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Risk of Hospitalized Infection and Initiation of Abatacept versus TNF Inhibitors among Patients with Rheumatoid Arthritis: a Propensity Score-Matched Cohort Study

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Abstract

Objective—We aimed to evaluate the comparative risk of hospitalized infection among patients with rheumatoid arthritis (RA) who initiated abatacept versus a TNF inhibitor (TNFi).

Methods—We identified RA patients aged ≥ 18 years with ≥ 2 RA diagnoses who initiated abatacept or a TNFi using claims data from Truven MarketScan database (2006–2015). The primary outcome was a composite endpoint of any hospitalized infection. Secondary outcomes were bacterial infection, herpes zoster, and infections affecting different organ systems. We performed 1:1 propensity score (PS) matching between the groups to control for baseline confounders. We estimated incidence rates (IR) and hazard ratio (HR) with 95% confidence intervals (CI) for hospitalized infection.

Results—We identified 11,248 PS-matched pairs of abatacept and TNFi initiators with median age of 56 years, and 83% female sex. The IR per 1,000 person-years for any hospitalized infection was 37 among abatacept initiators and 47 in TNFi initiators. The HR for the risk of any hospitalized infection associated with abatacept versus TNFi was 0.78 (95% CI 0.64–0.95) and remained lower when compared to infliximab (HR 0.63, 95% CI 0.47–0.85), while no significant difference was seen compared with adalimumab and etanercept. The risk of secondary outcomes was lower for abatacept for pulmonary infections, and similar to TNFi for the remaining outcomes.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publications. Drs. Chen and Kim had full access to all of the data in the study and take responsibility for the integrity for the data and the accuracy of the data analysis.

Study conception and design:

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Conclusions—In this large cohort of RA patients who used abatacept or TNFi as a first or second-line biologic agent, we found a lower risk of hospitalized infection after initiating abatacept versus TNFi which was driven mostly by infliximab.

Rheumatoid arthritis (RA) patients are at increased risk of infection compared to non-RA patients^{1–3}. Part of this elevated risk is secondary to RA disease and due to the impaired ability of the immune system to recognize and fight off infections^{4,5}. While new immunosuppressive therapies have led to dramatic improvements in controlling RA disease activity and damage, the risk of infection is further increased by immunosuppression, especially with the use of biologic disease-modifying anti-rheumatic drugs (DMARDs)^{6,7}. Tumor necrosis factor inhibitors (TNFi) and abatacept are both biologic DMARDs, used either as monotherapy or in combination with a nonbiologic DMARD, with comparable efficacy in the treatment of RA⁸. However, the two therapies may differ in the risk of infection with their use.

Infections are frequent adverse events associated with TNFi therapy in RA and the risk of infection with TNFi use is higher than with non-biologic DMARD use^{6,9,10}. While randomized clinical trial data for abatacept did not demonstrate increased risk of serious infections compared to placebo initially, subsequent studies have reported increased incidence of serious infections with its use, with reported IR for infection of 3.1 per 100-patient years^{11–15}. Although this rate is lower than the reported IR for TNFi of 6 per 100 patient-years⁶, there is a paucity of studies that have compared the two therapies directly. To date, no randomized clinical trial has compared the risk of infections between the different biologic therapies in RA. Previous observational studies have compared the risk of infections between abatacept and TNFi with mixed results^{16–19}. While some of these studies have demonstrated a lower risk of infection with abatacept, in one study the risk was similar between abatacept and TNFi¹⁸.

Given similar efficacy between abatacept and TNFi as biologic therapies for treatment of RA, one of the main determinants in choosing between the medications is minimizing the risk of infection. Therefore, the aim of this study was to compare the risk of hospitalized infections among RA patients who initiate abatacept versus TNFi in the real-world setting using a large US nationwide claims database. We hypothesized that the rates and risk of hospitalized infection would be lower among RA patients initiating abatacept compared to TNFi.

METHODS

Data Source and Cohort Definitions

We used de-identified medical and pharmacy claims data from the Truven MarketScan database (1/1/2006–9/30/2015), which contains longitudinal, comprehensive healthcare data for mostly commercially insured individuals in the U.S. from all 50 states²⁰.

