Risk of serious infections with bDMARDs in psoriasis/psoriatic arthritis patients: a large-scale cohort study using the Italian VALORE Project distributed database

Summary

Introduction

Psoriasis (PsO) is a common chronic, multisystem, immuno-mediated dermatologic disease.

PsO has different clinical phenotypes, but the most frequent and most easily recognized is chronic plaque or psoriasis vulgaris [Griffiths et al., 2021]. PsO is associated with many diseases, most notably with psoriatic arthritis (PsA), a seronegative inflammatory arthritis observed in 10–40% of patients with PsO, which can further deteriorate quality of life by affecting physical function [Vena et al., 2010; FitzGerald et al., 2021]. Estimated prevalence of PsO ranges from 0.1% in east Asia to 1.5-2.7% in western Europe and Italy. [Griffiths et al., 2021; Pezzolo et al., 2019; Ingrasciotta et al., 2021].

Several therapeutic options for PsO/PsA are available. Choice of treatment depends on disease severity, location, and multimorbidity. First-line PsO treatment involves topical therapies including

emollients, corticosteroids, vitamin D3 analogues, calcineurin inhibitors, keratolytics, and combination topical agents, as cream, ointment, foam, or gel formulations, as well as targeted phototherapy. Moderate to severe diseases require oral systemic therapies, with heterogeneous mechanisms of action, documented efficacy and safety profiles [Ogdie et al., 2020]. For the PsA treatment, nonsteroidal anti-inflammatory agents (NSAIDs) can be used as a symptomatic treatment, while glucocorticoids should be used only as a relief treatment at the lowest dose and for the shortest time duration [Ogdie et al., 2020; FitzGerald et al., 2021]. Other commonly used oral drugs for PsO/PsA treatment include acitretin, fumarates, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), e.g., methotrexate, sulfasalazine, leflunomide, cyclosporine, and, more recently, biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (PDE4 inhibitors – apremilast) and JAK inhibitors (tofacitinib, upadacitinib, baricitinib) [Griffiths et al., 2021; Bakshi et al., 2020]. As for bDMARDs, in Europe a large number of molecules for moderate to severe PsO/PsA treatment have been authorized (see **Table A1**) [Griffiths et al., 2021; Bakshi et al., 2020]: Tumour Necrosis Factor-α (TNF-α) antagonists (adalimumab, certolizumab pegol, golimumab, etanercept, infliximab), Interleukin-17 Receptor Antagonist (IL-17RA) (brodalumab), IL-17 antagonists (ixekizumab, secukinumab, bimekizumab), IL-23 antagonists (guselkumab, risankizumab, tildrakizumab), IL-12/IL-23 antagonists (ustekinumab), T cell modulator (abatacept).

PsO/PsA patients have an increased baseline risk for infections per se, due to the loss of the integrity of skin barrier and intrinsic cellular immunity alterations [Schön, 2019; Lowes et al., 2014; Haddad et al., 2016]. Based on record linkage analyses of claims and clinical databases (CPRD GOLD) in United Kingdom, Yiu et al. [Yiu et al., 2021] found around 30% increased risk of severe infections in patients with PsO, as compared to matched patients PsO-free, after adjustment for potential confounders such as systemic therapies and other comorbidities. Several RCTs and observational studies of patients with moderate-to-severe PsO/PsA reported a differential increase in the infection risk across various systemic drugs (see **Table A2**). While bDMARDs have shown dramatic improvement in terms of benefit, safety issues have been largely documented, including the risk of serious infection [Ingrasciotta et al., 2018; Cutroneo et al., 2014]. Results from a recent systematic review and meta-analysis [Yiu et al., 2016; Manounah et al., 2021] of RCTs of patients with PsO/PsA on bDMARDs therapies show that the total number of serious infections reported across all RCTs was low (n = 54) and eight studies did not report any serious infections in either study arm. However, most RCTs included past serious infection as an exclusion criteria. Indeed, many observational studies identified infection as one of the primary reasons for therapy discontinuation; however, these studies did not include more recently commercialized bDMARDs [Yiu et al., 2019; Yiu et al., 2017;

Li et al., 2019; Penso et al., 2021; Grijalva et al., 2011; Jin et al., 2022; Kalb et al., 2015; Dávila-Seijo et al., 2017; Wang et al., 2022]. Some cohort studies found that adalimumab and infliximab are associated to a higher risk of serious infections compared with other bDMARDs or non-biologic therapies, while ustekinumab is associated to a lower risk [Penso et al., 2021; Kalb et al., 2015; Jin et al., 2022; Penso et al., 2021; Quartuccio et al., 2018; Siegel et al., 2019]. In the aforementioned cohort studies, gastrointestinal, skin and subcutaneous tissue, pulmonary, and urinary tract infections were the most commonly reported severe infections.

To the best of our knowledge, no prior studies compared the risk of severe infections among bDMARDs in a large Italian cohort of patients affected by PsO/PsA, nor the risk related to more recently approved bDMARDs.

Objective

Primary objective: To evaluate the association between the use of individual bDMARDs approved for PsO/PsA treatment and the occurrence of severe infection risk in an Italian real-world setting in the years 2010-2021 among different drug class (TNF-alpha inhibitors, IL inhibitors, T cell modulator), using the large-scale "VALORE" project distributed database network.

Secondary objective: The assessment of the severe infection differential incidence between bDMARDs in monotherapy and in combination therapy with csDMARDs and/or systemic corticosteroids.

