



Persistence, effectiveness and safety of ustekinumab compared to TNF inhibitors in psoriatic arthritis within the Italian PsABio cohort

Elisa Gremese, Francesco Ciccia, Carlo Selmi, Giovanna Cuomo, Rosario Foti, Marco Matucci-Cerinic, Fabrizio Conti, Enrico Fusaro, Giuliana Guggino, Florenzo Iannone, et al.

► To cite this version:

Elisa Gremese, Francesco Ciccia, Carlo Selmi, Giovanna Cuomo, Rosario Foti, et al.. Persistence, effectiveness and safety of ustekinumab compared to TNF inhibitors in psoriatic arthritis within the Italian PsABio cohort. *Clinical and experimental rheumatology*, 2022, 10.55563/clinexprheumatol/j33pj . hal-03863607

HAL Id: hal-03863607

<https://hal.science/hal-03863607>

Submitted on 9 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

PERSISTENCE, EFFECTIVENESS AND SAFETY OF USTEKINUMAB COMPARED TO TNF INHIBITORS IN PSORIATIC ARTHRITIS WITHIN THE ITALIAN PSABIO COHORT

Elisa Gremese¹, MD, Francesco Ciccia², MD, PhD, Carlo Selmi^{3,4}, MD, PhD, Giovanna Cuomo², MD, Rosario Foti⁵, MD, Marco Matucci-Cerinic^{6,7}, MD, Fabrizio Conti⁸, MD, Enrico Fusaro⁹, MD, Giuliana Guggino¹⁰, MD, Florenzo Iannone¹¹, MD, PhD, Andrea Delle Sedie¹², MD, Roberto Perricone^{13,†}, MD, Luca Idolazzi¹⁴, MD, Paolo Moscato¹⁵, MD, Elke Theander¹⁶, MD, PhD, Wim Noël¹⁷, PhD, Paul Bergmans¹⁸, MSc, Silvia Marelli¹⁹, PharmD, Laure Gossec^{20,21}, MD, PhD, Josef S. Smolen²², MD

¹Fondazione Policlinico A. Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy;

²Università della Campania L Vanvitelli, Naples, Italy;

³Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy;

⁴IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy;

⁵Presidio Ospedaliero San Marco - AOU Policlinico Vittorio Emanuele, Catania, Italy;

⁶Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Florence, Italy;

⁷Unit of Immunology, Rheumatology, Allergy and Rare diseases (UnIRAR), IRCCS San Raffaele Hospital, Milan, Italy

⁸Dipartimento di Scienze Cliniche Internistiche, Anestesiologiche e Cardiovascolari

Sapienza Università di Roma, Rome, Italy;

⁹AOU Città della Salute e della Scienza di Torino, Turin, Italy;

¹⁰Dipartimento PROMISE, Università degli Studi di Palermo, Palermo, Italy;

¹¹Università degli Studi di Bari Aldo Moro, Bari, Italy;

¹²Università di Pisa, Pisa, Italy;

¹³Università degli Studi di Roma Tor Vergata e Policlinico Tor Vergata, Rome, Italy;

¹⁴Unità di Reumatologia, Dipartimento di Medicina, Università degli Studi di Verona, Verona, Italy;

¹⁵AOU San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy;

¹⁶Janssen-Cilag AB, Solna, Sweden;

¹⁷Janssen Pharmaceutica NV, Beerse, The Netherlands;

¹⁸Janssen-Cilag BV, Breda, The Netherlands;

¹⁹Janssen-Cilag SpA, Cologno Monzese (MI), Italy;

²⁰Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France;

²¹Pitié-Salpêtrière Hospital, AP-HP.Sorbonne Université, Rheumatology Department, Paris, France;

²²Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria.

†Prof. Roberto Perricone is deceased

Corresponding Author/Requests for reprints: Elisa Gremese, MD

UOSD di Immunologia Clinica, Fondazione Policlinico Universitario A. Gemelli

IRCCS, Presidio Columbus di Roma, Università Cattolica del Sacro Cuore

Via Giuseppe Moscati 31, 00168 Rome, Italy.

E-mail: elisa.gremese@unicatt.it

ORCID iD: 0000-0002-2248-1058

Running Title: Ustekinumab *vs* TNFi in PsA in Italy

Abstract

Objective. To compare real-world persistence, effectiveness and tolerability of ustekinumab versus TNF inhibitors (TNFi) in psoriatic arthritis (PsA).

Methods. One-year data from Italian subjects enrolled in the PsABio study (PsA patients receiving 1st- to 3rd-line treatment with ustekinumab or TNFi) were evaluated. Treatment persistence was analysed using Kaplan-Meier curves; hazard ratios (HR) of stopping treatment, and the corresponding 95% confidence intervals (CI), were computed through Cox regression models. Proportions of patients reaching clinical effectiveness endpoints were analysed using logistic regression, including propensity score (PS) adjustment for imbalanced baseline covariates, and non-response imputation if treatment was stopped/switched.

Results. Among 222 participants with follow-up data (effectiveness set), 101 received ustekinumab and 121 TNFi. In the ustekinumab group, 74.3% continued treatment up to 12 ± 3 months compared to 63.6% in the TNFi group. Ustekinumab showed better persistence than TNFi, overall and in specific subgroups (females, monotherapy without methotrexate, BMI <25 or >30 kg/m 2 , patients receiving ustekinumab as 2nd-line treatment instead of a second TNFi). Overall, the PS-adjusted HR of treatment discontinuation was 0.46 (95% CI: 0.26-0.82) for ustekinumab *vs* TNFi. cDAPSA LDA/remission was achieved in 43.5% of ustekinumab and 43.6% of TNFi-treated patients, while MDA was achieved in 24.2% and 28.0% of patients, respectively. After PS adjustment, odds ratios of clinical effectiveness did not differ significantly. Both treatments showed an acceptable safety profile.

Conclusion. This prospective, real-life study found a better persistence of ustekinumab than TNFi in PsA patients. At 1 year, both treatments showed similar effectiveness.

Keywords: Persistence; Effectiveness; Safety; Observational studies; TNF Inhibitors; Ustekinumab; Psoriatic Arthritis

Introduction

Psoriatic arthritis (PsA) is a complex, heterogeneous and potentially severe disease involving a large spectrum of manifestations, including the musculo-skeletal system, skin, nails and, less frequently, eyes and gut (1).

The European League Against Rheumatism (EULAR) recommendations for the management of PsA address non-steroidal anti-inflammatory drugs, local glucocorticoid injections and conventional synthetic disease-modifying antirheumatic drugs (csDMARD) as initial treatments for active PsA (1). An increasing number of effective treatment options are available for moderate-to severe PsA not responding to csDMARDs. These options include biologics as tumor necrosis factor (TNF) inhibitors, interleukin (IL)-12/23, IL-23 and IL-17 inhibitors, and small molecules as PDE4 and JAK inhibitors (1-3). The IL-12/23 inhibitor, ustekinumab, was the first new biologic drug for PsA to be developed after TNFi (4). The phase III PSUMMIT 1 and 2 trials demonstrated a greater clinical response at 24 weeks with ustekinumab compared to placebo in patients with PsA (5, 6).