We identified RA patients ages 18 and older with at least 2 RA International Classification of Diseases, 9th revision (ICD-9) codes (714.xx) separated by 7–365 days²¹. Among these RA patients, we selected new users of abatacept or TNFi (adalimumab, certolizumab,

etanercept, golimumab, and infliximab) by the National Drug Codes or J codes, with no dispensing of the medication during at least 365 days of continuous enrollment preceding the date of first dispensing (i.e., index date) of abatacept or TNFi. Patients were required to have the second RA diagnosis code on or before the index date. A diagram of cohort and study design is presented in Supplemental Figure S1. For abatacept initiators, we allowed patients to have used non-biologic DMARDs or TNFi during the baseline period. For TNFi initiators, we allowed patients to have used non-biologic DMARDs or abatacept during the baseline period. We excluded patients who used rituximab, tocilizumab or tofacitinib prior to the index date from the two groups, as the use of other biologic DMARDs could affect the risk of infection during follow-up. We also excluded patients with malignancy, renal dialysis, HIV/AIDS, and history of solid or bone marrow transplantation at baseline, as these are other known comorbidities that would increase the risk of infection.

Study patients were followed from the day following index date, until the earliest event of death, end of enrollment, switching of therapy from abatacept to TNFi or from TNFi to abatacept or outcome occurrence. In our primary analysis, we censored patients using as-treated analysis which used a threshold of less than 30 days of treatment or dispensing gap. In a separate sensitivity analysis, we allowed for any gap in treatment and censored patients at the last drug available date.

Data Collection

During the 365-day period prior to the index date, we collected baseline covariates that may be related to infectious risk including demographics (age, sex, calendar year of index date, region of residence), comorbidities including hypertension, diabetes, obesity, smoking, alcohol use, depression, cardiovascular disease, chronic renal disease, chronic liver disease, pulmonary disease, viral hepatitis, inflammatory bowel disease, hospitalization for infection by ICD-9 codes, and calculated combined comorbidity index at baseline²². We measured healthcare utilization characteristics including number of outpatient physician visits to primary care providers and specialists, emergency department visits, acute care hospitalizations, history of influenza vaccination and pneumonia vaccination, and number of unique generic drug prescriptions at baseline.

We assessed use of non-biologic DMARDs including methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, cyclosporine, tacrolimus, azathioprine, auranofin, and penicillamine. We also measured glucocorticoid use as any recent use in 30 days prior to the index date, any use during 365 days prior to the index date, and cumulative prednisone-equivalent dose for 365 days baseline period, calculated based on the total amount in milligrams of prednisone prescribed. We assessed any baseline use of non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 enzyme inhibitors (COXIBs), and proton-pump inhibitors. We also assessed use of opioids, antibiotics, and zoster treatment during the 365 days of baseline, and recent use within 30 days prior to the index date.

Outcomes

The primary outcome was the composite end point of any hospitalized infection including bacterial, viral or opportunistic infection based on the principal diagnosis for hospitalization.

We assessed secondary outcomes of bacterial infection, herpes zoster, and infections by affected organ system (bone/joint, cardiac, gastrointestinal, genitourinary, respiratory, skin/soft tissue, neurologic), based on the principal diagnosis for hospitalization. We used ICD-9 codes to identify hospitalized infection as previously described, with positive predictive value >80%^{16,23–25}.

Statistical Methods

We compared the baseline characteristics of the abatacept and TNFi cohorts. To control for over 40 potential confounders simultaneously, we generated propensity score (PS) for the predicted probability of a patient initiating abatacept versus TNFi given patient characteristics at baseline. We then performed a 1:1 PS nearest neighbor matching using a caliper of 0.025 on the PS scale²⁶. We compared the covariate balance after matching using standardized differences, and considered the absolute standard mean difference of <0.1 as balanced between the two matched groups²⁷. After PS matching, we estimated the incidence rates (IR) of the primary and secondary outcomes per 1,000 person-years in the two treatment groups. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for primary and secondary outcomes. We ensured the proportional hazards assumption was not violated by including the interaction term of exposure medication and survival time as a time-dependent covariate in our Cox model.

We performed separate PS matching for abatacept versus the 3 most commonly prescribed TNFi (adalimumab, etanercept and infliximab) and calculated the IR per 1,000 person-years and HR for the primary outcome of any hospitalized infection. In another sensitivity analysis, we identified and PS-matched patients who were treatment naïve and had not received either TNFi or abatacept in the baseline period and calculated the IR and HR for primary and secondary outcomes.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). The Institutional Review Board of the Brigham and Women's Hospital approved this study.

