



BRIEF REPORT

Frequency of Prescription Claims for Drugs that May Interact with Janus Kinase Inhibitors Among Patients with Rheumatoid Arthritis in the US

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ABSTRACT

Introduction: This study describes the frequency of prescription claims for drugs that may interact with Janus kinase (JAK) inhibitors among adult patients with rheumatoid arthritis (RA) in a large US claims database.

Methods: This observational, retrospective, cross-sectional study of the IBM[®] MarketScan[®] Research Commercial and the Medicare Supplemental Database included adults (≥ 18 years) with ≥ 2 outpatient claims 30 or more days apart or ≥ 1 inpatient visit claim with an RA diagnosis between January 1, 2013 and March 31, 2017 (the index period). During the study period, from January 1, 2013 to March 31, 2018, strong organic anion transporter (OAT3) inhibitors, strong cytochrome P450 (CYP) 3A4 inhibitors, and moderate or strong CYP3A4 inhibitors in combination with strong CYP2C19 inhibitors, were identified as drugs with

potential for drug–drug interactions (DDIs) with JAK inhibitors approved for RA treatment in the US. Descriptive statistics were conducted.

Results: A total of 152,853 patients met eligibility criteria. Approximately 76% were women and the median age was 57 years. Of these patients, $< 0.1\%$ had a claim for a strong OAT3 inhibitor, and 1% had claims for the combination of a strong CYP3A4 and strong CYP2C19 inhibitor; 3% of patients had a claim for a strong CYP3A4 inhibitor and almost 10% had claims for both a moderate CYP3A4 and a strong CYP2C19 inhibitor.

Conclusions: Up to 10% of RA patients have been prescribed a drug with a potential JAK interaction. Rheumatologists should consider potential DDIs when managing patients with RA.

Keywords: Baricitinib; Drug–drug interaction; Janus kinase inhibitors; Real-world study; Rheumatoid arthritis; Tofacitinib; Upadacitinib

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Key Summary Points

Why carry out this study?

To our knowledge, there are no studies assessing the relative frequency of prescription claims for drugs that may interact with Janus kinase (JAK) inhibitors in the US population of adult rheumatoid arthritis (RA) patients. Because of the rapidly changing treatment options for RA, information on the relative use of drugs with drug-drug interaction (DDI) potential may be informative in the shared decision making between the health care provider and patient.

The objective of this retrospective, cross-sectional study was to describe the frequency of prescription claims for drugs that may interact and require adjustment in therapy with JAK inhibitors, without documentation of concomitant administration, among adult patients with RA in a large, administrative US claims database.

What was learned from the study?

Up to 10% of patients with RA were prescribed a drug with the potential to cause a DDI with a JAK inhibitor.

This study highlights the need to consider the potential for DDIs for RA patients in the clinical setting.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13420463>.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation and subsequent joint pain and damage leading to functional impairment [1]. Among patients living with RA, polypharmacy is relatively common [2]. The concomitant exposure to multiple drugs may result in drug–drug interactions (DDIs) in which the efficacy and/or safety of one or more of the drugs are altered. The potential for DDIs is a clinical concern because they may be associated with increased morbidity, hospitalization, prolonged hospital stays, or worsened outcomes [3].

The development of biologic disease-modifying antirheumatic drugs (bDMARDs) and small molecule agents, also referred to as targeted synthetic DMARDs (tsDMARDs), has been a pivotal progression in the therapeutics for rheumatic diseases, such as RA. In contrast to conventional synthetic DMARDs (csDMARDs), bDMARDs and tsDMARDs are directed against specific targets in the immune cells and pathways important to RA pathogenesis. The bDMARDs can be classified by their mechanism of action as (1) anti-cytokines or cytokine receptor antagonists (i.e., tumor necrosis factor [TNF] α -, interleukin [IL]-6-, IL-1 inhibitors) and (2) cell function blockers (B- and T- cell modulators); whereas tsDMARDs target intracellular signaling pathways (i.e., Janus kinase [JAK] inhibitors), and have been successfully developed and implemented as RA therapies [4, 5]. Furthermore, bDMARDs have been formulated for the parenteral route (subcutaneous injections or intravenous infusions), while the JAK inhibitors are administered orally. In the US, the JAK inhibitors available as treatment options for patients with RA include baricitinib, tofacitinib, and upadacitinib [6].

These JAK inhibitors have demonstrated safety and efficacy in randomized controlled trials [7–10]. The safety profiles of JAK inhibitors are generally similar to bDMARDs, with the exception of an increased incidence of herpes zoster infection (with highest rates reported in Japan and Korea) and warnings for increased risk of thromboembolism [7, 9–11].