Methods

Data source

Fully anonymized data will be extracted from the VALORE project multi-regional claims databases, covering a total underlying population of around 2/3 of the total Italian population from 2010 to 2022. In particular, the following regional claims databases will be considered: (1) inhabitant registry, including demographic information about the date of birth, sex, and date of registration in the regional healthcare system; (2) drug dispensing from hospital and territorial pharmacy claims database; (3) Hospital Discharge Records (HDR), including information on the date of hospital admission and discharge, diagnosis-related group (DRG), principal diagnosis and up to five secondary diagnoses, and principal procedure and up to five secondary procedures; (4) Exemptions (EXE) from healthcare service co-payment database, collecting coded information about chronic diseases or socioeconomic factors and outpatient diagnostic tests and specialist's visits database. Coverage of all these healthcare services is very high since Italy has National Health Service offering universal care for all residents in each region. Drugs were coded using the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD) was used as the unit to estimate drug exposure for

bDMARDs, while indication of use and causes of hospitalization were coded using the International Classification of Disease, 9th revision, Clinical Modification (ICD 9-CM).

In Italy, bDMARDs with subcutaneous formulations are dispensed to patients by hospital pharmacists for outpatient use, whereas intravenous bDMARDs (e.g., infliximab) are administered in dedicated hospital ambulatory care centers. In each region, information on dispensing of bDMARDs, irrespective of the formulations, are collected in claims data. The VALORE project distributed database network has been previously described elsewhere [Trifirò et al., 2021].

An R-based open-source tool "TheShinISS," developed by the Italian National Institute of Health for conduction of distributed analyses and described elsewhere [Trifirò et al., 2021], was customized for the purposes of the study, in compliance with EU General Data Protection Regulation regulations.

Study design

A Retrospective, propensity score-matched, cohort study.

Cohort selection

All users of bDMARDs approved for PsO/PsA with at least one year of look-back period will be considered. Subjects will be included in the cohort only if all the following inclusion criteria will be met:

a) Incident users, defined as all bDMARDs users without any dispensing of bDMARD in the year prior to the index date (ID) (i.e., first date of bDMARD dispensing). The first dispensing of bDMARDs will be considered as the index drug.
b) A diagnosis of PsO/PsA registered anytime prior to ID, identified using a validated coding algorithm (**Table A3**) [Pezzolo et al., 2021]. As for those drugs approved exclusively for PsO/PsA (brodalumab, guselkumab, tildrakizumab, risankizumab) this criterion will not be considered.
c) At least two dispensing of bDMARDs during the study period. A sensitivity analysis will be conducted to include those patients with 1 dispensing of bDMARD.

Patients will be followed from the ID until one of the following events, whichever comes first: a) hospitalization for severe infection (see **Table A4** for the list of severe infections); b) switch/swap to different bDMARD, c) death; d) end of follow-up (31 December 2021), or e) emigration from the region.

Drug exposure

The list of biological drugs approved in Italy for the treatment of PsO/PsA up to 31st December 2022 to be included in the study is reported in Table A1 : a) Tumor Necrosis Factor (TNF)-alpha inhibitors: infliximab (L04AB02), etanercept (L04AB01), adalimumab (L04AB04), golimumab (L04AB06) and certolizumab pegol (L04AB05); b) Interleukin-17 Receptor Antagonists: brodalumab (L04AC12); c) Interleukin-17 antagonists: ixekinumab (L04AC13), secukinumab (L04AC10), bimekizumab (L04AC21); d) IL-23 antagonists: guselkumab (L04AC16), risankizumab (L04AC18), tildrakizumab (L04AC17); e) IL-12/IL-23 antagonists: ustekinumab (L04AC05); f) T cell modulator: abatacept (L04AA24).

Outcome

The occurrence of a serious infection during follow up will be considered the outcome. Infections reported either in the literature as potentially associated to the bDMARDs under study, or in section 4.4 "Special Warnings and Appropriate Precautions for Use" of summary of product characteristics or in the "Important identified or potential risks" section of the risk management plan of individual bDMARDs approved for PsO/PsA treatment were considered. In particular the following severe infections requiring hospitalization will be included in the outcome definition: herpes simplex, herpes zoster, primary tuberculosis, pulmonary tuberculosis, extra-pulmonary tuberculosis, non-invasive candidiasis, invasive candidiasis, sepsis, endocarditis, viral hepatitis, pneumonia, non-invasive fungal infections, invasive fungal infections, infections of conjunctiva and other infections of the eye, COVID-19, osteomyelitis/infection of joints, cystitis, infections of kidney, infections of skin and subcutaneous tissue, intestinal infectious diseases (See **Table A4** of the Appendix**)**.

Time to onset will also be estimated as number of days between the ID and the severe infection disease occurrence.

Other variables

Demographic characteristics: Gender (0: male; 1: female) and age (years) at index date.

Year of cohort entry.

Region.

Previous use of drugs (y/n): At least one drug dispensing in the year before index date for the following drugs: csDMARDs (methotrexate: L04AX03, sulfasalazine: A07EC01, leflunomide: L04AA13, cyclosporine: L04AD01), systematic corticosteroids (ATC: H02*).

Concomitant drugs (y/n): At least two dispensing of csDMARDs (1,0), systematic corticosteroids (1,0) in the 3 months pre and 3 moths after index date.

Charlson's Comorbidity Index: see table **Table A5** for definition.

Comorbidities (y/n): Previous record in the year before index date from exemptions and hospital discharge records of one of the following disease: obesity, diabetes mellitus, chronic obstructive pulmonary disease, history of infections, including HIV, concomitant autoimmune diseases other than PsO/PsA [i.e. rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, celiac disease, multiple sclerosis, autoimmune hepatitis; IBD (Crohn's disease and ulcerative colitis), hidradenitis suppurativa]. (Please see **Table A6** for those variables' codes and descriptions).