RESULTS

We identified 13,015 RA patients who were new initiators of abatacept and 52,719 RA patients who were new initiators of TNFi (Figure 1). After 1:1 PS matching, there were 11,248 pairs of patients initiating abatacept and TNFi. Baseline covariates were balanced after PS matching with absolute standardized mean difference <0.1. Prior to matching, the abatacept cohort was slightly older (54.8 ± 12.8 vs 52.1 ± 12.8) with a higher proportion of females (83% vs 76%) (Table 1). After PS matching, the abatacept cohort had a mean age of 55.3 ± 12.8 with 83% females, and TNFi cohort had a mean age of 55.5 ± 12.7 with 84% females.

The prevalence of several comorbidities was slightly higher among the abatacept cohort including diabetes, hypertension, cardiovascular disease, pulmonary disease but was well balanced between the two cohorts after PS matching. The combined comorbidity score was also higher among the abatacept cohort compared to the TNFi cohort (0.54 ± 1.38 vs 0.38 ± 1.18), and after PS matching was similar between the two cohorts (0.57 ± 1.42 vs 0.58

± 1.43). Measures of healthcare utilization were also generally higher in the abatacept cohort but was balanced after PS matching. Baseline hospitalized infection prevalence was 3% for both PS matched cohorts.

Use of RA-related medication was well-balanced between the PS matched cohorts, although prior to matching there was a lower prior use of methotrexate, hydroxychloroquine, and sulfasalazine in the abatacept cohort (Table 2). Steroid use was prevalent among both cohorts at 30 days prior to the index date (44% for abatacept, 42% for TNFi), and at 365 days prior (70% vs 69%). Notably, the 58% of the abatacept cohort had prescription dispensing for TNFi in the baseline period, compared to 4% of TNFi cohort patients who had prescription dispensing for abatacept.

The overall IR of the primary outcome for the composite endpoint of any hospitalized infections in our PS matched cohorts was 36.7 per 1,000 person-years (95% CI 31.8–42.3) for abatacept compared to 47.4 per 1,000 person-years (95% CI 41.5–54.1) for TNFi using as-treated analysis allowing for <30 days gap in treatment (Table 3). In the primary as-treated analysis allowing for <30 days gap in treatment, the mean follow-up time on active treatment was 0.46 ± 0.70 years for the abatacept group, and 0.41 ± 0.66 years for the TNFi group. The risk of hospitalized infection in abatacept was lower compared to TNFi initiators with a HR of 0.78 (95% CI 0.64–0.95).

In our PS matched sensitivity analyses between abatacept and the 3 most common TNFi, we found that the HR remained decreased for abatacept compared to infliximab (HR 0.63, 95% CI 0.47–0.85), but not statistically significantly higher or lower when compared to adalimumab (HR 0.78, 95% CI 0.57–1.06) and etanercept (HR 1.19, 95% CI 0.92–1.53) (Table 4). In a separate sensitivity analysis using as-treated analysis allowing for any gap in treatment the risk of infection was attenuated towards the null. When we broadened our outcome definition of infections using diagnosis codes at any position and not limited to the principal diagnosis code for hospitalization, the results were similar with HR of infection for abatacept compared to TNFi of 0.79 (95% CI 0.68–0.92). In secondary analyses assessing risk of separate types of infections, the HR was lower for respiratory infections among abatacept initiators compared to TNFi (Table 5). However, there was no significant difference in the risk of the other types of infections between the abatacept and TNFi cohorts.

As our abatacept initiator could have been treated with TNFi previously, and TNFi initiators could similarly have been treated with abatacept, we conducted sensitivity analysis for our primary and secondary outcomes for only patients who were treatment naïve to both therapies during the baseline period (Supplemental Table S1). After PS-matching we identified 4,574 treatment-naïve abatacept initiators and equal number of TNFi initiators. The HR for any hospitalized infection for abatacept compared to TNFi was 0.87 (95% CI 0.68–1.11).

DISCUSSION

RA patients are at increased risk of infections and this risk is further increased with use of immunosuppressive therapy. Whether there is a difference in infectious risk conferred by different biologic DMARDs is unclear. In this US nationwide study of RA patients, we found that the IR and risk of hospitalized infections were lower among patients initiating abatacept compared to TNFi. This difference in risk appears to be mostly driven by lower infection risk when compared to infliximab. In our secondary outcome analysis, risk of respiratory infections (e.g., pneumonia, empyema, upper respiratory tract infections) was also lower among patients in the abatacept cohort compared to the TNFi cohort. However, there was no significant difference in the risk of hospitalized infections by the remaining types of infections or by affected organ systems.