However, data from RCTs generally lack of external validity because of stringent inclusion and exclusion criteria, and only real-life observations can provide indications on long-term effectiveness and safety in everyday clinical settings. Moreover, further clinical outcomes are used in real-life studies, for example treatment persistence, i.e., a comprehensive outcome involving effectiveness and safety, mixed with patient and doctor satisfaction and preferences (7-9). For these reasons, real-world studies are central to integrate evidence from RCTs, as it was shown in Registry-based studies of patients with psoriasis and spondyloarthritis (SpA) (10-13).

PsABio study is an international, prospective, observational cohort study aimed to evaluate the persistence, effectiveness, and safety of 1st/2nd/3rd-line ustekinumab versus TNFi in a real-life setting of adult PsA patients. The study was conducted in 8 European countries enrolling 991 patients between December 2015 and June 2018 in 92 study sites. Participants were treated according to standard clinical practice in each country, with the choice of treatment (ustekinumab or any approved TNFi) being at the discretion of the treating Rheumatologist. The main findings at 6 months and 1-year of follow-up of the PsABio study – full population have been recently published (14, 15). Italian sites contributed with an important fraction of patients to this study, so a country analysis of 1-year data was performed.

Materials and methods

Study Design. PsABio study (registered at <http://www.clinicaltrials.gov>: NCT02627768) is an observational study conducted in 8 European countries including 991 adult patients with a confirmed diagnosis of PsA (fulfilling the Classification Criteria for Psoriatic Arthritis – CASPAR (16)) who started ustekinumab or TNFi as a 1st- to 3rd-line biological DMARD (bDMARD). The current interim analysis at month 12 (± 3 months) is based on the Italian PsABio cohort alone, involving 15 sites that enrolled a total of 238 consecutive PsA patients. Patients were ineligible for PsABio study if starting fourth or further line of biologic treatment, unwilling or unable to participate in long-term data collection, currently enrolled in an interventional study and if they had received an investigational drug or medical device within 30 days before the start of the study. All patients signed an informed consent form allowing data collection

and source data verification, in agreement with Italian regulations and trial sponsor policy, before data collection. The study was approved by the Ethic Committees of the Italian participating centers and was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines.

Participants were screened consecutively, and all those meeting the eligibility criteria were offered enrolment into the study. Treatment decision was taken by each investigator prior to, and independently of the patient inclusion in the study, following Italian standard clinical practice and regulations. TNFi therapies included any PsA approved TNFi (i.e., adalimumab, etanercept, golimumab, infliximab, certolizumab pegol), including biosimilars. Patients received bDMARDs in addition to other co-medication as treatment for PsA (e.g., methotrexate, steroids, NSAIDs, etc.) or psoriasis (e.g., systemic therapy, phototherapy) according to local standard clinical practice. After the study entry, patients were visited regularly by their treating rheumatologists according to clinical practice (at least every 6 months \pm 3 months), and could be switched to any other approved bDMARD (or to other classes of medications), changed recommended dosing schedules or stopped therapy, in accordance with physician's decision. This notwithstanding, data collection continued if the patient did not withdraw from the study.

Data collection at baseline and at the following visits included information available as for clinical practice, i.e., those related to demographic and clinical characteristics, PsA disease features (including 66/68 swollen/tender joint count, enthesitis, dactylitis, psoriasis, psoriatic nail disease, presence of back pain and/or chronic widespread pain assessed by the Fibromyalgia Rapid Screening Tool), previous TNFi and csDMARDs usage, medical history, other concomitant PsA medication, treatment persistence,

clinical response outcomes (including the proportions of patients reaching minimal disease activity [MDA], very low disease activity [VLDA], clinical Disease Activity index for Psoriatic Arthritis [cDAPSA] low disease activity [LDA] or remission, $\geq 50\%$ improvement in Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]), safety of therapies (i.e., occurrence of adverse events, serious adverse events, etc.), Patient-Reported Outcomes (PROs), data on comorbidities, use of concomitant medications, hospitalizations and resource utilization. Given the real-world study setting, cDAPSA was used instead of DAPSA. The two indexes previously showed consistent results (17, 18). Axial disease was defined by the investigator-treating rheumatologist. No imaging or HLAB27 result was required. In PsABIO, the patients have either pure axial disease (i.e., no signs of peripheral joint involvement) or combined peripheral and axial disease.

Primary outcomes of this interim analysis in the Italian cohort were 1-year treatment persistence and proportions of patients reaching effectiveness endpoints as MDA, VLDA, cDAPSA LDA/remission and cDAPSA remission. Secondary outcome was the number of participants with adverse events and serious adverse events. Adverse events were summarized under the initial treatment line as well as under all treatments started within a 91 days safety period after the initial treatment line prior to the adverse event.

Statistical methods

Data validation, development of a detailed analysis plan and all statistical analyses were performed by or under the authority of the sponsor (Janssen Pharmaceutica, Beerse). Analyses of treatment persistence and effectiveness were based on the effectiveness set, including all patients with baseline data and any effectiveness follow-up data. Analysis

of safety was based on the safety set including all patients with baseline data and any follow-up data. For validated scales, missing items were imputed according to recommendations of the scale developers. For other (partially) missing data, imputation rules were prespecified in the SAP prior to database lock. Percentages were calculated over non-missing data.

As the analysis was exploratory, no predefined hypotheses were tested and no adjustment for multiplicity was applied. Hence, and in consensus with recent recommendations (19), within- and between-group differences included the 95% CI, rather than by p-values, which provide no information about the variability of an estimated association.

Treatment persistence was calculated as the time from the initiation of the bDMARD at enrolment, up to the last injection of this bDMARD (plus one dispensing interval), or start of subsequent bDMARD, or withdrawal from the study, or data cut-off date for subjects who remained on their initial treatment.

In addition to descriptive analyses, comparative effectiveness analyses were performed to investigate between-cohort differences. In this analysis, the month-12 effectiveness data of patients who switched/stopped their original treatment during the one-year follow-up period, were imputed as non-responders.

Comparative effectiveness analyses included propensity score (PS) analysis-based adjustment for imbalanced baseline covariates. For all potential confounders, the balance between the treatment cohorts, and the prognostic effect on the outcome of interest were investigated. The PS was estimated using a logistic regression model with treatment as the dependent and a set of potential confounders as independent variables.

After optimization to achieve a good balance of all confounders, the PS, stratified on the quintiles, was used to estimate the adjusted treatment effects for the selected outcomes. Primarily based on clinical judgement and published evidence, the following potential baseline confounders were investigated: age, sex, smoking, number of comorbidities, BSA, PsA subtype according to Moll and Wright criteria (20), disease duration, cDAPSA score, 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) score, presence of enthesitis or dactylitis, Fibromyalgia Rapid Screening Tool (FiRST) score, line of bDMARD treatment, csDMARD co-treatment, and concomitant NSAID or oral corticosteroid use.

The difference in risk for stop/switch of initial treatment (persistence) was analyzed by means of a Cox proportional hazards model including the PS, presenting the PS-adjusted hazard ratios (HRs). The difference in one-year effectiveness endpoints MDA/VLDA, cDAPSA LDA and remission, was analyzed using logistic regression models including the PS, and presenting the PS-adjusted odds ratios (OR). All ratios are presented including the 95% CI.

The safety analysis included descriptive statistics of UST or TNFi treatment emerging adverse events.

