3)	70 (26.8)	93 (41.7)	40 (37.4)	7 (19.4)	54 (25.5)

GI = gastroenterology, Rheum = rheumatology, IFGRA = interferon gamma release assay, PPD = purified protein derivative, TB = tuberculosis

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Table 3.

Proportion of at-risk patients receiving pre-treatment screening for Hepatitis B and Hepatitis C

Treating Specialty	All Clinics N(%)	Rheum N(%)	Oncology N(%)	Derm N(%)	GI N(%)	Neurology N(%)	Solid Organ Transplant N(%)	Other Specialty N(%)
Total	**2027 (100)**	**454 (22.4)**	**402 (19.8)**	**264 (13.0)**	**247 (12.2)**	**204 (10.1)**	**81 (4.0)**	**375 (18.5)**
Screening in window from 12 months preceding through 60 days after medication initiation								
Hepatitis B [*]								
Screened [¶]	1,058 (52.0)	157 (34.6)	306 (76.1)	114 (43.2)	119 (48.2)	66 (32.4)	71 (87.7)	225 (60.0)
Not screened	969 (48.0)	297 (65.4)	96 (23.9)	150 (56.8)	128 (51.8)	138 (67.7)	10 (12.4)	150 (40.0)
Hepatitis C [*]								
Screened [§]	850 (42.0)	151 (33.3)	191 (47.5)	119 (45.1)	45 (18.2)	111 (54.4)	57 (70.4)	176 (46.9)
Not screened	1,177 (58.0)	303 (66.7)	211 (52.5)	145 (54.9)	202 (81.8)	93 (45.6)	24 (29.6)	199 (53.1)
Screening at any time preceding through 60 days after medication initiation								
Hepatitis B [*]								
Screened [¶]	1,317 (65.0)	240 (52.9)	349 (86.8)	138 (52.3)	145 (58.7)	84 (41.2)	81 (100)	280 (74.7)
Not screened	710 (35.0)	214 (47.1)	53 (13.2)	126 (47.7)	102 (41.3)	120 (58.8)	0 (0.0)	95 (25.3)
Hepatitis C [*]								
Screened [§]	1,167 (57.6)	237 (52.2)	270 (67.2)	148 (56.1)	71 (28.7)	129 (63.2)	77 (95.1)	235 (62.7)
Not screened	860 (42.4)	217 (47.8)	132 (32.8)	116 (43.9)	176 (71.3)	75 (36.8)	4 (4.9)	140 (37.3)

Rheum = rheumatology, Derm = dermatology, GI = gastroenterology

[¶] Documentation of testing for hepatitis B surface antigen

[§] Documentation of testing for hepatitis C antibody

[*] There was a statistically significant difference in the proportion of patients screened across treating specialties for HBV and HCV, in both screening windows ($p < 0.001$).

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Table 4.

Unadjusted and adjusted proportion of at-risk patients screened for TB and hepatitis, by treating specialty

	Unadjusted Proportions*	Adjusted Proportions** (95% CI)
All clinics	26.0	n/a
Rheumatology	32.8	31.7 (25.1, 37.5)
Dermatology	35.2	35.8 (29.2, 42.3)
Gastroenterology	21.3	21.9 (16.2, 27.6)
Pediatrics	1.3	1.5 (0.0, 3.6)
Oncology	20.0	14.8 (0.0, 34.8)
Other specialties	33.3	30.7 (23.1, 38.4)

*Proportion of patients who completed screening for TB, HBV, and HCV from 12 months preceding through 60 days after initiating a new, relevant specialty drug (excluding rituximab and belimumab, which do not require TB screening).

**Adjusted proportions calculated based on multivariate logistic regression adjusted for age, race, sex, and Charlson comorbidity score.

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Table 5.

Performance on recommended pre-treatment* medication-specific laboratory testing

Medication	Recommended Testing	N	CBC with differential N (%)	LFTs¶ N(%)	Lipids§ N(%)	Quantitative IgG N(%)
Rituximab	CBC+diff, Quantitative IgG	892	821 (92.0)	N/A	N/A	349 (39.1)
Anakinra	CBC+diff	34	29 (85.3)	N/A	N/A	N/A
Tocilizumab	CBC+diff, LFTs, Lipids	26	25 (96.2)	24 (92.3)	5 (19.2)	N/A
Tofacitinib	CBC+diff, LFTs, Lipids	47	42 (89.4)	40 (85.1)	21 (44.7)	N/A

LFT = liver function tests, IgG = immunoglobulin, CBC+diff = complete blood count with white blood cell differential

*Pre-treatment screening window was from 12 months preceding through 60 days after drug initiation.

¶LFT testing defined by testing for aspartate aminotransferase and alanine aminotransferase.

§Patients met criteria for lipid screening if they had a fasting lipid panel or a total cholesterol and HDL.