The IR for infections found in our study are similar to what has been reported for abatacept and TNFi in the literature, with reported IR for abatacept of 31 per 1,000 person-years, and 60 per 1,000 person-years for TNFi in separate studies^{6,13}. Further, the results are in line with most of the other studies that have compared the risk of infection between abatacept and TNFi. In a previous cohort study using Truven MarketScan data comparing the risk of infections in RA patients switching from first-line TNFi to rituximab, another TNFi or abatacept, the risk of infection was similar after switching to abatacept versus rituximab¹⁹. However, the infection risk was higher for those switching to another TNFi compared to rituximab. Similarly, a cohort study in Medicare data with RA patients who were previously treated with a biologic agent and newly switching to a different TNFi, rituximab, tocilizumab or abatacept found that the risk of one-year hospitalized infection was higher in the etanercept (HR 1.24, 95% CI 1.07–1.45), infliximab (HR 1.39, 95% CI 1.21–1.60) and rituximab (HR 1.36, 95% CI 1.21–1.53) groups compared to abatacept as reference¹⁷.

In another previous study using administrative claims data from 2005–2009, among RA patients who were initiating or switching biologic DMARD therapy, abatacept users had lower rates of hospitalized infection compared to infliximab (HR 0.68, 95% CI 0.48–0.96)¹⁶. The risk of infection was also lower for adalimumab and etanercept compared to infliximab in that study, while in our study we observed a lower infection risk for abatacept compared to infliximab (HR 0.63, 95% CI 0.47–0.85), a numerically lower risk for abatacept compared to adalimumab (HR 0.78, 95% CI 0.57–1.06), and similar risk for abatacept compared to etanercept (see Table 4).

In a predominantly male RA cohort of US veterans from 1998–2011, the risk of hospitalized bacterial infections was similar between abatacept compared to etanercept (HR 1.1, 95% CI 0.6–2.1), with IR for abatacept of 28 per 1,000 person-years (95% CI 17–47)¹⁸. These rates are in line with the hospitalized bacterial infection IR of 19.4 per 1,000 person-years (95% CI 15.9–23.6), and HR 0.81 (95% CI 0.62–1.06) in our study. Additionally, similar to our study results, previous reports comparing the risk of herpes zoster infections found no difference in the risk of zoster infections between abatacept and TNFi, with the IR of zoster infections slightly higher in previously reported literature for abatacept (IR 23.3 per 1,000 person-years, 95% CI 20.4–26.7 in one study²⁸, and IR 18.7 per 1,000 person-years, 95% CI

15.8–22.0 in another²⁹) compared to our study IR of 15.7 per 1,000 person-years (95% CI 12.7–19.6) in abatacept and 15.7 per 1,000 person-years (95% CI 12.5–19.8) in TNFi.

In our separate analysis comparing the risk of hospitalized infection in abatacept initiators versus the three most commonly prescribed TNFi, we found that the lower risk of hospitalized infection in abatacept initiators compared to TNFi was driven mostly by infliximab initiators (HR 0.63, 95% CI 0.47–0.85). The risk remained numerically, not statistically significantly, lower for abatacept in comparison to adalimumab initiators (HR 0.78, 95% 0.57–1.06), but the infection risk associated with abatacept was noted to be not significantly higher versus etanercept (HR 1.19, 95% CI 0.92–1.53). These results are in line with previously reported lower risk of serious infections in patients treated with etanercept compared to infliximab and adalimumab in a prospective cohort of RA patients in a Dutch registry³⁰. There are several potential explanations for this observed difference among TNFi. The peak concentration of infliximab which is delivered as an intravenous infusion is higher than that of adalimumab and etanercept which are administered as subcutaneous injections³¹. Additionally, the clearance of etanercept is significantly higher with lower steady-state drug level compared to infliximab and adalimumab, and the binding avidity to TNF subunits is lower for etanercept (1:1 ratio), compared to infliximab (up to 3:1 ratio)^{31,32}. Furthermore, etanercept is a TNF receptor fusion protein that binds only circulating TNF while infliximab is a monoclonal antibody against TNF and additionally has a cytotoxic effect by binding to cells that express TNF on their membranes³³.

