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# Use of biological drugs in patients with psoriasis and psoriatic arthritis in Italy: Results from the PSONG survey

Maria C. Potenza<sup>1</sup> | Ketty Peris<sup>2</sup> | Enzo Berardesca<sup>3</sup> | Luca Bianchi<sup>4</sup> |  
 Antonio Richetta<sup>4,5</sup> | Nicoletta Bernardini<sup>1</sup> | Clara De Simone<sup>2</sup> | Miriam Teoli<sup>4</sup> |  
 Arianna Zangrilli<sup>4</sup> | Sara D'epiro<sup>5</sup> | Diego Orsini<sup>6</sup> | Alessandra Narcisi<sup>6,7</sup> |  
 Sergio Chimenti<sup>4</sup> | Antonio Costanzo<sup>7,8</sup> 

<sup>1</sup>UOC di Dermatologia "Daniele Innocenzi", Università degli Studi "Sapienza" Roma I facoltà di Medicina e Chirurgia, Polo Pontino, Terracina, LT, Italy

<sup>2</sup>Istituto di Dermatologia Policlinico Gemelli, Rome, Italy

<sup>3</sup>Ambulatorio Psoriasi IFO-San Gallicano, Rome, Italy

<sup>4</sup>Clinica Dermatologica, Dipartimento di Medicina dei Sistemi, Università Tor Vergata, Rome, Italy

<sup>5</sup>Centro psoriasi, Dipartimento di Medicina Interna e Specialità Mediche, Università "La Sapienza" Policlinico Umberto I, Rome, Italy

<sup>6</sup>Clinica Dermatologica, Dipartimento di Neuroscienze Salute Mentale e Organi di Senso (NESMOS), Università Sapienza-Azienda Ospedaliera Sant'Andrea, Rome, Italy

<sup>7</sup>Humanitas Clinical and Research Center, Skin Pathology Lab, Rozzano-Milan, Italy

<sup>8</sup>Dermatology Unit, Department of Biomedical Sciences, Humanitas University, Rozzano-Milan, Italy

**Correspondence**

Antonio Costanzo, Dermatology Unit, Department of Biomedical Sciences, Humanitas University, IRCCS Istituto Clinico Humanitas, Via Alessandro Manzoni 113, 20089 Rozzano-Milan, Italy.  
 Email: antonio.costanzo@hunimed.eu

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**Abstract**

This Italian multicenter retrospective study compared the drug survival and efficacy of different anti-TNF agents in psoriasis (PsO) and psoriatic arthritis (PsA) patients. A database of PsO/PsA patients treated with adalimumab, etanercept, and infliximab from May 2013 to May 2014 was analyzed. PASI 75, 90, and 100 was calculated at each time point to evaluate efficacy. Drug survival rate and probability of maintaining PASI response were evaluated. The impact of dependent variables on probability of PASI 75 loss was evaluated by logistic regression. 1,235 patients were included, 577 with PsO and 658 with PsA. Highest survival rates were observed with adalimumab followed by etanercept and infliximab in PsO and PsA patients. The probability of maintaining PASI response was significantly higher for adalimumab followed by infliximab. For PsO patients, the odds of losing PASI 75 was higher in etanercept-treated patients (OR: 8.1; 95% CI: 4.2–15.6,  $p < .001$ ) or infliximab (OR: 6.6; 95% CI: 2.6–16.3,  $p < .001$ ) vs. adalimumab. Likewise, for PsA patients the odds of losing PASI 75 was higher in etanercept-treated patients (OR: 2.3; 95% CI: 1.4–3.8,  $p = .01$ ) or infliximab (OR: 2.2; 95% CI: 1.1–4.1,  $p = .018$ ) vs. adalimumab. Adalimumab could be the best therapeutic option over other anti-TNF agents for the treatment of PsO and PsA patients.

