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Original article

Comparative safety of biologic versus conventional synthetic DMARDs in rheumatoid arthritis with COPD: a real-world population study

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Abstract

Objectives. Abatacept, a biologic DMARD, was associated with respiratory adverse events in a small subgroup of RA patients with chronic obstructive pulmonary disease (COPD) in a trial. Whether this potential risk is specific to abatacept or extends to all biologics and targeted synthetic DMARDs (tsDMARDs) is unclear. We assessed the risk of adverse respiratory events associated with biologic and tsDMARDs compared with conventional synthetic DMARDs (csDMARDs) among RA patients with concomitant COPD in a large, real-world cohort.

Methods. We used a prevalent new-user design to study RA patients with COPD in the US-based MarketScan databases. New users of biologic DMARDs and/or tsDMARDs were matched on time-conditional propensity scores to new users of csDMARDs. Adverse respiratory events were estimated using Cox models comparing current use of biologic/tsDMARDs with csDMARDs.

Results. The cohort included 7424 patients initiating biologic/tsDMARDs and 7424 matched patients initiating csDMARDs. The adjusted hazard ratio of hospitalized COPD exacerbation comparing biologic/tsDMARD *vs* csDMARD was 0.76 (95% CI: 0.55, 1.06), while it was 1.02 (95% CI: 0.82, 1.27) for bronchitis, 1.21 (95% CI: 0.92, 1.58) for hospitalized pneumonia or influenza and 0.99 (95% CI: 0.87, 1.12) for outpatient pneumonia or influenza. The hazard ratio of the combined end point of COPD exacerbation, bronchitis and hospitalized pneumonia or influenza was 1.04 (95% CI: 0.89, 1.21).

Conclusion. In this large, real-world comparative safety study, biologic and tsDMARDs, including abatacept, were not associated with an increased risk of adverse respiratory events when compared with csDMARDs in patients with RA and COPD.

CLINICAL SCIENCE

Rheumatology key messages

- Abatacept has been suspected to increase adverse respiratory complications in patients with RA and concomitant COPD.
- It is unclear whether this potential risk extends to all biologic DMARDs.
- This study finds no increased risk with biologic DMARDs, including abatacept, compared with conventional synthetic DMARDs.

Introduction

RA is a chronic systemic inflammatory disease with an overall cumulative prevalence rate of 0.5%, an age-standardized incidence rate of 65.6 (95% CI: 63.7, 67.5) per 100 000 and an age-standardized all-cause mortality of 8.3 deaths per 1000, ~1.5 times higher than the general population [1]. Patients with RA are at an increased risk of infection when compared with the general population [2–4]. Respiratory infections are the most common type of infection in RA, accounting for almost 50% of RA hospital admissions for infection [5]. The incidence rates of hospitalized infections and hospitalized pneumonia in RA have been reported to have ranges of 1.41–3.53 and 0.27–1.31 per 100 patient-years, respectively [6]. Immune dysfunction due to the disease process as well as the use of corticosteroids and immunosuppressive drugs targeting key components of immunity have

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been implicated in this increased risk [7–9]. Comorbidities may also contribute to the increased risk of infection. Chronic obstructive pulmonary disease (COPD) is a common comorbidity in RA, affecting up to 10% of patients [10]. This is similar to the rate of COPD in the general population, estimated to be 8.12% in the USA in 2010 [11]. Patients with COPD are also at higher risk of respiratory infections [12, 13].

Abatacept is a selective co-stimulation modulator of T cell activation used to treat RA. It was shown to be safe and effective in the one-year ASSURE randomized trial [14]. However, in subgroup analyses, serious adverse respiratory events including COPD exacerbation, worsening of COPD, bronchitis and pneumonia were observed more often in RA patients with COPD receiving abatacept compared with placebo. However, the subgroup of RA patients with COPD included only 54 patients. A large observational study conducted to address this question, including over 1800 patients with RA and concomitant COPD who initiated treatment with abatacept, found no increase in the risk of adverse respiratory events compared with other biologic disease-modifying anti-rheumatic drugs (DMARDs) [15]. However, the potential risk of adverse respiratory events could have been obscured in the comparison between abatacept and other biologic DMARDs if the risk is associated with the entire class of biologic DMARDs.