Our study has several strengths as a large cohort of US patients with RA in a nationwide database with a new user design with active comparator. In comparison to the previously mentioned studies, we used PS matching to minimize confounding by indication and control for imbalance among the abatacept and TNFi treatment groups to including patient characteristics, regional variation and adjusted for a large number of baseline confounders between the two cohorts such as prior antibiotic and antiviral use, and history of vaccinations. We directly compared the IR and risk of infection between abatacept and TNFi inhibitors and found lower IR of infections for abatacept compared to TNFi, similar to the reported IR in the literature, and lower risk of infection among abatacept initiators. The reason for this decreased risk of infection found in our study and previous studies is unknown but may potentially be due to the fact that abatacept indirectly blocks T-cell costimulation rather than the mechanism of directly inhibiting cytokines for TNFi¹¹.

In a separate analysis using as-treated analysis allowing for any gap in treatment, there was no significant difference in risk of infection between the abatacept and TNFi cohorts. In our primary analysis, we used an as-treated analysis with <30 days of gap in treatment which requires high treatment adherence. Using this design, we observed a lower risk of hospitalized infection in abatacept initiators. This suggests that there may be selection bias for patients who are more adherent or continued on therapy versus those who discontinue their therapy for those on abatacept versus TNFi. Although it is not possible to ascertain the reasons for stopping the therapy after initiation using claims databases, one possibility is that there is a lower threshold to stop or switch from TNFi therapy if there was concern of risk of infection such as minor infections which may lower the rates of hospitalized infections for TNFi compared to abatacept.

It is notable that in our study which examined first-line or subsequent-line initiators of abatacept or TNFi, 58% of the abatacept cohort was previously on TNFi in the baseline period and would be classified as switchers, compared to only 4% of TNFi cohort who had previously used abatacept. In our sensitivity analysis, among patients who were treatment naïve to both abatacept and TNFi, the lower risk of infection among abatacept initiators compared to TNFi was attenuated toward the null. This suggests a potential role of RA disease severity of treatment history in addition to the types of biologics on the risk of infection in RA patients.

Our study has limitations. Although we used PS matching for confounding control, there is still a concern for partially measured covariates and lack of information on other covariates that may affect risk of infection. For instance, RA disease activity is an important factor that can affect the risk of infections³⁴, but is a covariate we are unable to capture in a claims database^{35–38}. Therefore, we included measures of steroid use, non-biologic DMARD use, number of rheumatology visits, and combined comorbidity index as covariates in our PS-matching. Steroid use was a covariate in our analysis, is another important factor in risk of infections and may be indirectly related to disease activity. However, there may be discrepancies between steroid dispensing measured in our study and actual use by patients^{39–41}. We also attempted to assess sero-status as a covariate were limited by power as less than 3% of patients in each cohort had available laboratory results. Additionally, socioeconomic status and race and ethnicity are important demographic factors in the US that contribute to health disparities and outcomes that we were unable to collect and adjust for in our study^{42,43}.