Results

The main demographic and clinical characteristics at baseline are showed in Table 1. Out of 222 patients in the effectiveness set, 101 (45.5%) were treated with ustekinumab and 121 (54.5%) with TNFi drugs. There were 137 women (61.7%) and 85 men (38.3%) enrolled. Forty-eight subjects (22.9%) were obese, 24 in each treatment group.

At baseline, 108 patients (48.6%) started for the first time a bDMARD treatment, 79 (35.6%) started a second-line and 35 (15.8%) a third-line biologic therapy. About one-third of patients had peripheral PsA with axial involvement clinically diagnosed by the treating Rheumatologist; 40.5% had enthesitis and 9.5% dactylitis. Methotrexate was used by 34.7% of patients at baseline. There were some imbalances in baseline demographic/disease-related covariates between ustekinumab and TNFi groups: in the ustekinumab group 11.9% of patients was younger than 40 years, whereas in the TNFi cohort this was 22.3%; patients were more frequently overweight or obese in the ustekinumab (64.3%) than TNFi (57.1%) group; first-line biological treatment was less frequent in the ustekinumab group (43.6% vs 52.9% in the TNFi group); and MTX at baseline was used less frequently in the ustekinumab group (31.7% vs 37.2% in the TNFi group). The mean (standard deviation) baseline cDAPSA was 26.3 (15.4) for ustekinumab and 23.5 (12.3) for TNFi.

Of patients starting ustekinumab and TNFi, 75/101 (74.3%) and 77/121 (63.6%), respectively (p-value from log-rank test = 0.047), persisted with treatment at one-year follow up visit (12 months \pm 3 months). The observed mean persistence was 410 days for ustekinumab and 363 days for TNFi, and time to reach the 75% percentile of the treatment persistence probability curve was 430 days (95% CI: 332-not estimable) for ustekinumab and 259 days (95% CI: 189-333) for TNFi. One out of 101 patients in the ustekinumab group switched/stopped initial treatment early, i.e., before week 12 (due to effectiveness reasons), while 9 out of 121 patients switched/stopped initial treatment early in the TNFi group (4 due to effectiveness and 5 due to safety reasons). Figure 1 presents Kaplan–Meier curves of treatment persistence up to 15 months for ustekinumab and TNFi, overall (panel A) and by line of treatment (panel B).

In the Cox proportional hazards model which included the PS, treatment and several factors of interest, the overall PS-adjusted HR for discontinuation showed significantly lower risk of discontinuation (HR [95% CI]) (so higher persistence) for ustekinumab versus TNFi (0.46 [0.26; 0.82]) (Figure 2). In addition to this, the model showed better persistence of ustekinumab compared to TNFi in patients receiving biologic monotherapy (HR 0.31 [0.15; 0.63]), in females (0.41 [0.20; 0.83]), in patients with body mass index (BMI) <25 kg/m 2 (0.34 [0.14; 0.87]) or >30 kg/m 2 (0.19 [0.06; 0.54]), in patients receiving 2nd-line bDMARD (0.33 [0.13; 0.87]) and in those with baseline BSA $<3\%$ (0.44 [0.19; 0.98], borderline finding). Of other factors included in the Cox regression model (enthesis Yes/No, axial involvement, oligo- or polyarticular PsA), no significant effect was shown.

Clinical DAPSA LDA/remission (cDAPSA \leq 13) was achieved by 43.5% of ustekinumab and 43.6% of TNFi-treated patients. The corresponding PS-adjusted OR of cDAPSA LDA/remission was 1.08 (95% CI: 0.54-2.15) for ustekinumab as compared to TNFi treatment (Figure 3). Clinical DAPSA remission (cDAPSA \leq 4) was reached in 19.6% of ustekinumab and 17.9% of TNFi-treated patients, with corresponding PS-adjusted OR of 0.80 (95% CI: 0.35-1.85). MDA was reached in 24.2% of patients treated with ustekinumab and in 28.0% of those treated with TNFi (PS-adjusted OR=0.96; 95% CI: 0.45-2.05). The corresponding proportions of patients achieving VLDA were 12.5% and 10.2%, respectively (PS-adjusted OR=0.99; 95% CI: 0.35-2.76).

Figure 4 reports findings restricted to the cohort of patients with axial involvement (i.e., 32 patients in the ustekinumab and 42 in the TNFi group) for the same endpoints of Figure 3, plus an endpoint for an improvement of at least 50% in BASDAI score as

compared to baseline. Results tended to indicate better performances for all endpoints examined in the ustekinumab than TNFi group, but PS-adjusted ORs could not be computed due to the limited number of patients.

Safety data are reported in Table 2. There were 23/113 (20.4%) patients reported with at least 1 treatment emergent adverse event (TEAE) with ustekinumab and 30/135 (22.2%) with TNFi. These events led to withdrawal of bDMARD in 6 (5.3%) patients treated with ustekinumab and 10 (7.4%) with TNFi. Two patients (1.8%) treated with ustekinumab had treatment emergent serious adverse events: 1 (0.9%) had skin infection and 1 (0.9%) had malignant parathyroid tumour; for TNFi, serious adverse events occurred in 1 patient (0.7%), who had pneumonia.

Discussion

This is an exploratory interim analysis of real-life data on the use of ustekinumab and TNFi in clinical practice, restricted to the Italian cohort only of the European PsABio study, thus important limitations to the quality and relevance of the data are acknowledged. In particular, the study has a relatively short follow-up period, thus sample size and related statistical power are not particularly high and did not allow to provide results separately for each TNFi. Other limitations of this analysis are those typical of real-life studies, e.g., lack of patient randomization, potential information or selection bias and presence of missing data. For example, presence at follow-up visits and completeness of data may be higher in compliant patients, treatment groups may be unbalanced at baseline for relevant characteristics, etc., leaving the analysis open to

potential biases. In order to try to overcome at least part of these limits, we performed a preliminary PS analysis, and adjusted treatment effects for the estimated PS.

Our findings showed a better persistence of ustekinumab compared to TNFi in PsA patients followed up to 15 months. Persistence was also higher for ustekinumab than TNFi in specific subgroups of patients i.e., females, those without methotrexate use, those with BMI >30 kg/m², and those receiving 2nd-line ustekinumab instead of a second TNFi. The clinical effectiveness - measured by cDAPSA responses, a measure of articular response only, and MDA/VLDA achievement, which cover also the skin, enthesis and PROs – was similar in both groups, with more than 40% of patients achieving cDAPSA LDA/remission at one year. Both treatments showed an acceptable safety profile.