We therefore undertook this study to assess the risk of adverse respiratory events associated with biologic DMARDs, including abatacept, compared with conventional synthetic DMARDs (csDMARDs), among RA patients with COPD, in a real-world observational setting.

Methods

Study design

We designed a prevalent new-user study in a cohort consisting of new users of biologic and csDMARDs matched on time-conditional propensity scores [16]. This design allows the inclusion of subjects who switched from csDMARD to biologic DMARDs and ensures a more comprehensive assessment of drug safety.

Data source

Data from two large US administrative databases were used in this study. The Truven MarketScan Commercial database is a US administrative claims database with patient information dating back to 2006. The database provides detailed information regarding over 70 million privately insured patients younger than 65 years, from >150 employers and 20 health plans. The MarketScan Medicare Supplemental Database covers patients over 65 years of age receiving Medicare coverage in the USA. This database includes data on ~6 million patients including demographics, drug information, enrolment information, etc. also dating back to 2006.

Study population

First, we created a base cohort of all patients with an RA diagnosis, identified from outpatient and inpatient physician codes, and a prescription for a biologic or csDMARD between January 2007 and December 2015. The algorithm to identify RA in administrative databases, using outpatient and inpatient physician codes (ICD-9 714.xx, ICD-10 M05, M06, M08) and prescription records for drugs used to treat RA, has been validated [17]. We then identified every prescription for which the patient had at least 180 days of prior medication insurance coverage, was 50 years of age or more, had at least two diagnoses of RA in the prior 180 days and had a prior COPD diagnosis. COPD was defined by the presence of at least one outpatient or inpatient diagnosis (ICD-9 codes 491.x, 492.x, or 496.x or ICD-10 codes J41-J44) in the patient's history any time between 2006 and cohort entry.

Prescriptions were then divided into those for biologic and csDMARDs. To identify new use of a biologic DMARD prescription, we excluded those with a prescription for a biologic drug in the prior 180 days and those with prescriptions for more than one biologic drug [18]. To identify new use of a csDMARD prescription, we excluded those with a biologic DMARD prescription in the prior 180 days, with a prescription for the same csDMARD in the prior 180 days or with two csDMARDs. Finally, new users of biologic DMARDs, as defined by episodes of new use, were matched 1 : 1 with new users of csDMARDs on time-conditional propensity scores (described below) [16].

Exposure definition

Exposure to DMARDs was defined using the National Drug Code (NDC) for dispensed medications and procedure codes for injection or infusion. The biologic DMARDs included abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab. Tofacitinib citrate is a synthetic DMARD, but because of its targeted mechanism of action, was included with the biologic DMARDs. The csDMARDs included auranofin, aurothioglucose, gold salt, hydroxychloroquine, leflunomide, methotrexate and sulfasalazine. Patients were considered to be current users of DMARD for a 60-day period from the date of the dispensed prescription. Thus, patients were considered continuously exposed if the 60-day duration of one prescription overlapped with the date of the next prescription. We used an as-treated definition of exposure, where patients were censored at the date of treatment discontinuation.

Outcomes

The primary outcomes of interest were: (i) severe COPD exacerbation requiring hospitalization, (ii) bronchitis (identified by a diagnosis for bronchitis from an outpatient physician visit and a prescription for a respiratory antibiotic on the same day or within 2 days of the diagnosis), (iii) severe pneumonia or influenza (denoted as pneumonia/influenza) requiring hospitalization, (iv) pneumonia/influenza identified from outpatient diagnoses, and (v) a combined outcome consisting of (i), (ii) and (iii).

Covariates

The covariates included age, sex, comorbidities and medications identified during the 180-day baseline

