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# Association Between Anti-TNF-α Therapy and Interstitial Lung Disease

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## Abstract

**Background—**Anti-TNF-α agents have been hypothesized to increase the risk of interstitial lung disease (ILD), including its most severe manifestation, pulmonary fibrosis.

**Methods—**We conducted a cohort study among autoimmune disease patients who were members of Kaiser Permanente Northern California, 1998–2007. We obtained therapies from pharmacy data and diagnoses of ILD from review of X-ray and computed tomography reports. We compared new users of anti-TNF-α agents to new users of non-biologic therapies using Cox proportional hazards analysis to adjust for baseline propensity scores and time-varying use of glucocorticoids. We also made head-to-head comparisons between anti-TNF-α agents.

**Results—**Among the 8,417 persons included in the analysis, 38 (0.4%) received a diagnostic code for ILD by the end of follow-up, including 23 of 4,200 (0.5%) who used anti-TNF-α during study follow-up, and 15 of 5,423 (0.3%) who used only non-biologic therapies. The age- and gender-standardized incidence rate of ILD, per 100 person-years, was 0.21 (95% CI 0–0.43) for rheumatoid arthritis and appreciably lower for other autoimmune diseases. Compared to use of non-biologic therapies, use of anti-TNF-α therapy was not associated with a diagnosis of ILD among RA patients (adjusted hazard ratio, 1.03; 95% CI 0.51–2.07). Nor did head-to-head comparisons across anti-TNF-α agents suggest important differences in risk, although the number of cases available for analysis was limited.

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**Conclusion—**The study provides evidence that compared to non-biologic therapies anti-TNF-α therapy does not increase the occurrence of ILD among patients with autoimmune diseases, and informs research design of future safety studies of ILD.

### Keywords

Rheumatoid arthritis; psoriatic arthritis; psoriasis; Crohn's Disease; ulcerative colitis; inflammatory bowel disease; pharmacoepidemiology; drug safety; drug toxicity; adverse events; cohort studies; propensity scores; automated healthcare data; interstitial lung disease; pulmonary fibrosis

## INTRODUCTION

A recent systematic review published in *Pharmacoepidemiology and Drug Safety* called for research to identify algorithms that can be used to identify interstitial lung disease (ILD) and pulmonary fibrosis (PF) for use in active surveillance of drug safety.[1] As part of the Safety Assessment of Biological Therapy collaborative,[2–4] we validated automated diagnoses of ILD/PF using computed tomography (CT) and X-ray reports. ILD and PF have been linked to use of anti-TNF-α therapy.[5] However, they have also been reported in rheumatologic diseases in the absence of exposure to anti-TNF-α therapy.[6,7] We used the results of the validation study to conduct a cohort study evaluating the association of anti-TNF-α therapy, compared with non-biologic therapy, with risk of ILD/PF among persons with several autoimmune diseases This comparison was selected to increase relevance to the clinician who is selecting from therapies intended for active autoimmune disease.

## METHODS

The study was approved by the Kaiser Foundation Research Institute Institutional Review Board.

The cohort study was conducted among the membership of Kaiser Permanente Northern California, 1998–2007.[8] Pulmonary function tests are performed as an office procedure; the results of these tests were not easily accessible for research or for this analysis. Reports from X-ray and computed tomography (CT) procedures have been electronically accessible since 1996, with CT utilization increasing rapidly around the year 2000; these X-ray and CT reports were reviewed for the present study.

### Study Population

Eligible cohort members included those aged 0–89 years with rheumatoid arthritis [RA], ankylosing spondylitis [AS], psoriatic arthritis [PsA], psoriasis [PsO], and inflammatory bowel disease [IBD]) as operationally defined in our earlier publication using specific ICD-9 codes, recorded during 1998 through 2007.[4] Patients who had physician diagnostic codes indicating human immunodeficiency virus (HIV) infection, solid organ transplantation, advanced kidney or liver disease, a cancer diagnosis, or who were treated with cyclosporine or tacrolimus during the 12-month period preceding study entry were excluded because these persons were few in number, and their conditions may represent a relative contraindication for biologic therapy. We also excluded patients with ≥1 diagnosis of ILD recorded in the computerized data before 1998, as well as patients whose confirmed ILD occurred before they initiated a study therapy.