During the last few years, an increasing number of studies have considered the real-world persistence of various biological drugs in PsA patients (21). However, comparative, prospective, observational studies like ours are scarce. Recently, an analysis of the multi-country PsABio full population after 1 year of treatment demonstrated a comparable overall persistence of ustekinumab and TNFi in presence - as observed in our Italian cohort - of a better drug persistence of ustekinumab in selected subgroups of patients (15). Further, published studies of ustekinumab in real-life clinical practice showed the effectiveness of this drug on different domains of PsA, with a good safety profile. The proportion of patients reaching MDA was between 30 and 70% (7, 22-25). Therefore, results in these terms indicate similar magnitudes of response versus TNFi, with some advantages for ustekinumab in case of concomitant psoriasis and/or enthesitis (1). In a recent analysis of Swedish population-based registry data, including a total of 3918 PsA patients, ustekinumab had a favorable treatment

persistence profile as compared to adalimumab in both biologic-naïve (HR=0.48; 95% CI: 0.33-0.69) and biologic-experienced (HR=0.65; 95% CI: 0.56-0.76) patients (26). Favorable outcomes were also observed in an Italian real-life prospective multicentric study of ustekinumab treatment after 24-months of follow up, where patients with PsA showed significant improvements in PASI, DAPSA, Leeds Enthesitis Index (LEI) and several other clinical and serologic features (23). In Italy, ustekinumab persistence and effectiveness in PsA was examined also in a regional registry-based study in Southern Italy (Apulia region) including 160 treated patients (7). Authors reported a 12-month ustekinumab drug survival of 74%, similar to our finding. On the other hand, in contrast to our data, treatment persistence in that registry study was higher in bDMARD naïve (87%) than in previously TNFi-treated patients (68%). Another Italian study of 34 PsA patients treated with ustekinumab after failure or inadequate response to csDMARDs or TNFi reported achievement of MDA –in 70.5% of subjects at month 24 (24), and maintenance of low or minimal disease activity status has been recently shown to have a great influence on patients' quality of life and perception of their clinical condition (27).

A recent European multinational registry-based study, the EuroSpA research collaboration network (EuroSpA RCN), examined data of over 14,000 patients with PsA starting a first anti-TNF drug (28). The study, published by Brahe et al, found a 12-month treatment persistence ranging between 68% and 90% in different countries/registries, with a median of 77%. Our data on first-line TNFi treatment are generally consistent with these findings – though the persistence proportion is closer to the lowest than to the median estimate of EuroSpA. Based on the same research collaboration network, Michelsen et al. (29) have recently published the real-life evaluation at 12-months of secukinumab in 2,017 PsA patients. This demonstrated a

76% retention rate, similar to the median persistence observed by Brahe et al. in first line TNFi users as well as to ustekinumab ones in our cohort.

Our findings on treatment persistence were consistent across several subgroups, including sex, use of concomitant methotrexate, and initial line of treatment, with a clear advantage for ustekinumab in patients receiving the drug as a first switch instead of a second TNFi.

In PsA patients, the best option for second-line biologic treatment after first-line TNFi failure is still uncertain and open to discussion (30). Both approaches of switching to a second TNFi or swapping to a biological drug with a different mechanism of action are possible (31-33), and comparative studies were advocated (34). A RCT including 300 patients with rheumatoid arthritis who were assigned, after insufficient response to a first TNFi drug, to a non-TNF biologic or to a second TNFi, found a more than doubled likelihood of response for patients in the swap (i.e., non-TNFi) *vs* those in the switch (i.e., second TNFi) strategy (35). However, to our knowledge, no similar studies are available in PsA. Many factors should be considered to optimize second-line biologic therapy in PsA, including disease characteristics, comorbidities, cardiometabolic risk factors, treatment history, and patient preferences. As reported by Merola et al, switching between TNFis can be effective for many patients, but bDMARDs with different mechanisms of action may be superior alternatives (32). In this setting, the severity of psoriasis, the predominance of enthesitis and the risk of developing concomitant IBD may drive the choice towards ustekinumab (1, 3, 36).

Taking into consideration other factors related to drug response, our data confirmed that female gender and obesity adversely affect persistence in therapy in patients treated with TNFi (37-39), but not in those treated with ustekinumab.

Providing data from one specific country – besides the limitations that have already been acknowledged – has the advantage of a more homogeneous setting, with the consequence to obtain results closer to the real Italian clinical practice in managing PsA. Other strengths of this investigation are the prospective, predefined collection of data and the availability of information for both specific clinical effectiveness and safety outcomes and treatment persistence.

In conclusion, our analysis provided comparative real-life information on treatment persistence and effectiveness of biological drugs with different mechanisms of action, in an Italian cohort of adult PsA patients followed up to 15 months. In this setting, ustekinumab showed better persistence than TNFi, overall and in specific subgroups (females, monotherapy without methotrexate, BMI <25 or >30 kg/m², patients receiving ustekinumab as 2nd-line treatment instead of a second TNFi), whereas clinical effectiveness, as measured by cDAPSA responses and MDA/VLDA achievement, and safety were similar.

Acknowledgements

Contributing author: Prof. Piercarlo Sarzi-Puttini, ASST Fatebenefratelli-Sacco, Università degli Studi di Milano, Italy. The authors thank Prof. Gianfranco Ferraccioli for contributing scientifically to the study design and to the study start at Fondazione Policlinico A. Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy. The

authors also thank Carlotta Galeone - Statinfo srl - for providing medical writing and editorial support.

Funding: The PsABio study was sponsored by Janssen. Medical writing and editorial support were funded by Janssen Italy.

Disclosure statement: **EG:** speaker fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, MSD, Novartis, Sanofi, UCB, Roche, Pfizer; **FCiccia:** consulting and/or speakers fees from Novartis, Galapagos, Amgen, Janssen, Pfizer, UCB, MSD, Abbvie, Sandoz, Sanofi, Roche, Lilly, Astra Zeneca, GSK; paid research activities, fellowships or grants from Pfizer, Novartis; **CS:** consulting and/or speakers fee from AbbVie, Amgen, Alfa-Wassermann, Biogen, Celgene, Eli Lilly, Gilead, Janssen, MSD, Novartis, Pfizer, Sanofi-Genzyme; research support from AbbVie, Amgen, Janssen, Pfizer; travel support from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer; **GC:** none declared; **RF:** speaker fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, MSD, Novartis, Sanofi, UCB, Roche, Pfizer; **MMC:** consulting fees or honoraria from Actelion, Janssen, Inventiva, Bayer, Biogen, BMS, Boehringer, CSL Behring, Corbus, Galapagos, Mitsubishi, Samsung, Regeneron, Acceleron, MSD, Chemomab, Lilly, Pfizer, Roche; **FConti:** consultancy fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, Galapagos, Pfizer; **EF:** speaker fees from Abbvie, Amgen, Eli Lilly, Galapagos; **GG:** consulting fees from Abbvie, Lilly, Novartis, Janssen, Pfizer, UCB, Galapagos; **FI:** consulting fees or honoraria from Actelion, Janssen, Biogen, BMS, Galapagos, MSD, Lilly, Pfizer, Roche, UCB, Sanofi; **ADS:** speaker fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, UCB; **RP:** none declared till June 2021, then not applicable; **LI:** fees from Celgene, Eli Lilly, MSD, Novartis, Sanofi, Sandoz; **PM:** none

declared; **LG**: research grants from Amgen, Galapagos, Lilly, Pfizer, Sandoz, Sanofi; consulting fees from AbbVie, Amgen, BMS, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Samsung Bioepis, Sanofi-Aventis, UCB; **JSS**: research grants from Abbvie, AstraZeneca, Lilly, Novartis, Roche; honoraria for consultancies and/or speaking engagements from AbbVie, Amgen, AstraZeneca, Astro, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Evapharm, Gilead, ILTOO, Janssen, Lilly, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, R-Pharm, Roche, Samsung, Sanofi, UCB; **ET, WN, PB** and **SM** are employees of Janssen.