Statistical analysis plan

Descriptive analysis: baseline characteristics of incident users of bDMARDs, stratified by drug class, will be reported as the mean along with the standard deviation (SD) and absolute and relative frequencies (percentages) for continuous and categorical variables, respectively. For continuous variables, the symmetry of their distributions will be assessed by the skewness index and the assumption of normality will be assessed by the Shapiro–Wilk test. For skewed variables, the median and interquartile range (IQR, i.e. first-third quartiles) will be reported instead of the mean and SD.

Incidence of severe infections:

- Primary objective: Estimation of the incidence of severe infection between different drug classes (TNF alpha vs IL-inhibitors/Selective Immunosuppressive agents).

Propensity score (PS) matching procedure: A 5 to 1 greedy 1:1 PS matching algorithm [Parsons et al., 2004] will be used to create two cohorts of bDMARDs users with the same baseline characteristics: TNF-alpha vs other bDMARDs (IL-inhibitors/selective immunosuppressive agents). This was done since selective immunosuppressive agents account only for abatacept which is reported to have a similar infection safety profile to IL-inhibitors [Chen et al., 2020]. To compute PS, a binary logistic regression will be built to predict the individual probability of having each drug class dispensed based on the following covariates: age at ID (categorical variable with the following groups: ≤18, 19-44, 45-64, 65-79, ≥80 years), sex, calendar year, previous use of csDMARDs, previous use of corticosteroids. The balance between the two PS matched cohorts will be assessed by computing the Standardized Mean Difference (SMD) for each covariate. This measure quantifies the magnitude of the overall difference in terms of "effect size": for SMD < 20% there is a small difference between groups (for SMD < 10% this difference is negligible) [Sawilowsky, 2009]. To statistically assess the adequacy of covariates balance, the non-parametric Wilcoxon signed rank and McNemar's tests will be performed for continuous and categorical variables, respectively. Moreover, to assess the "pre-matching" balance between the two cohorts (i.e. before the PS algorithm will be

performed), SMD will eventually be computed for each covariate at issue in the unmatched sample along with the Mann-Whitney U and Chi-Square (or Fisher as appropriate) tests for continuous and categorical variables, respectively.
The incidence of serious infections requiring hospitalization will be estimated as the number of occurred events out of the total number of person-years and will be reported per 100 person-years for ease of interpretation.

Cox Proportional-Hazards regression model: The effect of bDMARDs classes (using TNF-α antagonists as the reference drug class) on the incidence of serious infections requiring hospitalizations, among incident users of bDMARDs in PsO/PsA patients, will be estimated using the Cox Proportional-Hazards regression model. Risks will be reported as Hazard ratios (HR) along with their 95% confidence interval (CI) and will be estimated both in the unmatched cohort (crude and adjusted for other covariates) as well as in the PS matched cohort. In the latter case, the sandwich (robust) variance estimator will be used to adjust the covariance estimates of the model parameters to account for the correlations within paired individuals. The assumption of proportionality of the hazards over time will be checked for each covariate included in the model by the Kolmogorov-Type Supremum test [Lin et al., 1993]. In case of violation of this assumption, different strategies for dealing with the problem will be considered, such as stratification or the inclusion of a time-by-covariate interaction in the model as appropriate.

Moreover, both crude and fully-adjusted Cox models will be estimated to assess the effect of each active ingredient (using infliximab as the reference active ingredient) on the incidence of serious infections requiring hospitalizations in the unmatched cohort. The same covariates used for the propensity score matching procedure will be included in the fully-adjusted Cox model.

- Second objective: Risk of serious infections using bDMARDs alone vs bDMARDs + corticosteroids or csDMARDs

Cox Proportional-Hazards regression model: Also in this case, the effect of using bDMARDs alone vs bDMARDs + corticosteroids or csDMARDs on the incidence of serious infections requiring hospitalizations, among incident users of bDMARDs in PsO/PsA patients, will be estimated using both crude and fully-adjusted Cox Proportional-Hazards regression models in the unmatched cohort only. Risks will be reported as HRs along with their 95% CIs. The same covariates used for the propensity score matching procedure will be included in the fully-adjusted Cox model.

The assumption of proportionality of the hazards over time will be checked for each covariate included in the model by the Kolmogorov-Type Supremum test. In case of violation of this assumption, different strategies for dealing with the problem will be considered, such as stratification or the inclusion of a time-by-covariate interaction in the model as appropriate.

Sensitivity analyses

- For both primary and secondary objective analysis, discontinued users will be censored at the time of treatment discontinuation (i.e. interruption of more than 45 days after supply end).
- For both primary and secondary objective analysis, censoring for switch to different bDMARDs will not be performed and the exposure to drug categories will be considered as a time dependent variable.

Results plan

Patients' characteristics: The unmatched and the PS matched cohorts will be described for in terms of sex, median age, age bands (<18, 19-44, 45-64, 65-79, 80+ years), type of index drug (biosimilar or originator), concomitant use of medications, and comorbidities.