period. Co-morbidities were identified using diagnosis codes for inpatient and outpatient encounters, which included hospitalized infections, hypertension, diabetes, cancer (including lymphoma), peripheral vascular disease and cardiovascular disease (ischaemic heart disease, other heart disease, cerebrovascular disease and chronic rheumatic heart disease), as well as joint replacement. Medications included non-steroidal anti-inflammatory drugs (NSAIDs), oral and injection corticosteroids, cholesterol lowering medications, oral antidiabetic agents, insulin, ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, proton-pump inhibitors, narcotics, antidepressants, antipsychotics, benzodiazepines, anticonvulsants and antiparkinsonian drugs. Other immunosuppressants, including azathioprine, cyclophosphamide, penicillamine, tacrolimus, ciclosporin, everolimus and mycophenolate, were included, as was the presence of prior hospitalizations. COPD-specific covariates included a prior asthma diagnosis, COPD exacerbation requiring hospitalization and medications for COPD such as inhaled corticosteroids, long-acting β_2-agonists, long-acting muscarinic antagonists, short-acting β_2-agonists, ipratropium bromide, theophylline and antibiotics used for respiratory infections.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the cohort, stratified by new users of biologic and csDMARDs. A time-conditional propensity score of biologic DMARD initiation relative to csDMARD initiation was developed for each patient based on the time-dependent values of the covariates, estimated using a proportional hazards regression model. The propensity score derivation included demographic, comorbidities and medications listed above, present at or during the 6-month period prior to the exposure set date. The time-conditional propensity score allows patients who switched from a csDMARD to a biologic DMARD to be matched to a similar patient who was on a csDMARD at the same time point in the treatment course and switched to another csDMARD. Thus, each new user of a biologic DMARD was matched to a new user of csDMARD with the closest time-conditional propensity score and on the number of different csDMARDs in the last 6 months. To satisfy the assumption of positivity, the biologic DMARD users whose time-conditional propensity score value did not lie within the range of the propensity scores of the corresponding exposure set were excluded [16].

Cohort follow-up was from cohort entry date, namely the date of new biologic DMARD use and of matched new csDMARD use, until the date of the event of interest, treatment discontinuation, end of enrolment in the database, or end of data collection (31 December 2015), whichever occurred first. The Cox proportional hazard regression model was used to provide an estimate of the hazard ratio of each outcome associated with current use of biologic DMARDs relative to current use of csDMARDs, adjusted for the confounders using the propensity score matching. Covariates that were not included in the propensity score, namely prior hospitalizations, hospitalized infections, joint replacement, injection corticosteroids and other immunosuppressants, as well as those found to be imbalanced between the groups, were adjusted for in the regression model.

Several sensitivity analyses were performed. We first extended the baseline period to 1 year and varied the 60-day time window used to define continuous exposure from 30 to 90 days. We also performed stratified analyses by recent csDMARD use, and by degree of COPD severity, defined as prescriptions for triple therapy (long-acting muscarinic antagonists, long-acting β_2-agonists and inhaled corticosteroids) in the baseline period. Finally, a sensitivity analysis was performed evaluating short-term effect of the drugs using an as-treated analysis, where the follow-up was limited to one year after treatment initiation, as in the ASSURE randomized trial [14]. Statistical analyses were conducted using SAS, Version 9.4 (SAS Institute, Inc., Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). The study was approved by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada (no. 2019-1473).