### Exposure Assessment

To inform clinical decision-making, we sought to compare anti-TNF-α initiators with initiators of alternative therapy used for similarly active disease. We evaluated three anti-

TNF-α drugs (etanercept, infliximab, and adalimumab). Comparison non-biologic therapy was defined specifically for each autoimmune disease under study. For RA, the comparison therapy was intensification of methotrexate (MTX) by adding or switching to hydroxychloroquine, sulfasalazine, or leflunomide. We refer to this regimen as "MTX step-up". The anti-TNF-α initiators were not required to have a history of MTX use. For PsA and AS, the comparison was initiation of MTX or sulfasalazine; for PsO, initiation of MTX; and for IBD, initiation of azathioprine or 6-mercaptopurine. The start date of the first eligible treatment episode (biologic or comparison) served as the index date. Consistent with an incident user design, patients were required to have 12 months of enrollment without an eligible treatment episode (anti-TNF-α or nonbiologic) before their index date. The earliest possible start date was January 1, 1998. The patient's baseline morbidity and health care utilization were coded using information recorded during the 12-month look-back period except for prior ILD, for which all available data were searched.

## Ascertainment and Validation of ILD

We identified eligible cohort members with ≥1 diagnosis of ILD (ICD-9 codes 515, 516.3, 516.8, and 518.89) as preliminary cases. The date of the first radiology procedure that confirmed the diagnosis of ILD was identified as the outcome date.

Study resources permitted review of the computerized X-ray or CT report, but not the complete medical record. Thus, we did not ascertain pulmonary function tests (recorded in clinic notes only) or other diagnostic information except as referenced in the radiology report. We reviewed available X-ray and CT reports for all preliminary cases; one patient without an X-ray or CT report was excluded as a potential case.

We conducted a pilot study to assess the feasibility of confirming the diagnosis and establishing the diagnosis dates of ILD/PF. For the pilot study, two study pulmonologists trained one of the study co-authors (LL) to identify diagnoses of ILD, PF, and related conditions from X-ray and CT reports. Thereupon, imaging reports for a sample of 100 preliminary cases with RA were reviewed. Symptoms, findings, and diagnoses were recorded, together with the reviewer's judgment, for final adjudication by a pulmonologist. Upon completion of the pilot study, we made the following decisions: (1) computerized outpatient diagnoses from physician visits alone were not accurate enough to meet the goals of the study, and review of X-ray and CT reports would be performed for all preliminary cases; (2) the information used for the study was not adequate to categorize ILD/PF as separate entities; (3) the information available to the study was not adequate to categorize the reversibility of ILD; (4) staff without medical training could be taught to review the X-ray and CT reports as needed to meet the study goals; and (5) the date of the first radiology-confirmed diagnosis of ILD was the best outcome date for use in the statistical analysis, although for many patients we did not have confidence that it reflected a true incidence date. Subsequently, two other reviewers were engaged, one for RA and IBD, and the other for AS, PsA, and PsO. They were trained by the initial reviewer and their work was adjudicated, as needed, by the study pulmonologists. They were not aware of the patient's exposure status during their review, unless the drug was mentioned in the radiology report as a reason for the procedure, such as "Patient started Enbrel."

Because of the more highly detailed descriptions in CT relative to X-ray reports, the CT report was reviewed first to confirm the diagnosis, with the X-ray report being used only if there was no CT scan. Relevant keywords and word stems were highlighted to focus the review, including: interstiti, parenchy, fibro, scar, groundglass (multiple spellings), opacity (opacities), reticular, honeycomb, methotrexate, enbrel, and remicade. The radiologist's diagnosis of ILD was taken as definitive. If "interstitial lung disease", "interstitial pneumonitis", "interstitial pneumonia", "fibrotic changes", "fibrosis", "fibrosing alveolitis",

or “pulmonary fibrosis” was noted, the case was confirmed with “definite ILD”. A patient whose radiology report noted a single instance of “interstitial markings” without ILD was coded as “possible ILD”. However, if “interstitial markings” appeared multiple times, the patient was coded as “definite ILD”. “Rheumatoid lung” was accepted as a diagnosis of ILD. If none of these keywords was used, cases were coded as “not ILD”. If an earlier diagnosis of ILD in the X-ray report was later negated by a CT report with clear wording such as “no evidence of ILD”, the patient was coded as “not ILD”. Patients referenced as having chemical exposure were confirmed as cases because these references were generally quite vague, e.g., “asbestos exposure 20 years ago”. We did not consider three patients noted with cryptogenic organizing pneumonia (COP), formerly known as bronchiolitis obliterans organizing pneumonia (BOOP), to have ILD.