Table 1. Characteristics of incident users of bDMARDs by drug class

	PS unmatched cohort			**PS matched cohort**		
X	**TNF-alfa inhibitors**	**Anti-interleukin /IS**	**SMD before matching (p value)**	**TNF-alfa inhibitors**	**Anti-interleukin /IS**	**SMD after matching (p value)**
PS matching factors						
Female, n (%)						
Median age, years [IQR]						
Age bands, n (%)						
≤18						
19-44						
45-64						
65-79						
≥80						
Calendar year						
…						
Previous use of csDMARDs						
Previous use of corticosteorids						
Other covariates						
Concomitant use of						
Methotrexate						
Sulfasalazine						
Leflunomide						
Cyclosporine						
Corticosteroids						
Charlson comorbidity index, median IQR						
Comorbidities						

Previous serious infections						
Diabetes						
COPD						
Rheumatoid arthritis						
Ankylosing spondylitis						
Systemic lupus erythematosus						
Celiac disease						
Multiple sclerosis						
Crohn's disease						
Ulcerative colitis						
Hidradenitis suppurativa						

Abbreviations: bDMARDs: Disease-Modifying Antirheumatic Drugs; COPD: Chronic Obstructive Pulmonary Disease; csDMARDs: conventional synthetic Disease-Modifying Antirheumatic Drugs; IQR: Interquartile Range (i.e. first-third quartiles); PS: Propensity Score; SMD: Standardized Mean Difference

Time to onset: Time to onset of serious infections will only be computed among patients with the outcome (i.e. excluding the times of censored users) by drug class (TNF-alpha inhibitors, anti-IL, and selective immunosuppressant) and median, along with interquartile range, will be estimated. This calculation will also be performed by active ingredient and by concomitant medications. Kaplan Meier analysis will also be performed in the matched and unmatched cohorts, considering the entire follow-up period.

Incidence of serious infection (Table 2): The incidence of serious infections will be calculated among the drug class (TNF-alfa as reference) in the unmatched and matched cohorts as detailed in the statistical analysis plan. Moreover, a sensitivity analysis by active ingredient will be performed (results will not be reported in Table 2). Moreover, a risk analysis will be performed evaluating bDMARDs vs bDMARDs and the combination with csDMARDs and/or corticosteroids (table 3).

Table 2. Incidence of serious infections occurring after index date (primary objective)

	PS unmatched (original) cohort					**PS matched cohort**
Exposure	**Events**	**Person-years**	**N events per 100 person year**	**Crude HR and 95CI%**	**Adj HR* and 95CI%**	**HR (PS matched cohorts) and 95CI%**
TNF-α antagonists				REF	REF	REF
Anti-interleukins /IS						

Table 3. Incidence of serious infections occurring after index date (secondary objective)

Exposure	**Events**	**Person-years**	**N events per 100 person year**	**HR (Unadjusted cox model) CI95%**	**HR (Adjusted cox model) CI95%***
bDMARDs alone				REF	REF
bDMARDs + corticosteroids					
bDMARDs + csDMARDs					
bDMARDs + csDMARDs + corticosteroids					
bDMARDs + csDMARDs or corticosteroids					

*models will be adjusted for the following covariates: age at the index date, sex, calendar year, previous use of csDMARDs, previous use of corticosteroids.

Abbreviations: bDMARDs: Disease-Modifying Antirheumatic Drugs; csDMARDs: conventional synthetic Disease-Modifying Antirheumatic Drugs; HR: Hazard Ratio; CI: Confidence Interval; PS: Propensity Score

Limitations

Information regarding duration of the disease is missing. Additionally, we were unable to determine whether a drug was prescribed for PsO or PsA. Although the disease's severity (e.g., Psoriasis Area Severity Index) was unavailable, the patients were affected by moderate to serious PsO or PsA due to the cohort selection criteria (patients taking bDMARDs).

Ethics Statement

This retrospective study protocol was notified to the Ethical Committees of the Academic Hospital of Messina and Verona, according to the current national law [Ministero della Salute, 2007]. The manuscript does not contain clinical studies or patient data. Formal consent is not required for this type of study.

References (AMA format)

Bakshi H, Nagpal M, Singh M, Dhingra GA, Aggarwal G. Treatment of Psoriasis: A Comprehensive Review of Entire Therapies. Curr Drug Saf. 2020;15(2):82-104. doi:10.2174/1574886315666200128095958

Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. Psychother Psychosom. 2022;91(1):8-35. doi:10.1159/000521288

Chen SK, Liao KP, Liu J, Kim SC. Risk of Hospitalized Infection and Initiation of Abatacept Versus Tumor Necrosis Factor Inhibitors Among Patients With Rheumatoid Arthritis: A Propensity Score-Matched Cohort Study. Arthritis Care Res (Hoboken). 2020;72(1):9-17. doi:10.1002/acr.23824

Cutroneo PM, Isgrò V, Russo A, et al. Safety profile of biological medicines as compared with non-biologicals: an analysis of the italian spontaneous reporting system database. Drug Saf. 2014;37(11):961-970. doi:10.1007/s40264-014-0224-1

Dávila-Seijo P, Dauden E, Descalzo MA, et al. Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry. J Invest Dermatol. 2017;137(2):313-321. doi:10.1016/j.jid.2016.08.034

Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol. 2018;178(2):509-519. doi:10.1111/bjd.16102

FitzGerald O, Ogdie A, Chandran V, et al. Psoriatic arthritis. Nat Rev Dis Primers. 2021;7(1):59. Published 2021 Aug 12. doi:10.1038/s41572-021-00293-y

Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018;392(10148):650-661. doi:10.1016/S0140-6736(18)31713-6

Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. Lancet. 2021;397(10281):1301-1315. doi:10.1016/S0140-6736(20)32549-6

Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-α antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. JAMA. 2011;306(21):2331-2339. doi:10.1001/jama.2011.1692

Haddad A, Li S, Thavaneswaran A, Cook RJ, Chandran V, Gladman DD. The Incidence and Predictors of Infection in Psoriasis and Psoriatic Arthritis: Results from Longitudinal Observational Cohorts. J Rheumatol. 2016;43(2):362-366. doi:10.3899/jrheum.140067