Baricitinib, tofacitinib, and upadacitinib have unique pharmacokinetic profiles, and subsequently, drug interaction profiles. While the JAK inhibitors are metabolized through the cytochrome P450 (CYP) system, primarily via the CYP3A4 metabolizing enzyme, the extent of metabolism by this and other enzymes varies by agent, as does the extent of renal excretion [7, 9, 10]. Concomitant administration of baricitinib and a strong organic anion transporter (OAT3) inhibitor, such as probenecid, may increase the serum concentration of baricitinib and thus a dose reduction of baricitinib is recommended [9]. Tofacitinib labeling advises dose adjustment with concomitant strong CYP3A4 inhibitors (e.g., ketoconazole) or when moderate CYP3A4 inhibitors are used in combination with strong CYP2C19 inhibitors (e.g., fluconazole) [10]. Upadacitinib labeling recommends using concomitant strong CYP3A4 inhibitors with caution; no specific dosing recommendations are included [7].

To our knowledge, there are no studies assessing the relative frequency of prescription claims for drugs that may interact with JAK inhibitors in the US population of adult RA patients. Because of the rapidly changing treatment options for RA, information on the relative use of drugs with DDI potential may be informative in the shared decision making between the health care provider and patient.

The objective of this retrospective, cross-sectional study was to describe the frequency of prescription claims for drugs that may interact and require adjustment in therapy with JAK inhibitors, without documentation of concomitant administration, among adult patients with RA in a large, administrative US claims database.

METHODS

Data

This study used data from the IBM[®] MarketScan[®] Research Commercial and the Medicare Supplemental Database, which contains patient-level information on clinical utilization, expenditures, and enrollment across inpatient,

outpatient, prescription drug, and carve-out services from large US employers, health plans, government, and public organizations. The annual medical databases capture private sector health data from approximately 100 payers, with over 4.6 billion claim records available.

The database is compliant with the Health Insurance Portability and Accountability Act of 1996 and patient identifiers were removed to ensure patient privacy. The database is commercially available, therefore approval from an institutional review board was not required.

Study Population

We included patients who were ≥ 18 years of age and had either ≥ 2 outpatient claims at least 30 or more days apart or ≥ 1 inpatient visit claim with an RA diagnosis between January 1, 2013 and March 31, 2017 (index period). The first RA claim, determined by International Classification of Diseases Ninth (ICD-9) or Tenth Revision (ICD-10) codes (714.0x, 714.1x, 714.2x, M05.x%, M06.0%, M06.8%) was set as the index date. Patients were also required to have ≥ 12 months of continuous enrollment with medical and prescription benefits and were allowed a maximum 29-day gap.

We excluded patients with one or more claims for the following diagnoses: juvenile idiopathic arthritis (714.3x, M08.%), ankylosing spondylitis (720.0x, M45.%), psoriatic arthritis (696.0x, L40.5%), systemic lupus erythematosus (710.0x, M32.%), and lupus nephritis (583.81, M32.14).

Prescription claims for drugs with potential DDIs (described below) were quantified from January 1, 2013 to March 31, 2018.

Frequency of Variables of Interest

To characterize the patient sample, we evaluated the number and percentage of the following variables: demographic characteristics, such as sex and age; insurance type (commercial or Medicare supplement); US geographic region (Midwest, West, Northeast, South); comorbidities as quantified by the Charlson Comorbidity Index (CCI)(12, 13); and claims for csDMARDs

Table 1 Drug list [12]

Category	CYP3A4 inhibitors (strong)	CYP3A4 inhibitors (moderate)	CYP2C19 inhibitors (strong)	OAT3 inhibitors (strong)
Drugs	Atazanavir, boceprevir, clarithromycin, clotrimazole, cobicistat, conivaptan, curcumin, danoprevir, darunavir, delavirdine, econazole, efavirenz, elvitegravir, ergotamine, idelaisib, indinavir, itraconazole, ketoconazole, loperamide, lopinavir, mebefradil, midostaurin, naloxone, nefazadone, nelfinavir, nilotinib, posaconazole, ribociclib, ritonavir, saquinavir, stiripentol, telaprevir, telithromycin, terfenadine, tipranavir, troleandomycin, voriconazole	Amiodarone, amprenavir, anastrozole, aprepitant, barnidipine, cyclosporine, clobazam, clozapine, crizotinib, danazol, desvenlafaxine, diltiazem, dimethyl sulfoxide, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, fosnetupitant, fusidic acid, haloperidol, imatinib, idalpine, isavuconazole, isavuconazonium, isoniazid, isradipine, linagliptin, lovastatin, luliconazole, miconazole, mifepristone, milnacipran, netupitant, nicardapine, nilvadipine, paroxetine, primaquine, risperidone, sertraline, simeprevir, tioconazole, venetoclax, venlafaxine, verapamil, zimeldine, ziprasidone	Fluvoxamine, ticlopidine, fluconazole, chloramphenicol, delavirdine, gemfibrozil, stiripentol, fluoxetine, amitriptyline, imipramine, clomipramine, lansoprazole, isoniazid, zarfirlukast, tioconazole, miconazole	Probenecid, colchicine-probenecid