**KEYWORDS**

adalimumab, biological drugs, etanercept, infliximab, psoriasis, psoriatic arthritis

## 1 | INTRODUCTION

Psoriasis (PsO) and psoriatic arthritis (PsA) are chronic and invalidating diseases affecting 1–3% and 0.16–0.25% of the world population, respectively (Haddad & Chandran, 2012). Psoriasis is an inflammatory skin disease requiring lifelong care; plaque psoriasis being the most common form (~90%), characterized by painful and itchy erythematous plaques, usually covered with flaking silver scales and localized on scalp, elbows, and knees or generalized disease across wider areas of the body (Canadian Psoriasis Guidelines Committee, 2009; Menter, Gottlieb, and Feldman, 2008). PsA is a chronic inflammatory seronegative spondyloarthropathy associated with PsO (Gottlieb, Korman, & Gordon, 2008; Scottish Intercollegiate Guidelines Network (SIGN), 2010), with an estimated prevalence in PsO patients of 25–40% (Gottlieb & Dann, 2009; Laws, Barton, and Warren, 2010). The visible plaques of PsO have a strong impact on physical and mental functions similar to that of other severe chronic diseases, (Rapp, Feldman, Exum, Fleischer, & Reboussin, 1999) with high levels of stress, poor self-esteem, increased rates of mood disorders and detrimental effects on social functioning, interpersonal relationships and productivity (Eghlileb, Davies, & Finlay, 2007). PsA patients may develop severe skeletal changes in addition to cutaneous signs, with a negative impact on function and quality of life (Gossec & Smolen, 2015). A delay in the diagnosis of PsA that is associated with adverse long term outcome, such as joint damages and associated disabilities; the early detection of PsA can prevent these significant complications (Gossec & Smolen, 2015; McHugh, 2015).

Treatment strategies of severe or refractory/recalcitrant PsO/PsA recommended by International and National Guidelines are based on disease-modifying drugs (DMARDs), such as methotrexate and cyclosporine. In cases of inadequate response, contraindication or intolerance to at least one DMARD, a therapy with a biologic drug such as tumor necrosis factor (TNF) inhibitors (adalimumab, infliximab, etanercept, golimumab) or anti-interleukin therapies (ustekinumab) should be considered (Canadian Psoriasis Guidelines Committee, 2009; Gossec & Smolen, 2015; Gossec, Smolen, and Gaujoux-Viala, 2012; Il Trattamento della Psoriasi Nell'adulto, 2013; Menter et al., 2008; NICE Clinical Guideline Centre, 2012; Salvarani, Pipitone, and Marchesoni, 2011; Scottish Intercollegiate Guidelines Network (SIGN), 2010). Furthermore, in February 2016, adalimumab was approved by the European Medicines Agency for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy and not only after previous inadequate response/intolerance to systemic DMARDs (European Medicines Agency, 2016).

TNF, a pleiotropic cytokine which regulates several inflammatory reactions and immune functions through the control of cellular processes, plays a central role in the pathogenesis of PsO and PsA. The over-expression of TNF is able to promote pro-inflammatory conditions and is involved in several pathogenetic mechanisms such as the accumulation of leukocytes in the inflamed skin, induction of dermal vascular changes and itching, and inflammation and joint-bone damage (Blandizzi et al., 2014). TNF inhibitors represent effective therapeutic options for the treatment of PsO and PsA, significantly improving signs

and symptoms and reducing the disease activity. These drugs represent an outstanding innovation in the treatment of inflammatory immunomediated diseases and an important option for modifying the natural course and the unfavorable progression of these diseases (Blandizzi, 2013; Furst, Keystone, and Braun, 2012; Raval, Lofland, Waters, & Piech, 2011). The anti-TNF agents adalimumab, etanercept and infliximab are indicated both in PsA and PsO (Enbrel® (Etanercept), 2015; Humira® (Adalimumab), 2015; Remicade® (Infliximab), 2015; Simponi® (Golimumab), 2015; Stelara®, (ustekinumab), 2015).

National registries provide clinical data from the real-world setting, with the main aim to monitor long-term safety of specific treatments in the clinical setting, but they also contain other important information difficult to collect in clinical trials, such as drug usage, real-life long-term effectiveness, the impact on quality of life (QoL), and related economic issues (Armuzzi et al., 2014).