Ingrasciotta Y, Isgrò V, Ientile V, Tari M, Trifirò G, Guarneri C. Are Patients with Psoriasis and Psoriatic Arthritis Undertreated? A Population-Based Study from Southern Italy. J Clin Med. 2021;10(15):3431. Published 2021 Jul 31. doi:10.3390/jcm10153431

Ingrasciotta Y, Cutroneo PM, Marcianò I, Giezen T, Atzeni F, Trifirò G. Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction. Drug Saf. 2018;41(11):1013-1022. doi:10.1007/s40264-018-0684-9

Jin Y, Lee H, Lee MP, et al. Risk of Hospitalization for Serious Infection After Initiation of Ustekinumab or Other Biologics in Patients With Psoriasis or Psoriatic Arthritis. Arthritis Care Res (Hoboken). 2022;74(11):1792-1805. doi:10.1002/acr.24630

Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2015;151(9):961-969. doi:10.1001/jamadermatol.2015.0718

Li X, Andersen KM, Chang HY, Curtis JR, Alexander GC. Comparative risk of serious infections among real-world users of biologics for psoriasis or psoriatic arthritis. Ann Rheum Dis. 2020;79(2):285-291. doi:10.1136/annrheumdis-2019-216102

Lin D, Wei L, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals.Biometrika 1993;80(3):557–572

Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol. 2014;32:227-255. doi:10.1146/annurev-immunol-032713-120225

Manounah L, Z.Z.N. Yiu, S.K. Mahil, L.S. Exton, M.C. Ezejimofor, A.D. Burden, R. Murphy, C.M. Owen, R. Parslew, R.T. Woolf, C.H. Smith, M.F. Mohd Mustapa. Risk of Serious Infections in Patients with Psoriasis on Biologic Therapies: An Updated Systematic Review and Meta-Analysis. medRxiv 2021.08.27.21262722; doi: https://doi.org/10.1101/2021.08.27.21262722

Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. *Rheumatology (Oxford)*. 2020;59(Suppl 1):i37-i46. doi:10.1093/rheumatology/kez383

Parsons LS. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. Proceedings of the Twenty-Sixth Annual SAS users Group International Conference. Cary, NC: SAS Institute, Inc., 2004.

Penso L, Dray-Spira R, Weill A, Pina Vegas L, Zureik M, Sbidian E. Association Between Biologics Use and Risk of Serious Infection in Patients With Psoriasis. JAMA Dermatol. 2021;157(9):1056-1065. doi:10.1001/jamadermatol.2021.2599

Pezzolo E, Ciampichini R, Cazzaniga S, Sampietro G, Zucchi A, Naldi L. Psoriasis severity matters when dealing with all-cause mortality in psoriasis patients: a record linkage analysis in Northern Italy. Arch Dermatol Res. 2021;313(4):255-261. doi:10.1007/s00403-020-02101-1

Pezzolo E, Cazzaniga S, Colombo P, Chatenoud L, Naldi L. Psoriasis Incidence and Lifetime Prevalence: Suggestion for a Higher Mortality Rate in Older Age-classes among Psoriatic Patients Compared to the General Population in Italy. Acta Derm Venereol. 2019;99(4):400-403. doi:10.2340/00015555-3130

Quartuccio L, Zabotti A, Del Zotto S, Zanier L, De Vita S, Valent F. Risk of serious infection among patients receiving biologics for chronic inflammatory diseases: Usefulness of administrative data. *J Adv Res*. 2018;15:87-93. Published 2018 Sep 19. doi:10.1016/j.jare.2018.09.003

Sawilowsky, S (2009). "New effect size rules of thumb". Journal of Modern Applied Statistical Methods. 8 (2): 467–474

Schön MP. Adaptive and Innate Immunity in Psoriasis and Other Inflammatory Disorders. Front Immunol. 2019;10:1764. Published 2019 Jul 26. doi:10.3389/fimmu.2019.01764

Siegel SAR, Winthrop KL. In the Real World: Infections Associated with Biologic and Small Molecule Therapies in Psoriatic Arthritis and Psoriasis. *Curr Rheumatol Rep*. 2019;21(7):36. Published 2019 Jun 6. doi:10.1007/s11926-019-0832-y

Takeshita J, Gelfand JM, Li P, et al. Psoriasis in the US Medicare Population: Prevalence, Treatment, and Factors Associated with Biologic Use. *J Invest Dermatol*. 2015;135(12):2955-2963. doi:10.1038/jid.2015.296

Trifirò G, Isgrò V, Ingrasciotta Y, et al. Large-Scale Postmarketing Surveillance of Biological Drugs for Immune-Mediated Inflammatory Diseases Through an Italian Distributed Multi-Database Healthcare Network: The VALORE Project. BioDrugs. 2021;35(6):749-764. doi:10.1007/s40259-021-00498-3

Vena GA, Altomare G, Ayala F, Berardesca E, Calzavara-Pinton P, Chimenti S, Giannetti A, Girolomoni G, Lotti T, Martini P, Mazzaglia G, Peserico A, Puglisi Guerra A, Sini G, Cassano N, Cricelli C. Incidence of psoriasis and association with comorbidities in Italy: a 5-year observational study from a national primary care database. Eur J Dermatol. 2010 Sep-Oct;20(5):593-8. doi: 10.1684/ejd.2010.1017. Epub 2010 Jul 7. PMID: 20605768

Wang J, Geng X, Zhang X, Xiao Y, Wang W. Hepatitis B Virus Reactivation and Mycobacterial Infections Associated With Ustekinumab: A Retrospective Study of an International Pharmacovigilance Database. Front Pharmacol. 2022;13:921084. Published 2022 Jul 4. doi:10.3389/fphar.2022.921084