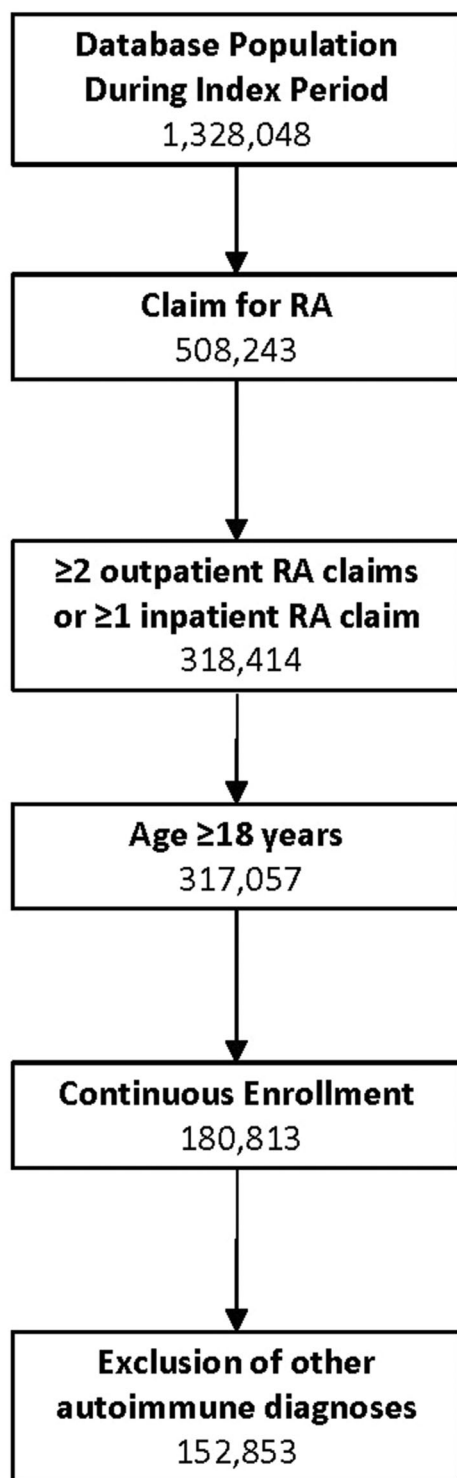
(i.e., hydroxychloroquine, leflunomide, methotrexate, or sulfasalazine), bDMARDs (i.e., abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, or tocilizumab) or tsDMARDs (i.e., tofacitinib; baricitinib and upadacitinib were not available during the study period).

We assessed the number and percentage of patients with claims at any time during the study period for strong OAT3 inhibitors, strong CYP3A4 inhibitors, and moderate or strong CYP3A4 inhibitors with strong CYP2C19 inhibitors in combination. Definitions of moderate

and strong followed the classifications on DrugBank, an online, publicly available database, as described by Wishart et al. [12]. The drugs evaluated for potential DDI are listed in Table 1. Two drugs were identified as strong OAT3 inhibitors, 47 as strong CYP3A4 inhibitors, 37 as moderate CYP3A4 inhibitors, and 16 as strong CYP2C19 inhibitors.

Statistical Analyses

Descriptive statistics were conducted. Sample selection and the creation of analytic variables were performed using the Instant Health Data



RA, Rheumatoid arthritis

Fig. 1 RA patient population identification

(IHD) platform (BHE, Boston, MA). Statistical analyses were conducted with R, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Selection and Demographics

We identified 508,243 unique patients with a diagnosis code for RA in the database. After applying the study inclusion and exclusion criteria, 152,853 patients were eligible for the analysis dataset (Fig. 1). Approximately 75% of the patients in this dataset were women and 60% were between 45 and 64 years of age. About 67% of patients had a claim for a csDMARD and 34% had a claim for a bDMARD; less than 2% had a claim for a tsDMARD (Table 2).