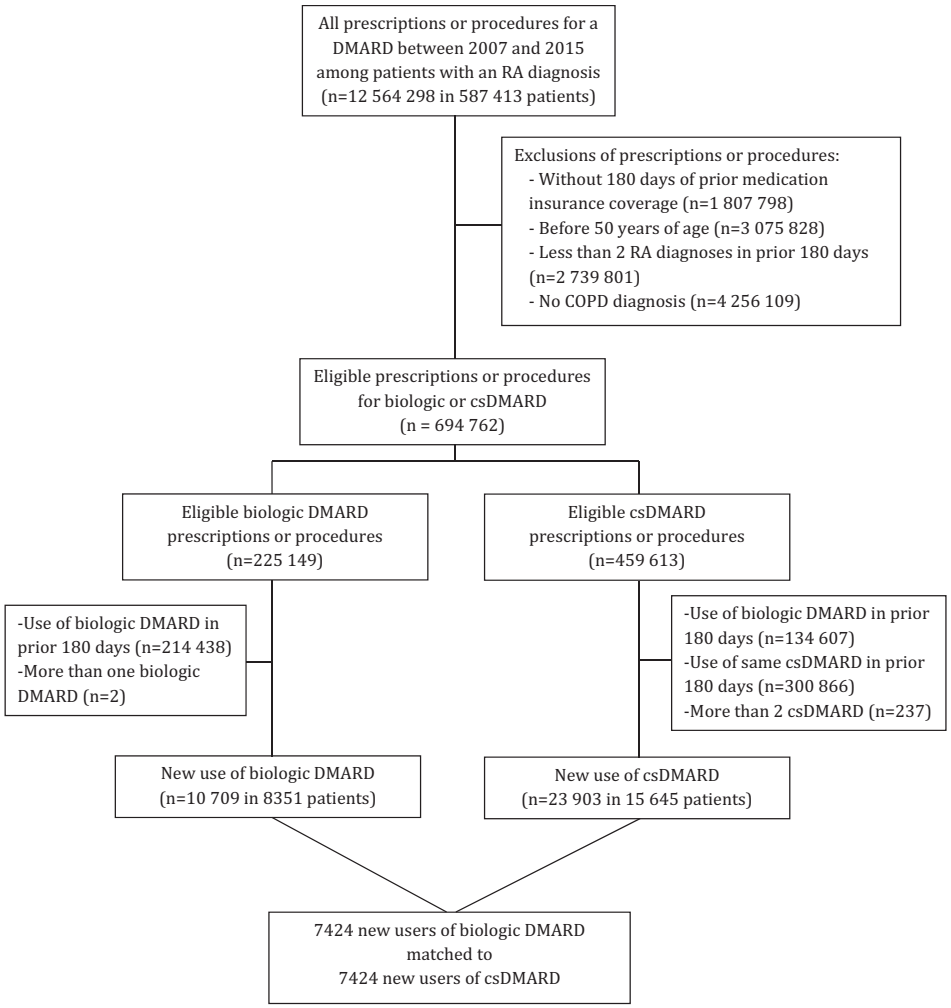
Results

The base cohort included 587 413 subjects with RA with a DMARD prescription or procedure between 2007 and 2015. After applying inclusion and exclusion criteria, the cohort included 8351 patients who initiated a biologic DMARD and 15 645 who initiated a csDMARD (Fig. 1). After one-to-one propensity score matching and trimming from non-overlap, the study cohort included 7424 patients who initiated biologic DMARD therapy and 7424 matched patients who initiated a csDMARD.

The initiators of biologic DMARD and their propensity score-matched initiators of csDMARDs were generally well balanced on all baseline covariates (Table 1). Imbalances were observed for methotrexate, hydroxychloroquine and leflunomide, factors that were further adjusted for. There were 69% of the patients who had recently used csDMARDs during the baseline period. The majority of drugs in the biologic DMARD group were etanercept (29%), adalimumab (22%), rituximab (15%), infliximab (13%) and abatacept (10%), while the majority of drugs in the csDMARD group were methotrexate (41%), hydroxychloroquine (35%), leflunomide (19%) and sulfasalazine (14%) (Supplementary Table S1, available at *Rheumatology* online).

In the patients who initiated a biologic DMARD, the incidence rate (IR) of severe COPD exacerbation was 1.8 per 100 person-years, while it was 4.9 for bronchitis, 3.2 for hospitalized pneumonia or influenza, and 14.7 for outpatient pneumonia or influenza (Table 2). Among the matched patients who initiated a csDMARD, the IR of severe COPD exacerbation was 2.5 per 100 person-years, while it was 5.0 for bronchitis, 3.1 for hospitalized pneumonia or

Fig 1 Flowchart of study cohort selection



COPD: chronic obstructive pulmonary disease.

influenza, and 16.1 for outpatient pneumonia or influenza. For the combined end point of severe COPD exacerbation, bronchitis and hospitalized pneumonia or influenza, there were 386 events in the biologic DMARD group (IR 9.8 per 100 person-years) and 352 events in the csDMARD group (IR 10.3 per 100 person-years).

The adjusted hazard ratio of attaining a first severe COPD exacerbation in patients starting a biologic DMARD *vs* a csDMARD was 0.76 (95% CI: 0.55, 1.06), while for bronchitis it was 1.02 (95% CI: 0.82, 1.27), for hospitalized pneumonia or influenza it was 1.21 (95% CI: 0.92, 1.58) and for outpatient pneumonia or influenza it was 0.99 (95% CI: 0.87, 1.12). For the combined end point of severe COPD exacerbation, bronchitis and hospitalized pneumonia or influenza, the hazard ratio was 1.04 (95% CI: 0.89, 1.21).