The aim of this retrospective study was to collect epidemiological and management information on PsO/PsA patients treated with TNF inhibitors in real life. Real life data reflect the daily clinical practice, differently from randomized clinical trials, where stricter inclusion/exclusion criteria are adopted for selecting study populations.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients and study design

PSONG was a retrospective longitudinal non-interventional epidemiological investigation performed by consulting a clinical database of PsO/PsA patients treated with biological drugs in 6 centers of Lazio region (Gemelli Polyclinic, Rome; "Daniele Innocenzi" Polo Pontino Dermatology Operating Unit, "La Sapienza" University, Rome; Psoriasis Centre, "La Sapienza" University, "Umberto I" Polyclinic, Rome; "La Sapienza" University S. Andrea, Rome; Psoriasis Clinic ISO Centre, S. Galliciano, Dermatology Unit, Tor Vergata Hospital, Rome) between May 2013 and May 2014. Anti-TNF agents administered to patients included etanercept, infliximab, and adalimumab at common doses (prescribed within the EU). All biologics were administered according to product guidelines (European Medicines Agency, 2016). Inclusion criteria included: male or female patients diagnosed with psoriasis or psoriatic arthritis currently being treated with an anti-TNF agent; patients  $\geq 18$  years and patients that have signed an informed consent form. Diagnosis of psoriasis and psoriatic arthritis was clinical. Psoriasis was diagnosed according to the criterion of the "rule of tens" by Finlay (BSA involved  $>10\%$  or PASI score  $>10$  or DLQI score  $>10$ ) (Finlay, 2005) and all PsA patients met the CASPAR (CIASSification criteria for Psoriatic ARthritis) criteria for the classification of PsA (Taylor, Gladman, & Helliwell, 2006). The database was designed to record demographic and anamnestic data, concomitant diseases, current and previous biologic treatments, Psoriasis Area Severity Index (PASI) score during the observational period (visits: 0, 3 months, 6 months, 1, 2, 3, 4, 5, 6, 7, 8 years). Ethics committee approval from all participating centers and written informed consent for the anonymous use of personal data was obtained from every patient, in compliance with Legislative Decree 196/2003. This study complies with the ethical standards laid down in the 1975 Declaration of Helsinki.

## 2.2 | Outcome measures

To evaluate the efficacy of each anti-TNF agent, the response rate of a 75%, 90%, and 100% improvement in the PASI score (respectively PASI 75, PASI 90, and PASI 100) was calculated at each time point. The survival rate and probability of maintaining PASI 75, 90, and 100 responses were evaluated for each treatment over the entire observation period.

## 2.3 | Statistical analysis

Data are presented as mean  $\pm$  standard deviation for continuous variables, and absolute and relative frequency distribution for categorical data. Comparisons between groups were performed by the Chi-squared test for categorical variables and the Wilcoxon test for non-parametric continuous variables. The survival rate for each biologic treatment and time to losing the PASI targets (PASI 75/90/100) were estimated by means of Kaplan-Meier survival curves. The comparison between drug survival rates was performed using the Log-rank test. Linear regression for repeated measures was applied to evaluate the association between the number of patients achieving PASI 75/90/100 among the different biological drugs. All analyses were stratified according to disease type (PsO or PsA).  $p < .05$  was considered statistically significant. All analysis was performed using SAS version 8.2 for Windows or Stata 12.

## 3 | RESULTS

### 3.1 | Baseline demographic and clinical characteristics

A total of 1,235 patients were included in the PSONG study, 577 in the PsO group and 658 in the PsA group. Patient clinical and demographic characteristics are presented in Supporting Information Table S1. There were a higher proportion of male patients in both the PsO (71.3%) and PsA (57.1%) groups. PsA patients were slightly older (55 vs. 50 years) and PASI score was higher in PsO patients (range 11–18 vs. 4–14). Clinical characteristics prior to initial anti-TNF treatment were well matched across groups (Supporting Information Table S1).

### 3.2 | Probability of maintaining treatment

In PsO patients the probability of maintaining treatment over the 8-year follow-up period was highest in those treated with adalimumab compared to those treated with etanercept ( $p = .061$ ) or infliximab ( $p < .001$ ) (Figure 1a). At 6 years, the probability of maintaining adalimumab treatment (0.62; 95%CI: 0.52–0.7) was approximately 10% higher than etanercept (0.49; 95% CI: 0.42–0.56) and about 30% higher than infliximab (0.33; 95% CI: 0.21–0.44).