## Data Analysis

**Positive predictive value of ILD/PF diagnoses—**The positive predictive value (PPV) of the ILD/PF diagnoses recorded in visit data was defined as the proportion of ILD/PF cases with the diagnosis code that were confirmed with ILD/PF during review of the CT or X-ray report. The 95% confidence interval (CI) was determined by approximating the binomial distribution with a normal distribution.[9]

**Propensity score methods—**To adjust for confounding factors and to bundle covariate information to mask personal health information for the Cox proportional hazards analysis, we computed the propensity score using >100 variables recorded during the 12-month baseline period (including 1997), as detailed in our earlier reports and in on-line material.[4, 10–13]

**Calculation of follow-up time—**For each analysis, patients entered follow-up on their index date. We continued to follow the patients after they stopped therapy, and censored them on the earliest of the death date, disenrollment, their 90$^{th}$ birthday, or the end of the study (December 31, 2007).

To describe the patterns of medication use after the index date, we categorized all follow-up time into mutually exclusive episodes defined by the biologic and comparison therapies under study, with some follow-up time being categorized as exposed to neither. The latter may have involved no treatment or treatment with a non-biologic drug that was outside the operational definition of comparison therapy (e.g., a non-steroidal anti-inflammatory agent alone).

To estimate the incidence rate and the association of anti-TNF-α therapy with risk of ILD, we categorized follow-up time differently. Patients who initiated an anti-TNF-α agent on the index date were coded as anti-TNF-α exposed to the end of follow-up even if they switched from anti-TNF-α therapy to a non-biologic comparison therapy or discontinued the anti-TNF-a therapy. In contrast, patients who initiated a comparison therapy on the index date were coded as such only until they switched to anti-TNF-α therapy. Thereafter they contributed person-time to the anti-TNF-α group. If they did not switch to anti-TNF-α therapy, they contributed cases and person-time to the non-biologic comparison group until the end of follow-up. This scheme was used in our previous study of anti-TNF-α therapy in relation to mortality;[3] it allows for the measurement of effects of therapy even after the therapy has been discontinued. Patients who switched from one anti-TNF-α drug to another (e.g., etanercept to infliximab), contributed outcomes and person-time to the first agent until they switched, whereupon they contributed person-time to the second agent, through the end of follow-up. Because ILD/PF generally develop as progressive diseases, and because the

number of cases available for analysis was limited, we continued to follow users even after they stopped therapy.

**Estimated incidence rate of ILD—**We tabulated the incidence rate of ILD using the 2000 Census data as the reference population to compute age- and sex-standardized mortality rates using the direct method with 5-year age groups. Calculation of 95% confidence intervals (CI) assumed a Poisson distribution.

**Association of anti-TNF-α therapy with incidence of ILD—**The adjusted hazard ratio (aHR) for the association of anti-TNF-α therapy with incidence of ILD was estimated using Cox proportional hazards modeling. The number of days from the index date, i.e., the date the patient initiated their first eligible treatment episode, was used as the time axis. We hypothesized that a recorded diagnosis of ILD was greater following initiation of anti-TNF-α therapy *versus* non-biologic comparison. In addition, in head-to-head comparisons, we hypothesized that a recorded diagnosis of ILD was greater for one anti-TNF-α drug than another. The Cox models included as independent variables exposure to anti-TNF-α or comparison therapy; propensity score quintile; average daily dose of oral glucocorticoid, averaged across and updated every 6 months; and data system, calendar year, race, gender, age group, smoking status, chronic pulmonary disease, and Charlson co-morbidity index.

Because patients could contribute episodes to both the comparison and anti-TNF-α cohorts, we used the Huber–White sandwich variance estimator to estimate the 95% confidence interval (CI).[14] In several analyses, we considered adalimumab and infliximab as a single exposure category.[15] Subgroup analyses were conducted in pre-specified vulnerable populations selected by the funding agency that comprised patients who were non-white, aged ≥75 years, or with ≥2 comorbidities. All statistical procedures were performed using SAS software version 9.2 (SAS Institute Inc, Cary, NC).