Yiu ZZN, Ashcroft DM, Evans I, et al. Infliximab is associated with an increased risk of serious infection in patients with psoriasis in the U.K. and Republic of Ireland: results from the British Association of Dermatologists Biologic Interventions Register (BADBIR) [published correction appears in Br J Dermatol. 2019 Sep;181(3):646]. Br J Dermatol. 2019;180(2):329-337. doi:10.1111/bjd.17036

Yiu ZZN, Exton LS, Jabbar-Lopez Z, Mohd Mustapa MF, Samarasekera EJ, Burden AD, Murphy R, Owen CM, Parslew R, Venning V, Ashcroft DM, Griffiths CEM, Smith CH, Warren RB. Risk of Serious Infections in Patients with Psoriasis on Biologic Therapies: A Systematic Review and Meta-Analysis. J Invest Dermatol. 2016 Aug;136(8):1584-1591. doi: 10.1016/j.jid.2016.03.035. Epub 2016 Apr 13. PMID: 27085754; PMCID: PMC4946794

Yiu ZZN, Parisi R, Lunt M, et al. Risk of hospitalization and death due to infection in people with psoriasis: a population-based cohort study using the Clinical Practice Research Datalink. Br J Dermatol. 2021;184(1):78-86. doi:10.1111/bjd.19052

Yiu ZZN, Smith CH, Ashcroft DM, et al. Risk of Serious Infection in Patients with Psoriasis Receiving Biologic Therapies: A Prospective Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2018;138(3):534-541. doi:10.1016/j.jid.2017.10.005

Appendix

Table A1. bDMARDs (originator/biosimilars) for the treatment of PsO/PsA by mechanism of action

Class	**Drug - ATC**	**Indication**	**Condition**	**Original (bold) and biosimilars approved by EMA**
TNF-alpha inhibitors	Infliximab - L04AB02	PsO	Adults: moderate to severe disease not responders to MTX, ciclosporin or PUVA	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
		PsA	Adults: active and progressive disease not responders to csDMARDs	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
	Etanercept - L04AB01	PsO	Adults: Moderate to severe disease not responders or intolerant to systematic therapy (ciclosporin, MTX, PUVA) Pediatric (6+): Chronic disease inadequately controlled or intolerant to systematic therapy or phototherapy	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
		PsA	Adults: active and progressive disease not responders to csDMARDs Pediatric (12+): not responders or intolerant to MTX	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
	Adalimumab - L04AB04	PsO	Adults: moderate to severe disease who are candidate to systemic therapy	**Humira®,** Hulio®, Hyrimoz®, Amgevita® Idacio® Imraldi®

			Pediatric (4+): Severe chronic disease not responders to topical therapy or phototherapy	Yuflyma® Hefiya® Libmyris® Amsparity®
		PsA	Adults: active and progressive disease not responders to csDMARDs	**Humira®,** Hyrimoz®, Amgevita® Idacio® Imraldi® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
	Certolizumab – L04AB05	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Cimzia®**
		PsA	Adults: active and progressive disease not responders to csDMARDs	**Cimzia®**
	Golimumab L04AB06	PsA	Adults: active and progressive disease not responders to csDMARDs	**Simponi®**
Interleukin-17 Receptor Antagonists	Brodalumab - L04AC12	PsO	Adults: Moderate to severe disease candidates to systematic therapy	**Kyntheum®**
Interleukin-17 antagonists	Ixekinumab - L04AC13	PsO	Adults: Moderate to severe disease candidates to systematic therapy	**Taltz®**
		PsA	Adults: active disease not responders to csDMARDs	**Taltz®**
	Secukinumab - L04AC10	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Cosentyx®**

		PsA	Adults: active disease not responders to csDMARDs	**Cosentyx®**
	Bimekizumab - L04AC21	PsO	Adults: Moderate to severe disease candidates to systematic therapy	**Bimzelx®**
IL-23 antagonists	Guselkumab - L04AC16	PsO	Adults: Moderate to severe disease candidates to systematic therapy	**Tremfya®**
		PsA	Adults: active disease not responders or intolerant to csDMARDs	**Tremfya®**
	Risankizumab - L04AC18	PsO	Adults: Moderate to severe disease candidates to systematic therapy	**Skyrizi®**
		PsA	Adults: active disease not responders or intolerant to csDMARDs	**Skyrizi®**
	Tildrakizumab - L04AC17	PsO	Adults: Moderate to severe disease candidates to systematic therapy	**Ilumetri®**
IL-12/IL-23 antagonists	Ustekinumab - L04AC05	PsO	Adults: Moderate to severe disease not responders or intolerant to systematic therapy (ciclosporin, MTX, PUVA) Pediatric (6+): Moderate to severe disease inadequately controlled or intolerant to systematic therapy or phototherapy	**Stelara®**
		PsA	Adults: active disease not responders to csDMARDs	**Stelara®**

T cell modulator	Abatacept – L04AA24	PsA	Adults: active disease not responders or intolerant to csDMARDs or MTX (addiotional systematic therapy not required)	**Orencia®**

Abbreviations: DMARDs: disease-modifying antirheumatic drugs; MTX: Methotrexate; PUVA: psoralen and ultraviolet-A light

Table A2. Articles by reference number: disease, study design, study drugs and findings