In this large nationwide cohort of RA patients in the U.S. initiating abatacept or a TNFi as a first- or second-line biologic therapy, we found a lower risk of any hospitalized infections associated with abatacept versus TNFi, particularly in comparison to infliximab, suggesting that RA patients with specific concerns about infections may benefit from use of abatacept compared to TNFi.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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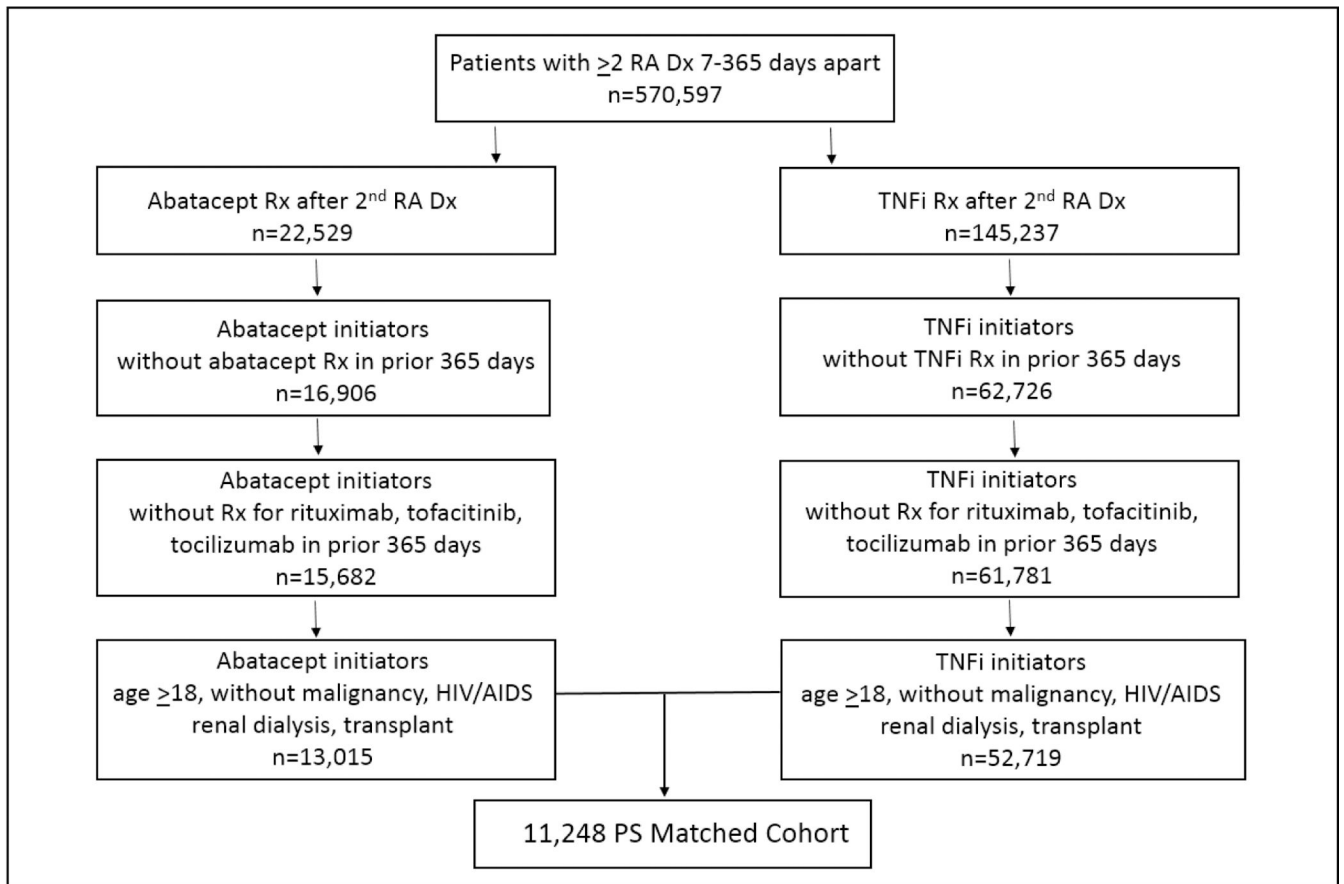
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Significance and Innovation

- Comparative safety of infection risk associated with biologic immunosuppression with TNF inhibitors versus abatacept in RA patients is unclear
- In this propensity score-matched study of 11,248 pairs of RA patients initiating abatacept or TNF inhibitor, the incidence rate and risk of hospitalized infections were lower among abatacept initiators (HR 0.78, 95% CI 0.64–0.95)
- In subgroup analysis, the risk of infection for abatacept remained lower when compared to infliximab initiators, but not for etanercept and abatacept initiators
- Use of abatacept is associated with a lower risk of hospitalized infections compared to TNF inhibitors among RA patients, in particular when compared to infliximab.



RA: rheumatoid arthritis; Dx: diagnosis; TNFi: TNF inhibitor; PS: propensity score

Figure 1. Flow chart of study cohort selection

RA: rheumatoid arthritis; Dx: diagnosis; TNFi: TNF inhibitor; PS: propensity score

Table 1.

Baseline characteristics of study cohorts, prior to and after 1:1 propensity score-matching