Data sharing statement: Access to anonymized individual participant-level data will not be provided for this study as it meets one or more of the exceptions described on <https://yoda.yale.edu/> under “Data Use Agreement – Janssen Pharmaceuticals DUA”.

References

1. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis.* 2020;79(6):700-12.
2. Mourad A, Gniadecki R. Treatment of dactylitis and enthesitis in psoriatic arthritis with biologic agents: a systematic review and metaanalysis. *J Rheumatol.* 2020;47(1):59-65.
3. Singh JA, Guyatt G, Oggie A, Gladman DD, Deal C, Deodhar A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheum.* 2019;71(1):5-32.
4. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet.* 2009;373(9664):633-40.
5. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis.* 2014;73(6):990-9.
6. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet.* 2013;382(9894):780-9.

7. Iannone F, Santo L, Bucci R, Semeraro A, Carlino G, Paoletti F, et al. Drug survival and effectiveness of ustekinumab in patients with psoriatic arthritis. Real-life data from the biologic Apulian registry (BIOPURE). *Clin Rheumatol*. 2018;37(3):667-75.
8. Mease PJ, Accortt NA, Rebello S, Etzel CJ, Harrison RW, Aras GA, et al. Persistence of tumor necrosis factor inhibitor or conventional synthetic disease-modifying antirheumatic drug monotherapy or combination therapy in psoriatic arthritis in a real-world setting. *Rheumatol Int*. 2019;39(9):1547-58.
9. Favalli EG, Becciolini A, Carletto A, Conti F, Amato G, Fusaro E, et al. Efficacy and retention rate of adalimumab in rheumatoid arthritis and psoriatic arthritis patients after first-line etanercept failure: the FEARLESS cohort. *Rheumatol Int*. 2020;40(2):263-72.
10. Menter A, Papp KA, Gooderham M, Pariser DM, Augustin M, Kerdel FA, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Eur Acad Dermatol Venereol*. 2016;30(7):1148-58.
11. Lapadula G, Ferraccioli G, Ferri C, Punzi L, Trotta F. GISEA: an Italian biological agents registry in rheumatology. *Reumatismo*. 2011;155-64.
12. Manara M, Caporali R, Favalli EG, Grosso V, Atzeni F, Sarzi Puttini P, et al. Two-year retention rate of golimumab in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: data from the LORHEN registry. *Clin Exp Rheumatol*. 2017;35(5):804-9.
13. Ziade NR. Registries in Spondyloarthritis: What have we Learned. *MOJ Orthop Rheumatol*. 2017;9(2):00347.

14. Smolen JS, Siebert S, Korotaeva TV, Selmi C, Bergmans P, Gremese E, et al. Effectiveness of IL-12/23 inhibition (ustekinumab) versus tumour necrosis factor inhibition in psoriatic arthritis: observational PsABio study results. *Ann Rheum Dis.* 2021;80:1419–28.
15. Gossec L, Siebert S, Bergmans P, De Vlam K, Gremese E, Joven-Ibanez B, et al. Persistence and effectiveness of the IL-23 pathway inhibitor ustekinumab or tumour necrosis factor inhibitor treatment in patients with psoriatic arthritis: 1-year results from the real-world PsABio study. *Ann Rheum Dis.* 2022;In Press.
16. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* 2006;54(8):2665-73.
17. Schoels MM, Aletaha D, Alasti F, Smolen JS. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis.* 2016;75(5):811-8.
18. McIlroy T, Tuzil J, Sedova L, Stolfa J, Urbanova M, Suchy D, et al. Mapping Quality of Life (EQ-5D) from DAPSA, Clinical DAPSA and HAQ in Psoriatic Arthritis. *Patient.* 2018;11(3):329-40.
19. Harrington D, D'Agostino RB, Sr., Gatsonis C, Hogan JW, Hunter DJ, Normand ST, et al. New Guidelines for Statistical Reporting in the Journal. *N Engl J Med.* 2019;381(3):285-6.
20. Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum.* 1973;3(1):55-78.
21. Calabresi E, Monti S, Terenzi R, Zanframundo G, Perniola S, Carli L. One year in review 2019: psoriatic arthritis. *Clin Exp Rheumatol.* 2020;38(6):1046-55.

22. Almirall M, Rodriguez J, Mateo L, Carrascosa JM, Notario J, Gallardo F. Treatment with ustekinumab in a Spanish cohort of patients with psoriasis and psoriatic arthritis in daily clinical practice. *Clin Rheumatol*. 2017;36(2):439-43.
23. Chimenti MS, Ortolan A, Lorenzin M, Triggianese P, Talamonti M, Costa L, et al. Effectiveness and safety of ustekinumab in naive or TNF-inhibitors failure psoriatic arthritis patients: a 24-month prospective multicentric study. *Clin Rheumatol*. 2018;37(2):397-405.
24. Napolitano M, Costa L, Caso F, Megna M, Scarpa R, Balato N, et al. Minimal disease activity in patients with psoriatic arthritis treated with ustekinumab: results from a 24-week real-world study. *Clin Rheumatol*. 2017;36(7):1589-93.
25. Queiro R, Brandy A, Rosado MC, Lorenzo A, Coto P, Carriles C, et al. Minimal disease activity and patient-acceptable symptom state in psoriatic arthritis: a real-world evidence study with ustekinumab. *JCR: J Clin Rheumatol*. 2018;24(7):381-4.
26. Geale K, Lindberg I, Paulsson EC, Wennerstrom ECM, Tjarnlund A, Noel W, et al. Persistence of biologic treatments in psoriatic arthritis: a population-based study in Sweden. *Rheumatol Adv Pract*. 2020;4(2):rkaa070.
27. Navarini L, Currado D, Caso F, Costa L, Chimenti MS, D'Antonio A, et al. Duration of clinical remission and low disease activity impacts on quality of life and its domains in psoriatic arthritis patients: results from an Italian multicentre study. *Clin Exp Rheumatol*. 2021.
28. Brahe CH, Ornbjerg LM, Jacobsson L, Nissen MJ, Kristianslund EK, Mann H, et al. Retention and response rates in 14 261 PsA patients starting TNF inhibitor treatment-results from 12 countries in EuroSpA. *Rheumatology (Oxford)*. 2020;59(7):1640-50.

29. Michelsen B, Georgiadis S, Di Giuseppe D, Loft AG, Nissen MJ, Iannone F, et al. Real-world 6 and 12-month Drug Retention, Remission and Response Rates of Secukinumab in 2,017 Psoriatic Arthritis patients in 13 European Countries. *Arthritis Care Res (Hoboken)*. 2021.
30. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis*. 2016;75(3):499-510.
31. Cantini F, Niccoli L, Nannini C, Cassara E, Kaloudi O, Giulio Favalli E, et al. Second-line biologic therapy optimization in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *Semin Arthritis Rheum*. 2017;47(2):183-92.
32. Merola JF, Lockshin B, Mody EA. Switching biologics in the treatment of psoriatic arthritis. *Semin Arthritis Rheum*. 2017;47(1):29-37.
33. Costa L, Perricone C, Chimenti MS, Del Puente A, Caso P, Peluso R, et al. Switching Between Biological Treatments in Psoriatic Arthritis: A Review of the Evidence. *Drugs R D*. 2017;17(4):509-22.
34. Reddy SM, Crean S, Martin AL, Burns MD, Palmer JB. Real-world effectiveness of anti-TNF switching in psoriatic arthritis: a systematic review of the literature. *Clin Rheumatol*. 2016;35(12):2955-66.
35. Gottenberg JE, Brocq O, Perdriger A, Lassoued S, Berthelot JM, Wendling D, et al. Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. *JAMA*. 2016;316(11):1172-80.