Sensitivity analyses based on the as-treated approach are shown in Table 3 for the combined end point and in Supplementary Tables S2–S5 available at *Rheumatology* online for severe COPD exacerbation, bronchitis, hospitalized pneumonia or influenza, and outpatient pneumonia or influenza. Globally, results were consistent with the main analysis.

Discussion

In this large real-world US claims database study, which included over 7400 patients with RA and concomitant COPD who initiated treatment with a biologic DMARD, the risk of adverse respiratory events was not increased compared with a propensity-matched group of patients initiating treatment with a csDMARD. These adverse events included severe COPD exacerbation requiring hospitalization, bronchitis, as well as hospitalized and outpatient pneumonia or influenza. The risk was also not elevated for the combined end point of severe COPD

Table 1 Characteristics of patients with RA and COPD initiating biologic or conventional synthetic DMARD

	Biologic DMARD	csDMARD	Standardized difference
Number of subjects	7424	7424	
Age at cohort entry, mean (s.d.), years	64.7 (9.3)	66.6 (9.9)	−0.1926
50–59	2476 (33.4)	2063 (27.8)	0.1210
60–69	2751 (37.1)	2579 (34.7)	0.0483
70–79	1588 (21.4)	1869 (25.2)	−0.0896
80+	609 (8.2)	913 (12.3)	−0.1353
Women, *n* (%)	5174 (69.7)	5202 (70.1)	−0.0082
Prior DMARD use	5083 (68.5)	5083 (68.5)	0.0000
Comorbidities in baseline period			
Hospitalization for COPD	113 (1.5)	108 (1.5)	0.0056
Hospitalization for other infection	469 (6.3)	540 (7.3)	−0.0380
Any hospitalization	1602 (21.6)	1603 (21.6)	−0.0003
Asthma	1216 (16.4)	1238 (16.7)	−0.0080
Hypertension	3634 (48.9)	3925 (52.9)	−0.0785
Ischaemic heart disease	1385 (18.7)	1483 (20.0)	−0.0334
Cerebrovascular disease	569 (7.7)	622 (8.4)	−0.0263
Chronic rheumatic heart disease	134 (1.8)	135 (1.8)	−0.0010
Other form of heart disease	1889 (25.4)	2083 (28.1)	−0.0591
Diabetes	1616 (21.8)	1610 (21.7)	0.0020
Malignancy	717 (9.7)	809 (10.9)	−0.0408
Chronic kidney disease	466 (6.3)	553 (7.4)	−0.0464
Peripheral vascular disease	877 (11.8)	926 (12.5)	−0.0202
Joint replacement	415 (5.6)	360 (4.8)	0.0333
RA medications in baseline period			
Methotrexate	3528 (47.5)	2174 (29.3)	0.3818
Hydroxychloroquine	1464 (19.7)	2163 (29.1)	−0.2205
Leflunomide	1124 (15.1)	614 (8.3)	0.2149
Sulfasalazine	533 (7.2)	529 (7.1)	0.0021
Auranofin	5 (0.1)	12 (0.2)	−0.0279
Aurothioglucose	0 (0.0)	0 (0.0)	
Gold salt	6 (0.1)	4 (0.1)	0.0104
Other medications in baseline period			
Oral corticosteroids	4948 (66.6)	4785 (64.5)	0.0462
Injection corticosteroids	428 (5.8)	362 (4.9)	0.0396
Other immunosuppressants	305 (4.1)	126 (1.7)	0.1440
Inhaled corticosteroids	1618 (21.8)	1747 (23.5)	−0.0415
Long acting β_2-agonist	1421 (19.1)	1537 (20.7)	−0.0391
Long-acting muscarinic antagonist	825 (11.1)	909 (12.2)	−0.0352
Short-acting β_2-agonist	1883 (25.4)	2046 (27.6)	−0.0498
Ipratropium	532 (7.2)	589 (7.9)	−0.0291
Theophylline	65 (0.9)	78 (1.1)	−0.0179
Antibiotics used in respiratory infections	4395 (59.2)	4369 (58.8)	0.0071
NSAIDs	2802 (37.7)	2738 (36.9)	0.0178
Cholesterol-lowering medication	2678 (36.1)	2825 (38.1)	−0.0410
ACE inhibitors	1543 (20.8)	1650 (22.2)	−0.0351
Angiotensin II receptor blockers	1321 (17.8)	1308 (17.6)	0.0046
Diuretics	2674 (36.0)	2847 (38.3)	−0.0482
Calcium channel blockers	1609 (21.7)	1713 (23.1)	−0.0336
Beta-blockers	2188 (29.5)	2364 (31.8)	−0.0514
Insulin	458 (6.2)	394 (5.3)	0.0371
Oral anti-diabetics	992 (13.4)	975 (13.1)	0.0068
Proton-pump inhibitors	2967 (40.0)	2849 (38.4)	0.0326
Narcotics	4688 (63.1)	4391 (59.1)	0.0821
Antidepressant	2846 (38.3)	2694 (36.3)	0.0423
Antipsychotics	210 (2.8)	191 (2.6)	0.0158
Benzodiazepines	1736 (23.4)	1737 (23.4)	−0.0003
Anticonvulsants	1129 (15.2)	1162 (15.7)	−0.0123
Antiparkinsonian	269 (3.6)	302 (4.1)	−0.0231