| | Prior to matching | | Propensity score-matched | |
|--------------------------------------|-----------------------|------------------|--------------------------|------------------|
| | Abatacept N=13,015 | TNFi N=52,719 | Abatacept N=11,248 | TNFi N=11,248 |
| Demographics | | | | |
| Mean age (SD), years | 54.8 (12.8) | 52.1 (12.8) | 55.3 (12.8) | 55.5 (12.7) |
| Female sex | 83% | 76% | 83% | 84% |
| Region | | | | |
| Northeast | 13% | 14% | 13% | 13% |
| South | 39% | 40% | 39% | 39% |
| North central | 21% | 22% | 21% | 21% |
| West | 15% | 16% | 15% | 15% |
| Unknown | 11% | 9% | 12% | 12% |
| Comorbidities | | | | |
| Obesity | 9% | 9% | 9% | 9% |
| Smoking | 12% | 12% | 12% | 13% |
| Alcohol use | 1% | 1% | 1% | 1% |
| Depression | 12% | 11% | 12% | 12% |
| Diabetes | 17% | 15% | 18% | 18% |
| Hypertension | 42% | 37% | 43% | 43% |
| Hyperlipidemia | 32% | 30% | 32% | 32% |
| Cardiovascular disease | 56% | 49% | 57% | 57% |
| Heart failure | 4% | 2% | 4% | 5% |
| Pulmonary disease | 19% | 16% | 20% | 20% |
| Chronic kidney disease | 4% | 3% | 4% | 4% |
| Chronic liver disease | 5% | 5% | 5% | 5% |
| Viral hepatitis | 1% | 1% | 1% | 1% |
| Inflammatory bowel disease | 1% | 3% | 1% | 1% |
| Hospitalized infection | 3% | 2% | 3% | 3% |
| Mean combined comorbidity score (SD) | 0.54 (1.38) | 0.38 (1.18) | 0.57 (1.42) | 0.58 (1.43) |
| Healthcare utilization | | | | |
| Mean No. PCP visits (SD) | 6.1 (7.8) | 5.3 (6.5) | 6.1 (7.9) | 6.1 (7.9) |
| Mean No. Rheumatology visits (SD) | 4.5 (4.7) | 3.4 (3.7) | 4.4 (4.7) | 4.2 (4.7) |
| ED visits | 31% | 28% | 31% | 31% |
| Any hospitalization | 17% | 13% | 18% | 18% |
| Mean No. unique prescriptions | 14.4 (8.2) | 13.2 (7.5) | 14.1 (8.3) | 14.1 (8.2) |
| Flu vaccination | 30% | 25% | 29% | 29% |
| Pneumonia vaccination | 7% | 8% | 7% | 7% |

Table 2.

Baseline medications of study cohorts, prior to and after 1:1 propensity score-matching

| | Prior to matching | | Propensity score-matched | |
|---|-----------------------|------------------|--------------------------|------------------|
| | Abatacept N=13,015 | TNFi N=52,719 | Abatacept N=11,248 | TNFi N=11,248 |
| Prior use of biologic DMARDs | | | | |
| Abatacept | 0% | 2% | 0% | 4% |
| TNFi | 64% | 0% | 58% | 0% |
| Adalimumab | 24% | 0% | 16% | 0% |
| Certolizumab | 4% | 0% | 2% | 0% |
| Etanercept | 24% | 0% | 16% | 0% |
| Golimumab | 4% | 0% | 3% | 0% |
| Infliximab | 21% | 0% | 20% | 0% |
| Prior use of non-biologic DMARDs | | | | |
| Methotrexate | 56% | 69% | 55% | 55% |
| Hydroxychloroquine | 23% | 27% | 23% | 23% |
| Leflunomide | 18% | 14% | 18% | 18% |
| Sulfasalazine | 9% | 12% | 9% | 8% |
| Other* | 8% | 5% | 8% | 8% |
| Steroid use | | | | |
| Steroid use | 70% | 69% | 68% | 67% |
| Recent steroid use (30 days prior) | 44% | 42% | 43% | 43% |
| Mean steroids cumulative dose 365 days in mg (SD) | 1235.9 (3484.3) | 1184.7 (9042.6) | 1192.9 (3572.8) | 1191.6 (6178.4) |
| Other Medications | | | | |
| Antibiotics | 69% | 64% | 69% | 68% |
| Recent antibiotics (30 days prior) | 19% | 16% | 19% | 19% |
| Antiviral for zoster | 8% | 6% | 8% | 8% |
| Recent antiviral for zoster | 3% | 2% | 3% | 3% |
| NSAIDs | 44% | 54% | 43% | 42% |
| COXIBs | 11% | 11% | 11% | 11% |
| Opioids | 68% | 64% | 67% | 67% |
| Recent opioids (30 days prior) | 40% | 33% | 39% | 40% |
| Proton-pump inhibitors | 30% | 26% | 30% | 30% |

* Other non-biologic DMARDs: cyclosporine, tacrolimus, azathioprine, auranofin, penicillamine

Table 3.