Potential for Drug–Drug Interactions

Less than 0.1% of patients had a claim for a strong OAT3 inhibitor, and 1% had claims for the combination of a strong CYP3A4 and strong CYP2C19 inhibitor. Claims for a strong CYP3A4 inhibitor alone were identified in 3% of patients, and almost 10% had claims for the combination of a moderate CYP3A4 and strong CYP2C19 inhibitor (Table 3). The most common drugs identified in each metabolic pathway and the combination of metabolic pathways are described in Table 3.

Claims stratified by patient age group showed similar trends to the overall population (Table 4). Of note, patients from the ages of 18 to 44 tended to have more prescription claims for moderate CYP3A4 and strong CYP2C19 inhibitors than older patients. Fluconazole was more likely to be prescribed for the 18 to 44-year-old age group.

DISCUSSION

This analysis investigated the frequency of prescription claims for drugs that have DDI potential when co-administered with JAK

Table 2 Patient demographics

Demographic	RA cohort <i>N</i> = 152,853 (<i>n</i> , %; unless noted otherwise)
Sex	
Female	116,093 (75.95%)
Male	36,760 (24.05%)
Age at index (years, mean \pm SD; median)	57.14 \pm 13.38; 57
Age groups	
18–24	1546 (1.01%)
25–34	6209 (4.06%)
35–44	17,173 (11.23%)
45–54	37,138 (24.30%)
55–64	52,804 (34.55%)
65–74	20,887 (13.66%)
\geq 75	17,096 (11.18%)
Primary insurance type	
Commercial	113,125 (74.01%)
Medicare	39,728 (25.99%)
Region	
Midwest	38,738 (25.34%)
Northeast	27,616 (18.07%)
South	62,476 (40.87%)
West	21,930 (14.35%)
Unknown	2093 (1.37%)
Use of DMARD	
csDMARDs ^a	102,597 (67.12%)
bDMARDs ^b	51,591 (33.75%)
tsDMARDs ^c	2471 (1.62%)
Charlson Comorbidity Index	
Mean score (SD)	1.73 (1.33)

Percentages may not add up to 100% because of rounding

bDMARDs biologic disease-modifying antirheumatic drugs, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *DMARD* disease modifying antirheumatic drug, *n*, *N* sample size, *RA* rheumatoid arthritis, *SD* standard deviation, *tsDMARDs* targeted synthetic disease-modifying antirheumatic drugs

^a csDMARDs included: hydroxychloroquine, leflunomide, methotrexate, sulfasalazine

^b bDMARDs included: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab

^c tsDMARDs included: tofacitinib. Baricitinib and upadacitinib were not available during the study period

Table 3 Number and percentage of patients by metabolic pathway, with the five most commonly prescribed drugs, and for the combination of metabolic pathways

Metabolic pathway	RA Cohort <i>N</i> = 152,853 <i>n</i> (%)
Strong OAT3 inhibitors	96 (0.06%)
Probenecid	54 (0.04%)
Colchicine-probenecid	44 (0.03%)
Strong CYP3A4 inhibitors	4825 (3.16%)
Clarithromycin	2337 (1.53%)
Clotrimazole Troche	684 (0.45%)
Clarithromycin ER	539 (0.35%)
Loperamide hydrochloride	311 (0.20%)
Suboxone	203 (0.13%)
Moderate CYP3A4 inhibitors	33,951 (22.21%)
Fluconazole	11,676 (7.64%)
Sertraline hydrochloride	7102 (4.65%)
Venlafaxine hydrochloride ER	3801 (2.49%)
Paroxetine hydrochloride	2308 (1.51%)
Lovastatin	1828 (1.20%)
Strong CYP2C19 inhibitors	23,940 (15.66%)
Fluconazole	11,676 (7.64%)
Amitriptyline hydrochloride	4802 (3.14%)
Fluoxetine hydrochloride	4599 (3.01%)
Lansoprazole	3131 (2.05%)
Gemfibrozil	698 (0.46%)
Moderate CYP3A4 AND strong CYP2C19 inhibitors	14,726 (9.63%)
Strong CYP3A4 AND strong CYP2C19 inhibitors	1528 (1%)

CYP cytochrome P450, *ER* extended release, *n*, *N* sample size, *OAT3* organic anion transporter, *RA* rheumatoid arthritis

inhibitors. Among the JAK inhibitors currently indicated for RA in the US, there is great variability in the number of potentially interacting

drugs by metabolic pathway, with the highest number associated with strong CYP3A4 inhibition (described in the product labeling for tofacitinib and upadacitinib) and the lowest number associated with strong OAT3 inhibition (described in the product labeling for baricitinib). In this large US claims database, we observed that up to 10% of RA patients had claims for drugs with DDI potential. These results confirm that DDIs are a risk for RA patients and, subsequently, there is a need to recognize and manage DDIs to minimize the risk of therapeutic failure or of adverse drug effects [13].