ACE: angiotensin converting enzyme; COPD: chronic obstructive pulmonary disease; csDMARD: conventional synthetic DMARD; *n*: number.

TABLE 2 Associations between study endpoints and biologic compared with conventional synthetic DMARD

Initial treatment	Number of patients	Number of events	Person-years	Rate per 100 person-years	Crude matched HR	Adjusted[a] HR (95% CI)
Severe COPD exacerbation						
Biologic DMARD	7424	74	4058	1.8	0.74	0.76 (0.55, 1.06)
csDMARD	7424	90	3533	2.5	1.00	1.00 (reference)
Bronchitis						
Biologic DMARD	7424	195	4000	4.9	1.00	1.02 (0.82, 1.27)
csDMARD	7424	175	3483	5.0	1.00	1.00 (reference)
Severe pneumonia/influenza						
Biologic DMARD	7424	130	4042	3.2	1.06	1.21 (0.92, 1.58)
csDMARD	7424	109	3530	3.1	1.00	1.00 (reference)
Outpatient pneumonia/influenza						
Biologic DMARD	7424	575	3855	14.9	0.96	0.99 (0.87, 1.12)
csDMARD	7424	537	3335	16.1	1.00	1.00 (reference)
Combined respiratory endpoint[b]						
Biologic DMARD	7424	386	3927	9.8	0.98	1.04 (0.89, 1.21)
csDMARD	7424	352	3414	10.3	1.00	1.00 (reference)

[a]Adjusted for age, injection corticosteroids, other immunosuppressants, prior hospitalization, prior hospitalized infection, prior joint replacement, methotrexate, hydroxychloroquine and leflunomide. [b]Includes the first of severe COPD exacerbation, severe pneumonia or influenza, or bronchitis. csDMARD: conventional synthetic DMARD; COPD: chronic obstructive pulmonary disease; HR: hazard ratio.

exacerbation, bronchitis and hospitalized pneumonia or influenza.

This study provides important complementary observations to two studies investigating the safety of abatacept in RA. The ASSURE 1-year randomized trial compared abatacept ($n = 959$) *vs* placebo ($n = 482$) [14]. The subset of patients with COPD included 37 patients in the abatacept arm and 17 on placebo. Among those, serious adverse respiratory events were more common in the abatacept compared with the placebo group (10.8% *vs* 0%). However, the uneven number of RA patients with COPD exposed to abatacept and placebo, and the small number of serious adverse respiratory events ($n = 1$ for each of COPD exacerbation, worsening of COPD, bronchitis and pneumonia) contributed to considerable uncertainty around the association. Nevertheless, these data contributed to the current abatacept product label warning that 'COPD patients may develop more frequent respiratory adverse events'. To examine this question more carefully, a large observational study including over 1800 patients with RA and concomitant COPD was undertaken. Using the same data sources as in this study, it found that the risk of adverse respiratory events in those treated with abatacept was not increased compared with other biologic DMARDs: hazard ratio 0.87 (95% CI: 0.68, 1.12) for the combined end point of hospitalized COPD exacerbation, bronchitis and hospitalized pneumonia or influenza [15]. However, the comparison between abatacept and other biologic DMARDs could have obscured the risk of respiratory adverse events if such risk was associated with the entire class of biologic DMARDs. For this reason, this study was undertaken to compare the risks of adverse respiratory events comparing biologic to csDMARDs. The data again do not support an increased risk of adverse respiratory events in RA patients with COPD treated with biologic compared with csDMARDs.