Risk of hospitalized infection in abatacept versus TNFi initiators: 1:1 PS-matched analysis

| | Abatacept (N=11,248) | | | | TNFi (N=11,248) | | | |
|---------------------------|----------------------|--------------|--------------------------|------------------|-----------------|--------------|--------------------------|-------------|
| | No. Events | Person-Years | IR, per 1000 PY (95% CI) | HR (95% CI) | No. Events | Person-years | IR, per 1000 PY (95% CI) | HR (95% CI) |
| As-Treated (<30 days gap) | 188 | 5,126 | 36.7 (31.8–42.3) | 0.78 (0.64–0.95) | 219 | 4,621 | 47.4 (41.5–54.1) | 1.0 |
| As-Treated (Any gap) | 298 | 8,201 | 36.3 (32.4–40.7) | 0.86 (0.74–1.01) | 321 | 7,639 | 42.0 (37.7–46.9) | 1.0 |

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Table 4. Risk of hospitalized infection in abatacept versus adalimumab, etanercept and infliximab: 1:1 PS-matched analyses

| | Abatacept | | | | | | TNFi | | | | | |
|--------------------------|--------------|------------|--------------|--------------------------|------------------|--------------|------------|--------------|--------------------------|-------------|--|--|
| | No. Patients | No. Events | Person-Years | IR, per 1000 PY (95% CI) | HR (95% CI) | No. Patients | No. Events | Person-years | IR, per 1000 PY (95% CI) | HR (95% CI) | | |
| Abatacept vs. adalimumab | 3,737 | 77 | 2,668 | 28.9 (23.1–36.1) | 0.78 (0.57–1.06) | 3,737 | 85 | 2,306 | 36.9 (29.8–45.6) | 1.0 | | |
| Abatacept vs. etanercept | 4,550 | 128 | 3,161 | 40.5 (34.1–48.2) | 1.19 (0.92–1.53) | 4,550 | 112 | 3,284 | 34.1 (28.3–41.1) | 1.0 | | |
| Abatacept vs. infliximab | 2,118 | 70 | 1,677 | 41.8 (33.0–52.8) | 0.63 (0.47–0.85) | 2,118 | 104 | 1,573 | 66.1 (54.5–80.1) | 1.0 | | |

Table 5.

Risk of secondary outcomes for abatacept versus TNFi initiators: 1:1 PS-matched analysis for as-treated (<30 days gap)

| | Abatacept (N=11,248) | | | | TNFi (N=11,248) | | | |
|------------------------|----------------------|--------------|--------------------------|------------------|-----------------|--------------|------------------|-------------|
| | No. Events | Person-Years | IR, per 1000 PY (95% CI) | HR (95% CI) | No. Events | Person-years | IR, per 1000 PY | HR (95% CI) |
| Bacterial infection | 100 | 5,160 | 19.4 (15.9–23.6) | 0.81 (0.62–1.06) | 112 | 4,621 | 24.0 (20.0–28.9) | 1.0 |
| Herpes zoster | 81 | 5,141 | 15.8 (12.7–19.6) | 1.00 (0.73–1.37) | 73 | 4,639 | 15.7 (12.5–19.8) | 1.0 |
| By organ system | | | | | | | | |
| Bone/Joint | 7 | 5,190 | 1.4 (0.6–2.8) | 0.91 (0.32–2.60) | 7 | 4,696 | 1.5 (0.7–3.1) | 1.0 |
| Cardiac | 0 | 5,191 | - | - | 1 | 4,697 | 0.2 (<0.1–1.5) | 1.0 |
| Gastrointestinal | 20 | 5,186 | 3.9 (2.5–6.0) | 0.75 (0.41–1.35) | 24 | 4,689 | 5.1 (3.4–7.6) | 1.0 |
| Genitourinary | 17 | 5,185 | 3.3 (2.0–5.3) | 1.04 (0.52–2.07) | 15 | 4,690 | 3.2 (1.9–5.3) | 1.0 |
| Respiratory | 65 | 5,160 | 12.6 (9.9–16.1) | 0.71 (0.52–0.99) | 83 | 4,666 | 17.8 (14.4–22.1) | 1.0 |
| Skin/soft tissue | 30 | 5,179 | 5.8 (4.1–8.3) | 0.68 (0.42–1.09) | 40 | 4,683 | 8.5 (6.3–11.6) | 1.0 |
| Neurologic | 1 | 5,191 | 0.2 (<0.1–1.4) | 0.91 (0.06–14.5) | 1 | 4,697 | 0.2 (<0.1–1.5) | 1.0 |