36. Araujo EG, Englbrecht M, Hoepken S, Finzel S, Kampylafka E, Kleyer A, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: Results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. *Semin Arthritis Rheum.* 2019;48(4):632-7.
37. Gremese E, Bernardi S, Bonazza S, Nowik M, Peluso G, Massara A, et al. Body weight, gender and response to TNF-alpha blockers in axial spondyloarthritis. *Rheumatology (Oxford).* 2014;53(5):875-81.
38. Hojgaard P, Ballegaard C, Cordtz R, Zobbe K, Clausen M, Glintborg B, et al. Gender differences in biologic treatment outcomes-a study of 1750 patients with psoriatic arthritis using Danish Health Care Registers. *Rheumatology (Oxford).* 2018;57(9):1651-60.
39. Ogdie A, Palmer JL, Greenberg J, Curtis JR, Harrold LR, Solomon DH, et al. Predictors of Achieving Remission among Patients with Psoriatic Arthritis Initiating a Tumor Necrosis Factor Inhibitor. *J Rheumatol.* 2019;46(5):475-82.

Table 1. Main demographic and clinical characteristics at baseline of PsABio Italian cohort, overall and according to treatment type (effectiveness set).

Characteristic	UST (n=101)	TNFi (n=121)	Overall (n=222)
Age			
< 40	12 (11.9%)	27 (22.3%)	39 (17.6%)
40-50	34 (33.7%)	31 (25.6%)	65 (29.3%)
50-60	34 (33.7%)	35 (28.9%)	69 (31.1%)
60-65	8 (7.9%)	11 (9.1%)	19 (8.6%)
≥65	13 (12.9%)	17 (14.0%)	30 (13.5%)
Mean (SD)	51.4 (11.3)	49.9 (12.9)	50.6 (12.2)
Sex			
Female	61 (60.4%)	76 (62.8%)	137 (61.7%)
BMI *			
< 25	35 (35.7%)	48 (42.9%)	83 (39.5%)
25-30	39 (39.8%)	40 (35.7%)	79 (37.6%)
> 30	24 (24.5%)	24 (21.4%)	48 (22.9%)
Mean (SD)	28.1 (6.2)	26.7 (5.4)	27.4 (5.8)
Time since diagnosis (years), mean (SD)	6.2 (6.9)	5.9 (6.4)	6.0 (6.6)
Line of biological treatment			
First line	44 (43.6%)	64 (52.9%)	108 (48.6%)
Second line	39 (38.6%)	40 (33.1%)	79 (35.6%)

Characteristic	UST (n=101)	TNFi (n=121)	Overall (n=222)
Third line	18 (17.8%)	17 (14.0%)	35 (15.8%)
Type of PsA ^Y			
Presence of axial involvement	32 (31.7%)	42 (35.0%)	74 (33.5%)
Presence of enthesitis			
	39 (38.6%)	51 (42.1%)	90 (40.5%)
Presence of dactylitis			
	9 (8.9%)	12 (10.0%)	21 (9.5%)
MTX use at baseline	32 (31.7%)	45 (37.2%)	77 (34.7%)
BSA ^{*,Y}			
<3%	41 (51.3%)	69 (67.0%)	110 (60.1%)
3%–10%	29 (36.3%)	27 (26.2%)	56 (30.6%)
>10%	10 (12.5%)	7 (6.8%)	17 (9.3%)
cDAPSA, mean (SD)	26.3 (15.4)	23.5 (12.3)	24.8 (13.9)
Extra-articular manifestations			
Uveitis	1 (1.0%)	3 (2.5%)	4 (1.8%)
IBD	5 (5.0%)	4 (3.3%)	9 (4.1%)

* The sums do not add up to the total because of a few missing data.

^Y Psoriasis skin involvement.

BMI: Body mass index; BSA: Body surface area; cDAPSA: clinical Disease Activity index for Psoriatic Arthritis; CI: confidence interval; IBD: inflammatory bowel disease; MTX: methotrexate; SD: standard deviation; UST: ustekinumab; TNFi: Tumor necrosis factor inhibitor.

Table 2. Treatment emergent adverse events occurring in the PsABio Italian cohort, by treatment (safety dataset)^{*}.

	UST* (n=113)	TNFi* (n=135)
No. of patients with ≥ 1 TEAE	23 (20.4%)	30 (22.2%)
<i>System organ class/Preferred term</i>		
Infections and infestations	12 (10.6%)	9 (6.7%)
Skin and subcutaneous tissue disorders	4 (3.5%)	8 (5.9%)
General disorders and administration site conditions	4 (3.5%)	5 (3.7%)
Gastrointestinal disorders	0	4 (3.0%)
Nervous system disorders	2 (1.8%)	2 (1.5%)
Musculoskeletal and connective tissue disorders	2 (1.8%)	1 (0.7%)
Neoplasms (benign, malignant and unspecified)	2 (1.8%)	1 (0.7%)
Vascular disorders	1 (0.9%)	2 (1.5%)
Cardiac disorders	1 (0.9%)	1 (0.7%)
No. of patients with ≥ 1 bDMARD agent related TEAE	7 (6.2%)	15 (11.1%)
No. of patients with ≥ 1 serious TEAE	2 (1.8%)	1 (0.7%)
<i>System organ class/Preferred term</i>		
Infections and infestations	1 (0.9%)	1 (0.7%)
Pneumonia	0	1 (0.7%)
Skin infection	1 (0.9%)	0
Neoplasms (benign, malignant and unspecified)	1 (0.9%)	0
Parathyroid tumour malignant	1 (0.9%)	0
No. of patients with ≥ 1 bDMARD agent-related serious TEAE	0	0
No. of patients with ≥ 1 TEAE leading to withdrawal of	6 (5.3%)	10 (7.4%)

bDMARD drug		
No. of patients with ≥1 bDMARD agent-related TEAE leading to withdrawal of bDMARD drug	5 (4.4%)	7 (5.2%)
No. of patients with ≥1 TEAE leading to permanent discontinuation of study	1 (0.9%)	0
No. of patients with ≥1 bDMARD agent-related TEAE leading to permanent discontinuation of study	0	0
No. of deaths	0	0

* Adverse events were summarized under the initial treatment line as well as under all treatments that started within a 91 days safety period after the initial treatment line prior to the adverse event. Therefore, the sum of subjects is higher than the total number in the safety set (n=237).

bDMARD: biological disease-modifying antirheumatic drugs; TEAE: treatment emergent adverse event; UST: ustekinumab; TNFi: Tumor necrosis factor inhibitor.