## RESULTS

### Validation of ILD

It was necessary to validate ILD/PF before the study population was identified to exclude patients with a history of ILD. Therefore, the validation study included patients who ultimately were excluded from the analysis. We identified 1,656 preliminary cases (≥2 diagnosis codes) of ILD, of which 446 cases (27%) had multiple autoimmune diseases of interest (Table 1). Only one preliminary case had neither an X-ray nor CT report. The number with both an X-ray and a CT report was 1,459 (88%); with an X-ray report only, 191 (12%); and with a CT report only, 6. The average number of CT reports per preliminary case was 3.4. The number of cases with ILD confirmed through review of the radiology report was 1,043, yielding a positive predictive value of 63% (95% CI, 60–65%) for those with ≥2 diagnosis codes of ILD. Among the 1,043 patients confirmed with ILD, 849 (81%) had the diagnosis recorded before the index date, making them ineligible for the study.

### Characteristics of the Study Population

Before computing the propensity scores, the number of eligible persons identified for the study was 9,053 of which 4,283 (47%) initiated an anti-TNF-α therapy and 4,770 (53%) did not, with 1,314 (31%) of the anti-TNF-α patients contributing person-years as non-biologic users before switching to anti-TNF-α. A total of 83 (2%) anti-TNF-α treated patients and 553 (11%) non-biologic comparator treated patients were excluded due to non-overlapping propensity scores, leaving 8,417 patients for the primary analysis. The average length of follow-up was 3.14 years (SD=2.30) among anti-TNF-α treated patients and 3.13 years (SD=2.40) among those not treated with anti-TNF-α.

Characteristics of the study population are shown in Table 2. Patients initiating anti-TNF-α differed from those initiating non-biologic comparison therapy in several ways. They entered the study later, were older on the index date, were more likely to have exposure to steroid during baseline, were more likely to be current smokers, and had greater co-morbidity (all $p<0.01$). In addition, they had slightly lower median household income ($59,059 vs. $60,529 ($p<0.01$). Because of the large numbers of subjects included, even modest differences were statistically significant.

Among the 4,200 patients who initiated anti-TNF-α therapy and had propensity scores that overlapped with propensity scores in the comparator group, the average time on anti-TNF-α therapy was 1.87 years (59% of total); average time on non-biologic comparison therapy was 0.28 years (9%); and average time on neither was 1.0 years (32%). Among the 4,217 propensity-score matched patients who initiated comparison non-biologic therapy but not anti-TNF-α therapy, the average time on non-biologic comparison therapy was 1.36 years (43%) and average time not on a study therapy was 1.77 years (57%). For both anti-TNF-α initiators and non-biologic comparison subjects, 52% used MTX after the index date, during the follow-up period.

### Estimated Incidence Rate of ILD

Among the 8,417 patients with autoimmune diseases who were eligible for the study, 38 were diagnosed with ILD. (Other cases of ILD enumerated in the validation study occurred in patients without eligible treatment episodes or whose propensity scores did not overlap.) The 38 cases included 23 of the 4,200 (0.5%) who used anti-TNF-α, and 15 of the 4,217 (0.3%) who used only comparison regimen. The overall incidence rate of ILD, standardized to the age and sex distribution of the 2000 U.S. population, per 100 person years, was 0.21 (95% CI 0–0.43) for RA and appreciably lower for PsO/PsA/AS at 0.03 (95% CI 0–0.12). No case of ILD occurred in an IBD patient.

### Association of anti-TNF-α with incidence of ILD

Among patients with RA, compared with MTX step-up who were included in the study, the HR for the relationship of any anti-TNF-α agent with risk of ILD was 1.03 (95% CI 0.51–2.07) (Table 3). In head-to head comparisons among anti-TNF-α therapy, aHRs were in the range of 0.54 to 1.40, with none reaching statistical significance. There were few ILD/PF cases among patients with PsO/PsA/AS; the resulting aHR was 2.87 with 95% CI of 0.44–18.61. We also sought to assess vulnerable subgroups, but their numbers were too small to permit meaningful interpretation, with confidence intervals ranging widely (online Table).

## DISCUSSION

We evaluated the relationship between anti-TNF-α therapy and risk of ILD in patients with several autoimmune diseases. Nearly all cases of ILD occurred among patients with RA and the standardized incidence rate of ILD/PF was 7 times higher in patients with RA than among those with PsO/PsA/AS. The number of ILD patients with prior anti-TNF-α use was small, limiting our ability to evaluate the relationship. Compared with RA patients stepping-up their MTX therapy, we observed no association of anti-TNF-α use with risk of ILD (HR 1.03, 95% CI 0.51–2.07) for the population included in the study.