The recognition and management of DDIs is difficult. Prescribers may not identify potential DDIs without the assistance of reference materials [14]. Additionally, drugs identified with potential DDI are often prescribed by primary care providers; whereas DMARDs, such as JAK inhibitors, are more likely prescribed by rheumatologists [15]. Thus, DDIs may be missed at the point of prescribing.

There are limitations to this analysis. First, there are inherent limitations when working with an administrative claims database. Namely, the claims reflect prescription of a drug, but not necessarily subsequent consumption. Second, the database does not provide information on over-the-counter drugs, supplements, or foods that may affect DDIs. Some interacting drugs, such as antibiotics and antifungals, may be used for a short duration, and temporary interruptions or dose adjustments may be employed to address potential DDIs. The co-administration of JAK inhibitors and the drugs in this analysis could not be evaluated because of the limited number of JAK inhibitor prescription claims during the study period; this is a potential analysis for future study. Clinical outcomes were not evaluated, so we are unable to determine if RA patients encountered any adverse clinical outcomes with the administration of drugs with DDI potential.

To our knowledge, no other administrative claims database analysis has investigated the use of drugs that have the potential to cause DDIs among RA patients in a real-world setting. With commonly used administrative claims database methodologies, this analysis provides a

Table 4 Number and percentage of patients by age group and their prescription claims by metabolic pathway

Metabolic pathway	Age group (years), <i>n</i> (%)						
	18–24	25–34	35–44	45–54	55–64	65–74	≥ 75
Strong OAT3 inhibitors	0 (0%)	0 (0%)	4 (0.02%)	13 (0.04%)	40 (0.08%)	17 (0.08%)	22 (0.13%)
Strong CYP3A4 inhibitors	39 (2.52%)	203 (3.27%)	578 (3.37%)	1205 (3.24%)	1718 (3.25%)	652 (3.12%)	430 (2.52%)
Moderate CYP3A4 inhibitors	261 (16.88%)	1367 (22.02%)	4051 (23.59%)	7918 (21.32%)	11,249 (21.30%)	4847 (23.21%)	4258 (24.91%)
Strong CYP2C19 inhibitors	246 (15.91%)	1128 (18.17%)	3538 (20.60%)	6410 (17.26%)	7883 (14.93%)	2880 (13.79%)	1855 (10.85%)
Moderate CYP3A4 AND strong CYP2C19 inhibitors	179 (1.10%)	908 (14.62%)	2569 (14.96%)	4036 (10.87%)	4450 (8.43%)	1555 (7.44%)	1029 (6.02%)
Strong CYP3A4 AND strong CYP2C19 inhibitors	17 (1.10%)	69 (1.11%)	208 (1.21%)	419 (1.13%)	517 (0.98%)	198 (0.95%)	100 (0.58%)

CYP cytochrome P450, *n* sample size, OAT3 organic anion transporter

new perspective on the treatment experience for a large, representative sample of RA patients in the US.

CONCLUSIONS

In this analysis, up to 10% of patients with RA may be prescribed a drug with the potential to cause a DDI with a JAK inhibitor. As treatment options and polypharmacy management expand, rheumatologists should consider potential DDIs and adjust treatment according to the respective drug-label recommendations. Many of the potentially interacting drugs observed in this real-world analysis may be used acutely (e.g., antifungals), which may require a temporary treatment interruption or dose adjustment of the chronic RA therapy. This study highlights the need to consider the potential for DDIs for RA patients in the clinical setting.

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Compliance with Ethics Guidelines. The database is compliant with the Health Insurance Portability and Accountability Act of 1996 and patient identifiers were removed to ensure patient privacy. The database is commercially available and the data are de-identified, therefore approval from an institutional review board was not required.

Data Availability. Lilly provides access to relevant anonymized patient-level data from studies on approved medicines and indications as defined by the sponsor-specific information on www.vivli.org. For details on submitting a request, see the instructions provided at www.vivli.org.

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