Figure 1. Kaplan–Meier estimates of treatment persistence for ustekinumab and TNFi in the PsABio Italian cohort, overall (panel A) and by line of treatment (panel B)

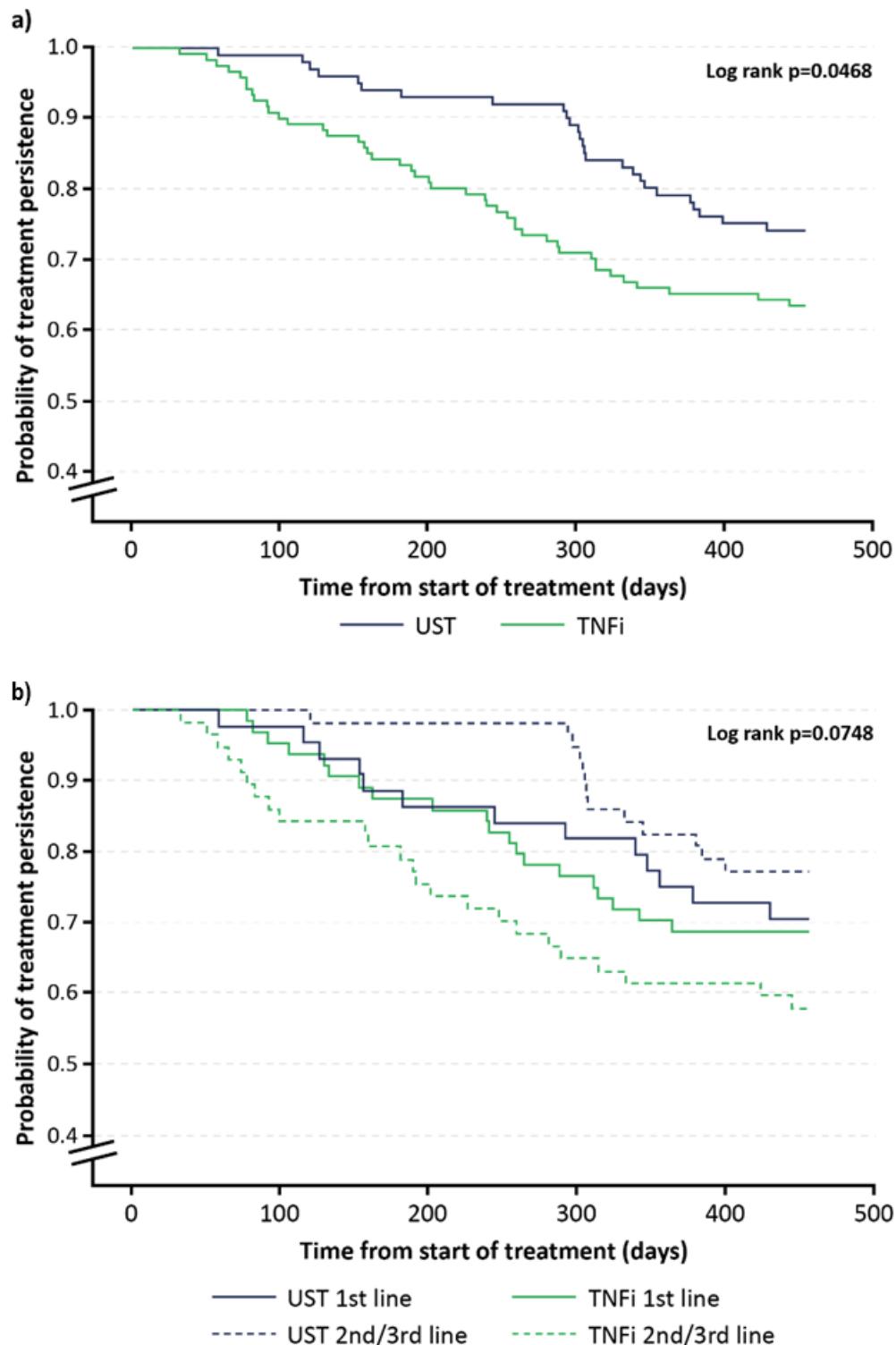
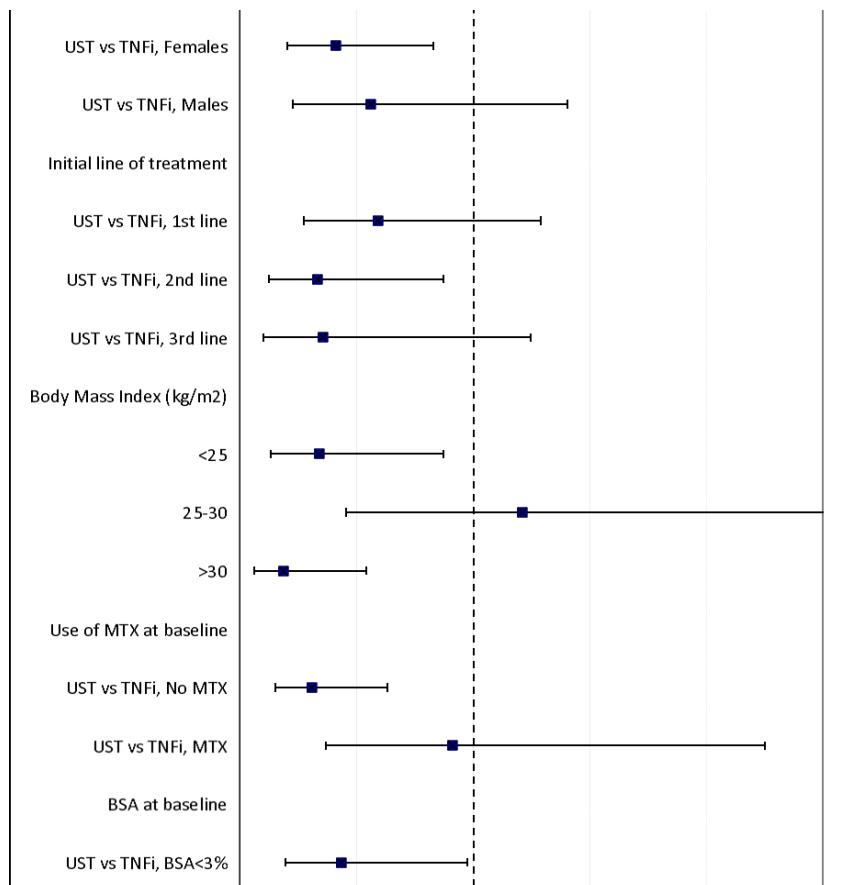
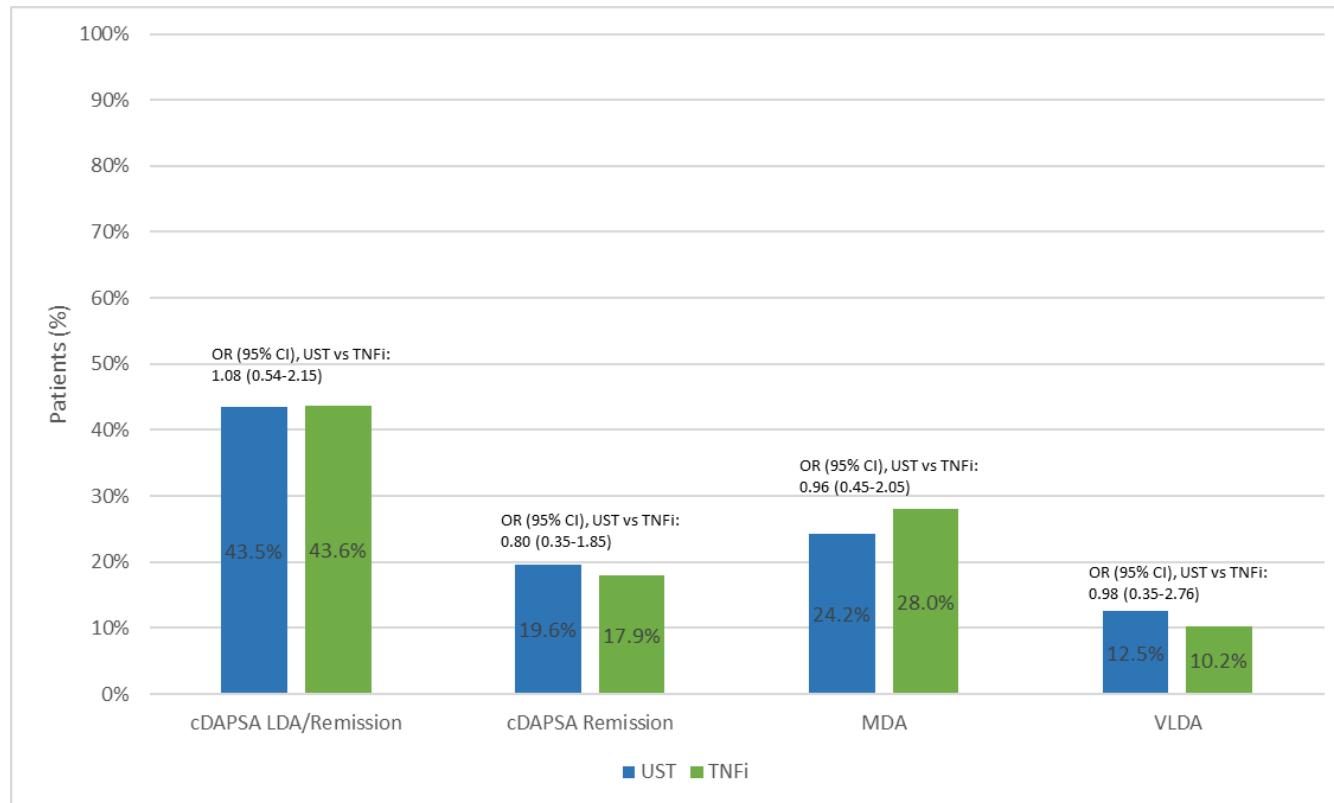