A hypothesized relationship of anti-TNF-α therapy with risk of ILD and PF was proposed largely in response to case reports, which led to the inclusion of ILD as a potential adverse reaction in the package insert. Not only anti-TNF-α, but also MTX and leflunomide have been identified for possible associations with ILD and PF in RA, although these associations with MTX and leflunomide may have resulted from confounding by indication.[16] Further

challenging this enquiry is that the definition of drug-induced ILD is unrelated to any pathophysiologic findings, but instead is circumstantial.[16–18] One animal study has been reported; it demonstrated a *benefit* of anti-TNF-α therapy in reducing pulmonary inflammation in mice.[19] For a detailed discussion of the hypothesized pathogenetic link of this association, we refer the reader to the work of Ramos-Casals and colleagues.[5]

Case ascertainment is a challenge in studying ILD in autoimmune disease, especially inflammatory arthritis. Diagnosis of ILD/PF in Kaiser Permanente patients with RA, and in other populations not subject to tight diagnostic protocols, is highly variable. The symptoms of ILD/PF are non-specific, and the decision to refer a patient to radiology based on symptoms may be quite subjective. In addition, for some patients the first recorded diagnosis occurred after their true incidence date, although we could not measure this.

In a few patients, the indication for the imaging procedure was recorded as “patient to start Enbrel”. This would create detection bias, a spurious association between drug therapy and risk of ILD. However, for other patients, the indication was “patient to start MTX.” The indication for the scan was not systematically recorded on the imaging report, and it would be necessary to review the clinic and hospital notes to better understand why the procedure was done. Lung CT is most commonly ordered for the RA patient when the presenting symptoms are respiratory, or when the established RA patient’s joint symptoms respond to treatment but their respiratory symptoms do not, for which CT is used to rule-out co-morbid respiratory disease. We noted numerous indications for the index scan, including dyspnea, cough, emphysema, chronic obstructive pulmonary disease, pulmonary nodules, lung cancer, rule-out pulmonary embolism, congestive heart failure, and chemical exposure. ILD/PF at times was recorded as a serendipitous finding. Under-ascertainment of ILD for this study could affect the HR in either direction, depending on whether the ascertainment was or was not systematically related to drug exposure.

For patients with a one-time CT reading, we do not have a basis for assuming that the condition was chronic or acute. ILD/PF is not always permanent: drug-induced ILD/PF may be transient or treatable. Many preliminary cases had only a single CT scan, and among those with multiple scans, ILD/PF was confirmed only if a diagnosis in the CT report was not negated by a later CT report, as when the initial finding had been tentative. This influenced case-finding for only a small number of subjects.

Contemporary diagnostic criteria for ILD, in the absence of surgical lung biopsy, include (1) abnormal pulmonary function studies that include evidence of restriction with or without impaired gas exchange, (2) chest X-ray or high-resolution CT with findings of bibasal reticular abnormalities with ground glass opacities, and (3) bronchoalveolar lavage showing no features to support an alternative diagnosis.[2] CT is considered the most sensitive procedure for identifying early ILD. Because of study resources, we did not review clinical history or lung function tests, so that the diagnosis of ILD/PF was based on the presence of a diagnostic code in visit data together with confirmation through review of the radiology report. We also accepted the diagnosis if the finding was supported by the radiologist reviewing an X-ray report, although the number of such cases was very small.

ILD in the RA patient is treated using the same drug regimens that are used to treat joint and other systemic disease; thus, the diagnosis typically does not lead to a therapeutic change. While reading the CT scans, we observed that some physicians ordered the CT early in the course of ILD while others requested the procedure late in the course of the disease. Thus, with some patients, an annual scan was available, and it was possible to assess reports longitudinally as radiographs changed from “clear” to “possible ILD”. With other patients, the very first scan revealed “severe ILD with scarring.” Future studies of ILD/PF should

seek to understand the reason for the referral to imaging, and to record the severity and duration of any respiratory symptoms; the present study did not have the resources needed for the detailed chart review that would be needed to ascertain the reason for the procedure.