Articles (by reference number)	**Study Design**	**Disease**	**Study drugs**	**Findings**
Yiu ZZN, Ashcroft DM, Evans I, et al	Prospective cohort study	chronic plaque psoriasis	Infliximab vs nonbiologic systemic therapies	Infliximab: increased risk of serious infections
Yiu ZZN, Smith CH, Ashcroft DM, et al	Retrospective cohort study	moderate to severe psoriasis	etanercept, adalimumab, ustekinumab vs non-biologic systemic therapies	No significant increases in the risk of serious infection
Grijalva CG, Chen L, Delzell E, et al	Retrospective cohort study	rheumatoid arthritis, IBD, psoriasis, psoriatic arthritis, ankylosing spondylitis	TNF-α antagonists vs nonbiologic comparators	Not association with an increased risk of hospitalizations for serious infections
Li X, Andersen KM, Chang HY, Curtis JR, Alexander GC	Retrospective cohort study	Psoriasis and psoriatic arthritis	IL-17 (ixekizumab or secukinumab) vs IL-12/23 (ustekinumab) vs TNF (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) antagonists	Relative to TNF and IL-17, IL-12/23 inhibitors were associated with a reduced risk of serious infection

Jin Y, Lee H, Lee MP, et al	Retrospective cohort study	Psoriasis and psoriatic arthritis	ustekinumab versus other bDMARDs or apremilast	Other bDMARDs and apremilast were associated with a 1.4- to 3-times higher risk of hospitalization for serious infections when compared to ustekinumab
Penso L, Dray-Spira R, Weill A, Pina Vegas L, Zureik M, Sbidian E	Retrospective cohort study	moderate to severe psoriasis	tumor necrosis factor inhibitor, interleukin (IL) 12/23 inhibitor, IL-17 inhibitor, IL-23 inhibitor, apremilast	risk of serious infections was increased in infliximab and adalimumab vs etanercept, whereas ustekinumab had lower risk and no differences for IL-17 and IL-23 inhibitors or apremilast
Kalb RE, Fiorentino DF, Lebwohl MG, et al	Prospective cohort study	Psoriasis	ustekinumab, infliximab, adalimumab, etanercept, and nonbiologics	higher risk of serious infections with adalimumab and infliximab compared with nonmethotrexate and nonbiologic therapies. No increased risk was observed with ustekinumab or etanercept
Dávila-Seijo P, Dauden E, Descalzo MA, et al	Prospective cohort study	Psoriasis	bDMARDs (infliximab, etanercept, adalimumab, and ustekinumab) and nonbiological drugs (acitretin, cyclosporine, and methotrexate)	overall infections was significantly increased in the groups treated with adalimumab with methotrexate, infliximab, cyclosporine, and ustekinumab combined with methotrexate. Cyclosporine was the

				only drug that showed a significant increased risk of serious infections compared with methotrexate. Adalimumab in combination with methotrexate had the highest risk of infection recurrence
van der Schoot, LS, Groenewoud, HJMM, van Gelder, MMHJ, Otero, ME, Arnold, WP, Berends, MAM, et al	Prospective cohort study	Psoriasis and psoriatic arthritis	adalimumab, apremilast, certolizumab, etanercept, golimumab, ixekizumab, secukinumab, ustekinumab	Other bDMARDs and apremilast were associated with a 1.4- to 3-times higher risk of hospitalization for serious infections compared to ustekinumab
Wang J, Geng X, Zhang X, Xiao Y, Wang W	Retrospective cohort study	Patients in ustekinumab treatment	Ustekinumab vs Hepatitis B Virus Reactivation and Mycobacterial Infections	Apparently no harm
Egeberg A, Ottosen MB, Gniadecki R, et al	Retrospective cohort study	moderate-to-severe plaque psoriasis treated with bDMARDs	adalimumab, etanercept, infliximab, secukinumab and ustekinumab (also comparing originator vs biosimilars	highest rate of infections occurred with secukinumab, infliximab had a lower incidence of infections which may reflect that patients with high risk of infections are not started on this therapy

Menter A, Tyring SK, Gordon K, et al	Multicenter RCT	moderate to severe psoriasis	adalimumab (40 mg) vs placebo	nonserious infectious were greater among adalimumab-treated patients, serious infections were comparable
Gordon KB, Strober B, Lebwohl M, et al	Multicenter RCT	moderate-to-severe chronic plaque psoriasis	150 mg risankizumab, 45 mg or 90 mg ustekinumab (weight-based per label), or placebo	infections were more frequently reported in patients receiving risankizumab or ustekinumab compared with those receiving placebo

Table A3. Coding algorithm to identify the PsO/PsA indications for use of bDMARDs from regional claims databases.

	Source	Criteria
Algorithm (PsA e PsO)	*HDR* | *ETP*	696.0 **OR** 696.1
		OR
	EXE	045 (045.696.0 045.696.1) **OR** 696.0 **OR** 696.1
		OR
	pharmacy claims	Adalimumab
		OR
	pharmacy claims	Certolizumab
		OR
	pharmacy claims	Efalizumab
		OR
	pharmacy claims	Etanercept
		OR
	pharmacy claims	Golimumab
		OR
	pharmacy claims	Infliximab
		OR
	pharmacy claims	Secukinumab
		OR
	pharmacy claims	Ustekinumab
		OR
	pharmacy claims	Brodalumab
		OR
	pharmacy claims	Guselkumab
		OR
	pharmacy claims	Tildrakizumab
		OR
	pharmacy claims	Risankizumab
		OR
	pharmacy claims	Ixekizumab
		OR