This study is not without limitations inherent to observational studies, in particular, information bias that can arise from misclassification of exposure or outcome. However, this bias was likely non-differential between the two study groups. Moreover, we used the age limit of 50 years to minimize misclassification of COPD and asthma diagnoses. Also, we cannot rule out the potential for residual confounding from unmeasured covariates such as disease severity, which are not captured in these databases. However, such confounders would have to be moderately prevalent, strongly predictive of outcome and likely to affect the treatment decision to prescribe a biologic or csDMARD to an RA patient with COPD. We cannot exclude such residual confounding due to smoking or steroid dosage.

On the other hand, the study design and sophisticated analytical plan represent important strengths of the study. Indeed, the prevalent new user design allowed the inclusion of subjects who switched from csDMARD to biologic DMARDs, thereby permitting a more comprehensive and realistic assessment of drug safety [16]. In addition, the use of time-conditional propensity scores allowed identification of comparable patients and minimization of confounding. Finally, the sensitivity analyses provided support for the robustness of the results. Another important strength of the study is the use of a large claims database. This allowed efficient identification a large number of patients with both RA and COPD, maximization of power to detect potential adverse effects, and real-world estimates of effects.

Biologic drugs have revolutionized the treatment of RA. However, safety remains an important consideration when

TABLE 3 Sensitivity analyses for the combined respiratory end point

Initial treatment	Number of patients	Number with event	Person-years	Rate per 100 person-year	Crude HR	Adjusted[a] HR (95% CI)
One-year baseline period						
Biologic DMARD	5806	314	3373	9.3	0.90	0.95 (0.81, 1.12)
csDMARD	5806	304	2846	10.7	1.00	1.00 (reference)
Current use defined by 30-day exposure						
Biologic DMARD	7424	136	1233	11.0	0.99	1.00 (0.77, 1.29)
csDMARD	7424	133	1209	11.0	1.00	1.00 (reference)
Current use defined by 90-day exposure						
Biologic DMARD	7424	541	5726	9.4	0.96	1.02 (0.90, 1.16)
csDMARD	7424	522	5228	10.0	1.00	1.00 (reference)
No recent DMARD use						
Biologic DMARD	2341	106	1011	10.5	1.15	1.16 (0.87, 1.55)
csDMARD	2341	81	853	9.5	1.00	1.00 (reference)
Recent DMARD use						
Biologic DMARD	5083	280	2916	9.6	0.93	1.00 (0.83, 1.20)
csDMARD	5083	271	2561	10.6	1.00	1.00 (reference)
Severe COPD patient						
Biologic DMARD	436	39	215	18.2	0.99	0.99 (0.62, 1.56)
csDMARD	462	40	211	19.0	1.00	1.00 (reference)
Mild COPD patient						
Biologic DMARD	6988	347	3713	9.3	0.99	1.05 (0.89, 1.23)
csDMARD	6962	312	3203	9.7	1.00	1.00 (reference)
Follow-up limited to 1 year						
Biologic DMARD	7424	331	3074	10.8	1.00	1.06 (0.90, 1.25)
csDMARD	7424	307	2811	10.9	1.00	1.00 (reference)

[a]Adjusted for age, injection corticosteroids, other immunosuppressants, prior hospitalization, prior hospitalized infection, prior joint replacement, methotrexate, hydroxychloroquine and leflunomide. COPD: chronic obstructive pulmonary disease; csDMARD: conventional synthetic DMARD; HR: hazard ratio.

initiating any treatment for this disease. COPD is a common comorbidity in RA and both conditions are associated with increased risk of respiratory complications. This study provides reassurance to physicians who treat RA patients with COPD that the risk of adverse respiratory events is not increased with biologic compared with csDMARDs.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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