Another limitation of our study concerned the coding of drug use following the index date. We used a conservative assumption, coding patients who initiated an anti-TNF-α agent on the index date as anti-TNF-α exposed to the end of follow-up even if they switched from anti-TNF-α therapy to a non-biologic comparison therapy or discontinued the anti-TNF-a therapy. The alternative was to code this follow-up time as not exposed to anti-TNF-α, which would have generated a lower incidence of ILD in those with a history of anti-TNF-α therapy. Despite this conservative assumption, we did not observe an association of anti-TNF-α therapy with risk of ILD. Furthermore, only 9% of these patients' follow-up time involving exposure to the non-biologic comparator therapy, so the issue is minor.

There has been little work to understand the diagnosis or progression of ILD as needed for community-based epidemiological research. In the UK-based General Practice Research Database, 128 cases of drug-/radiation-induced ILD were identified during 1997–2008, for an incidence rate of 4.1 (95% confidence interval 3.4–4.9) per million person-years.[20] This should be considered against the much higher background rate we measured of 0.21 per 100 person-years in patients with RA. Underascertainment of ILD was documented in a study conducted at the National Institutes of Health, Bethesda, Maryland in which 21 patients (33%) with RA but without dyspnea or cough had preclinical ILD identified by CT. By 24 months follow-up, the CT abnormalities progressed in 12 (57%) of the patients.[21] The prevalence of ILD in an inception cohort of 582 patients with RA identified during 1955–95 was reported for the Rochester Epidemiology Project, Minnesota.[17] The case definition for ILD was more specific than used in the present study, requiring a diagnosis of ILD by a pulmonologist together with positive findings on 2 of 3 tests: (1) CT or chest radiograph, (2) pulmonary function, and (3) bronchoscopic or surgical lung biopsy. The observed prevalence was 7.9% with an average follow-up of 16.4 years; however, these results cannot be compared with the present report because we excluded patients with a history of ILD before newly initiating anti-TNF-α or MTX step-up therapy.

Progression of ILD was evaluated in relation to use of anti-TNF-α therapy in the British Society for Rheumatology Biologics Register using cause-specific death as the outcome.[18] The mortality in RA patients with ILD at baseline was not increased following treatment with anti-TNF-α therapy compared with traditional agents (adjust mortality rate ratio, 0.80 with 95% CI, 0.34–1.87). However, the proportion of deaths attributable to ILD was higher in patients treated with anti-TNF-α therapy. The authors hypothesized that selection of frail patients with ILD for traditional therapy over anti-TNF-α therapy may have biased the mortality rate ratio downward.

Our study was designed to compare risk of ILD in anti-TNF-α initiators compared with patients using non-biologic DMARD, defined among RA patients as stepping-up from MTX. We observed a higher prevalence of ILD among patients with RA compared to patients with other autoimmune diseases, and we did not find evidence that anti-TNF-α increases or decreases the risk of ILD in RA or other autoimmune diseases relative to the comparison regimens. Detection bias linked to case-finding of incident ILD, which would shift the hazard ratio upward, presents an inherent challenge to studying this relationship. Further, the small number of ILD cases limited our ability to draw inferences. Greater understanding of the onset and progression of ILD will improve studies of its etiology and clarify interpretation of the role of detection bias in drug safety studies of these respiratory diseases. The study should assist clinicians choosing among therapies for patients with active autoimmune disease.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Validation and Eligibility of ILD Cases, Kaiser Permanente Northern California, 1998–2007.

| Validation and Eligibility | Autoimmune disease | | | Number of autoimmune diseases | | Total number of patients* |
|---|---|---|---|---|---|---|
| | RA | PsO/PsA/AS | IBD | 1 | ≥2 | |
| One or more computerized diagnosis of ILD | 828 | 854 | 431 | 1210 | 446 | 1,656 |
| ILD confirmed by review of the radiology report | 529 (64%) | 531 (62%) | 251 (58%) | 779 (64%) | 264 (59%) | 1,043 (63%) |
| ILD recorded before the index date** | 342 | 523 | 246 | 591 | 258 | 849 |
| ILD recorded in a patient without exposure to a study therapy or with a propensity score that did not overlap | 151 | 6 | 5 | 150 | 6 | 156 |
| ILD recorded after the index date in an eligible study subject with PS score that overlapped** | 36 | 2 | 0 | 38 | 0 | 38 |

*No preliminary cases were observed with juvenile idiopathic arthritis.