		≥ 2 drug dispensing:
	pharmacy claims	Acitretin
		OR
	pharmacy claims	Cyclosporine
		OR
	pharmacy claims	MTX
		OR
	pharmacy claims	Betamethasone **AND** Salicylic acid
		OR
	pharmacy claims	Calcipotriol
		OR
	pharmacy claims	Calcipotriol **AND** Betamethasone
		OR
	pharmacy claims	Tacalcitol (≥ 2 drug dispensing in the last year)
		OR
	pharmacy claims	Tazarotene ((≥ 2 drug dispensing in the last year)
		OR
	Specialist consultation registry	Outpatient specialist consultation code: 99.82 ((≥ 2 in the last year)
		AND NOT
	pharmacy claims	Anti-TNFα **OR** MTX **OR** Cyclosporine
		AND
	HDR | *EXE* | *ETP*	720.0 **OR** 054
		OR
	SDO | *EXE* | *ETP*	555 **OR** 556 **OR** 009
		OR
	Specialist consultation registry	Phototherapy
		AND
	HDR | *EXE* | *ETP*	Atopic dermatitis **OR** Lymphoma **OR** Systemic corticosteroids
		OR
	EXE	045.696.0 **OR** 045.696.1
		AND
	HDR | *EXE* | *ETP*	714* **OR** 716.9

Abbreviations: HDR : Hospital Discharge Records, EXE : Exemptions, ETP: Electronic Therapeutic Plan, MTX: methotrexate

Table A4. Severe infectious diseases variables in HDRs: ICD-9 codes

Variable	Codes	Description
Herpes simplex	054	Herpes simplex
Herpes zoster	053	Herpes zoster
Primary tuberculosis	010	Primary tuberculous infection
Pulmonary tuberculosis	011, 012	Pulmonary tuberculosis and other respiratory tuberculosis
Extra-pulmonary tuberculosis	013, 014, 015, 016, 017, 018, 137	Tubercolosis of meninges and central nervous system, tuberculosis of intestines, peritoneum, and mesenteric glands, tuberculosis of bones and joints, tuberculosis of genitourinary system, tuberculosis of other organs, miliary tuberculosis
Non-invasive candidiasis	1120, 1121, 1122, 1223	Candidiasis of the skin, nails and mucosa
Invasive candidiasis	1124, 1125, 1228, 1129	Candidiasis of the lung, other organs or disseminated
Sepsis	99591, 99592, 78552, 7907, 038	Sepsis, septic shock
Endocarditis	03642, 07422, 0932, 09884, 421, 42292	Endocarditis (mainly infectious)
Viral hepatitis	070	Viral hepatitis (A, B, C, others)
Pneumonia	480-486, 07889	Viral pneumonia, bacterial pneumonia
	4870	Influenza with pneumonia
Non-invasive fungal infections	0390, 0394	Fungal infections infections of the skin, scalp and nails (except Candida albicans)

Invasive fungal infections	0391, 0392, 0393, 0398, 0399, 114, 115, 116, 117, 118, 4846, 4847, 7116	Visceral fungal infections (except Candida albicans)
Infections of conjunctiva	077	Infections of conjunctiva
Infections of the eye	3731, 3732, 3734, 3735, 3736	Infections of the eye, except diseases of conjunctiva
COVID-19	4803, 07982	With or without pneumonia, but severe disease
Osteomyelitis/ infection of joints	730, 711, 00323, 05671, 0985, 00324, 37603, 5264	Osteomyelitis, periostitis, infection of joints
Cystitis (UTI)	5950, 5954, 597, 5990	Cystitis
Infections of kidney	590	Pyelonephritis
Infections of skin and subcutaneous tissue	686, 035, 0400, 56961, 681, 682, 72886, 7854	Severe infections of skin and subcutaneous tissue
Intestinal infectious diseases	001-009	Intestinal infectious diseases
	567	Peritonitis and retroperitoneal infections
	566	Abscess of anal and rectal regions

Table A5. Definition of the Charlson comorbidity index [Charlson ME et al, 2022], ICD-9 codes.

Disease	ICD-9 codes
Myocardial infarction	410.x, 412.x
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x
Peripheral vascular disease:	093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular disease	362.34, 430.x - 438.x
Dementia	290.x, 294.1, 331.2
Chronic pulmonary disease	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8
Rheumatic disease	446.5, 710.0 - 710.4, 714.0 - 714.2, 714.8, 725.x
Peptic ulcer disease	531.x - 534.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Diabetes without chronic complication	250.0 - 250.3, 250.8, 250.9
Diabetes with chronic complication	250.4 - 250.7
Haemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin	140.x - 172.x, 174.x - 195.8, 200.x - 208.x, 238.6
Moderate or severe liver disease	456.0 - 456.2, 572.2- 572.8
Metastatic solid tumour	196.x - 199.x
HIV/AIDS	042.x - 044.x

Table A6. Other variables, ICD-9 codes.

Variable	ICD-9	Description
Obesity		
Diabetes mellitus	250, 3572, 3620, 36641, 6488, 7751, 79029, 2490-2499	Diabetes mellitus including type 1, congenital diabetes, gestational diabetes, diabetes complications.
COPD	491	Chronic bronchitis and chronic obstructive pulmonary disease
History of infections	V120	Personal history of infectious and parasitic diseases
HIV	042	Human Immunodeficiency Virus infection
Rheumatoid arthritis	714	Rheumatoid arthritis
Ankylosing spondylitis	720	Ankylosing spondylitis
Systemic lupus	7100, 6954	Systemic lupus erythematosus, Lupus erythematosus including erythematodes (discoid) and erythematosus (discoid) not disseminated
Celiac disease	5790	Celiac disease
Multiple sclerosis	340	Multiple sclerosis
Autoimmune hepatitis	57142	Autoimmune hepatitis
Crohn's disease	555	Regional enteritis Includes: Crohn's disease, Granulomatous enteritis
Ulcerative colitis	556	Ulcerative colitis
Hidradenitis suppurativa	70583	Hidradenitis suppurativa