Figure 2. PS-adjusted hazard ratios of discontinuation of treatment, and corresponding 95% confidence intervals, for ustekinumab and TNFi in the PsABio Italian cohort, overall and by selected covariates.



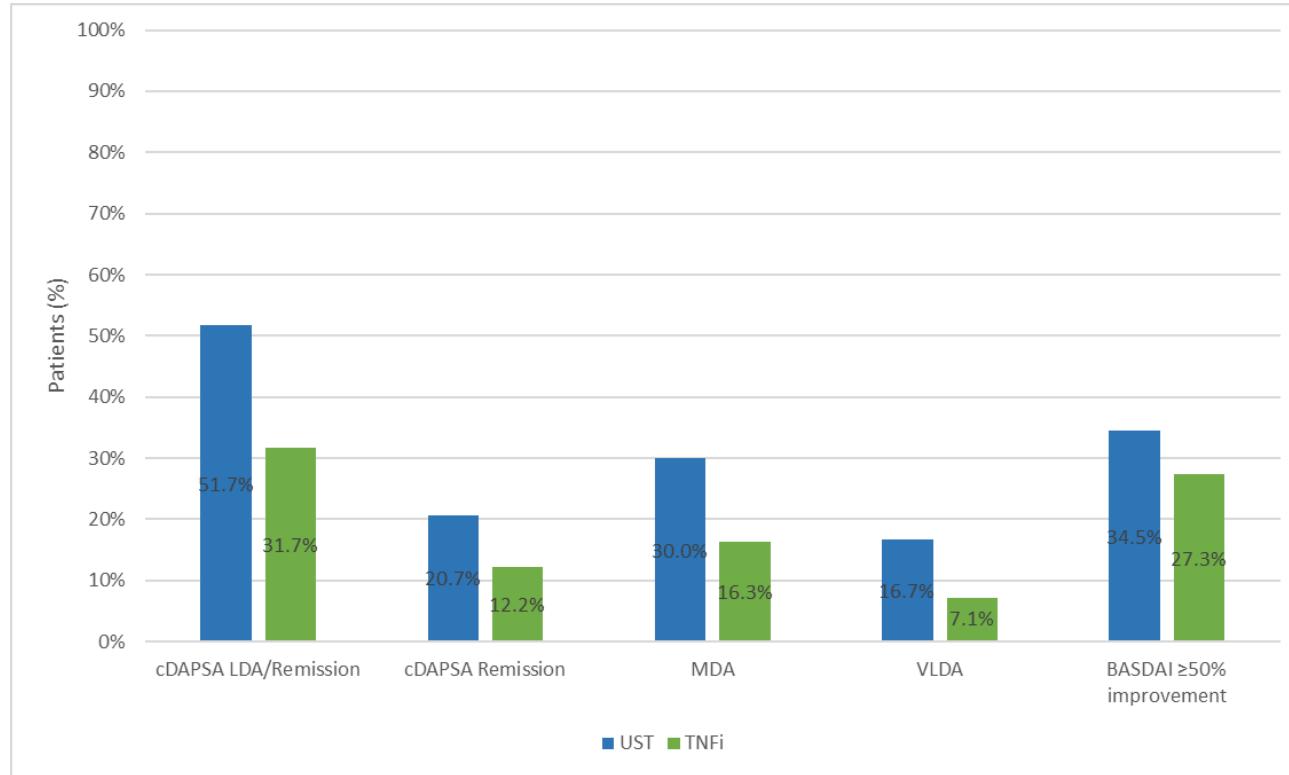
BSA: body surface area; MTX: methotrexate; PS: propensity score; TNFi: Tumor necrosis factor inhibitor; UST: ustekinumab

Figure 3. Proportion of patients achieving cDAPSA LDA/remission and MDA/VLDA at one-year follow up for ustekinumab and TNFi in the PsABio Italian cohort and corresponding PS-adjusted odds ratios (95% confidence intervals).



cDAPSA: clinical Disease Activity index for Psoriatic Arthritis; CI: confidence interval; LDA: low disease activity; MDA: minimal disease activity; OR: PS-adjusted odds ratio; PS: propensity score; TNFi: Tumor necrosis factor inhibitor; UST: ustekinumab; VLDA: very low disease activity

Figure 4. Proportion of patients with axial involvement achieving cDAPSA LDA/remission, MDA/VLDA, and improvement of at least 50% in BASDAI score at one-year follow up for ustekinumab and TNFi in the PsABio Italian cohort.^a



BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cDAPSA: clinical Disease Activity index for PSoriatic Arthritis; LDA: low disease activity; MDA: minimal disease activity; TNFi: Tumor necrosis factor inhibitor; UST: ustekinumab; VLDA: very low disease activity

^a PS-adjusted odds ratios and 95% confidence intervals could not be calculated as the combination of the small number of observations in the subgroup of patients with axial involvement and the large number of factors in the model lead to the separation of data.