**The start date of the first eligible treatment episode (biologic or comparison) served as the index date. Consistent with an incident user design, patients were required to have 12 months of enrollment without an eligible treatment episode (biologic or comparison) before their index date.

## Table 2

Characteristics of the Study Population at Baseline (N=8,417)*, %

| Characteristic* | Anti-TNF-α** N=4,200 | Non-biologic comparison*** N=4,217 |
|---|---|---|
| Year at index**** | | |
| 1998–1999 | 5 | 9 |
| 2000–2001 | 12 | 17 |
| 2002–2003 | 21 | 21 |
| 2004–2005 | 30 | 25 |
| 2006–2007 | 32 | 27 |
| Sex | | |
| Female | 66 | 59 |
| Age at index, years | | |
| 0–39 | 19 | 25 |
| 40–49 | 22 | 20 |
| 50–59 | 28 | 23 |
| 60–69 | 17 | 17 |
| 70–90 | 13 | 15 |
| Race/ethnicity | | |
| African-American | 7 | 8 |
| Asian | 11 | 11 |
| Hispanic | 6 | 5 |
| Native American | 2 | 2 |
| White | 66 | 66 |
| Other | 8 | 10 |
| Steroid exposure during 12-month baseline | | |
| Yes | 56 | 51 |
| Smoking | | |
| Never | 79 | 82 |
| Former | 6 | 7 |
| Current | 14 | 11 |
| Charlson comorbidity index | | |
| 0 | 29 | 53 |
| 1 | 54 | 34 |
| 2+ | 18 | 13 |
| Chronic pulmonary disease | | |
| Yes | 12 | 13 |
| Methotrexate during the 12-month look-back | | |
| Yes | 53 | 34 |
| Chest imaging | | |
| X-ray | 35 | 27 |
| Computed tomography | 3 | 2 |

*Restricted to patients with propensity scores that overlapped.

** Each patient is shown in the table only once. The 1,206 patients contributing person-years to both the anti-TNF-α group and the non-biologic comparison group are shown with the anti-TNF-α group.

*** All variables except gender and race are significant at $p<0.01$ in logistic regression models that contain all variables in this table.

**** The start date of the first eligible treatment episode (biologic or comparison) served as the index date. Consistent with an incident user design, patients were required to have 12 months of enrollment without an eligible treatment episode (biologic or comparison) before their index date.

**Table 3**

Adjusted Hazard Ratio (aHR) with 95% Confidence Intervals (CI) for the Association of Initiating Use of Anti-TNF-α with the occurrence of ILD among 8,417 Persons with Autoimmune Diseases,* of Whom 38 were identified with ILD.

| Autoimmune disease | Anti-TNF-α No. of cases/no. of patients | Comparison No. of cases/no. of patients | aHR** | 95% CI |
|---|---|---|---|---|
| **RA** | | | | |
| Anti-TNF-α vs MTX step-up | 22/2,698 | 14/2,074 | 1.03 | 0.51–2.07 |
| INF vs ETA*** | 8/874 | 12/1,586 | 0.74 | 0.30–1.84 |
| ADA vs ETA | 3/951 | 8/1,267 | 0.54 | 0.13–2.21 |
| ADA or INF vs ETA | 11/1,657 | 11/1,617 | 0.68 | 0.29–1.61 |
| ADA vs INF | 4/938 | 3/559 | 1.40 | 0.33–5.94 |
| **PsO/PsA/AS** | | | | |
| Anti-TNF-α vs non biologic DMARDs | 1/961 | 1/1,218 | 2.87 | 0.44–18.61 |

* Restricted to patients with propensity scores that overlapped. Patients are shown multiple times in the table if they had multiple autoimmune diseases. Incidence was age- and sex-standardized to 2000 Census population using 5-year age groups.

** In addition to using a propensity score, the analysis controlled for baseline dose of steroid during the 12-month look-back period, data system, calendar year, race, gender, age group, smoking status, chronic pulmonary disease, Charlson co-morbidity index, and daily dose of steroid following index date as a time-dependent variable. The start date of the first eligible treatment episode served as the index date. Consistent with an incident user design, patients were required to have 12 months of enrollment without an eligible treatment episode before their index date.

*** INF, infliximab; ETA, etanercept; ADA, adalimumab.