In PsA patients, although patients treated with etanercept had a similar probability of maintaining treatment compared to adalimumab at 2 years (0.76; 95% CI: 0.72–0.80 vs. 0.74; 95% CI: 0.68–0.79, respectively), adalimumab-treated patients had higher probability of maintaining treatment for the remainder of the follow-up period (Figure 1b). As expected, no statistically significant difference was noted between the probability of maintaining treatment for these 2 groups ( $p = .91$ ), over

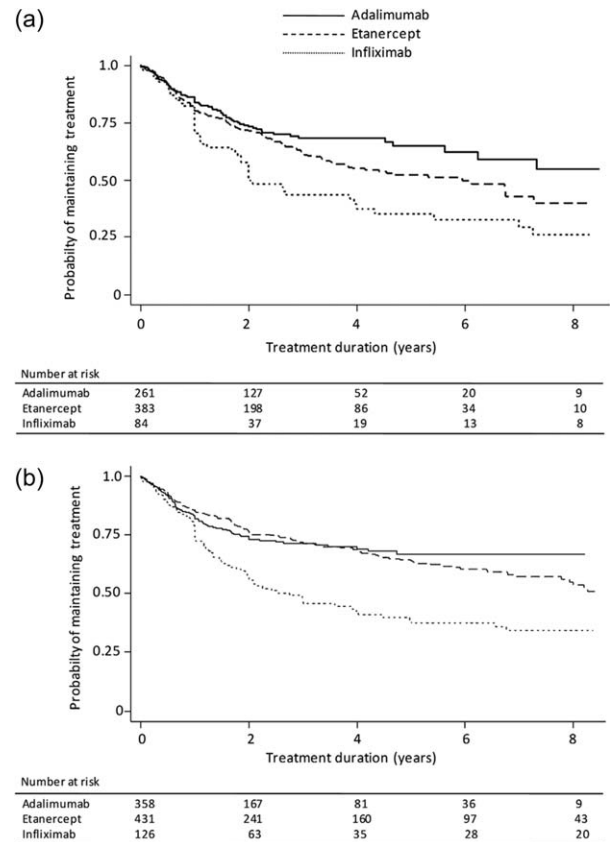


FIGURE 1 Drug survival rates of 3 different anti-TNF agents in PsO and PsA patients

the entire follow-up period however, infliximab treated patients revealed significantly lower probability of maintaining treatment compared to adalimumab ( $p < .001$ ) and etanercept ( $p < .001$ ).

### 3.3 | Probability of maintaining PASI 75, 90, and 100

The probability of the 3 different anti-TNF therapies maintaining PASI 75, 90, and 100 for PsO, and PsA patients are summarized in Figure 2. PsO patients treated with adalimumab had a significantly higher probability of maintaining PASI 75, 90, and 100 compared to etanercept or infliximab (Figure 2a–c). The probability of maintaining PASI 75 was higher for adalimumab compared to etanercept ( $p < .001$ ) or infliximab ( $p = .05$ ) (Figure 2a). Similarly, adalimumab was more effective in maintaining PASI 90 compared to etanercept ( $p < .01$ ) or infliximab ( $p = .002$ ) (Figure 2b). This trend was also observed for PASI 100, where adalimumab was more effective compared with etanercept ( $p < .01$ ) or infliximab ( $p < .01$ ) (Figure 2c). The magnitude of the difference between adalimumab can be reflected in the difference in probability at 4 years compared to etanercept (0.57; 95% CI: 0.43–0.69 vs. 0.098; 95% CI: 0.04–0.20). In PsA patients, apart from PASI 75 (Figure 2d), adalimumab was superior in maintaining PASI 90 and 100 compared to etanercept or infliximab. For maintenance of PASI 90, adalimumab was more effective compared with etanercept ( $p = .044$ ) or infliximab ( $p = .024$ ) (Figure 2e). This difference was also maintained for PASI 100

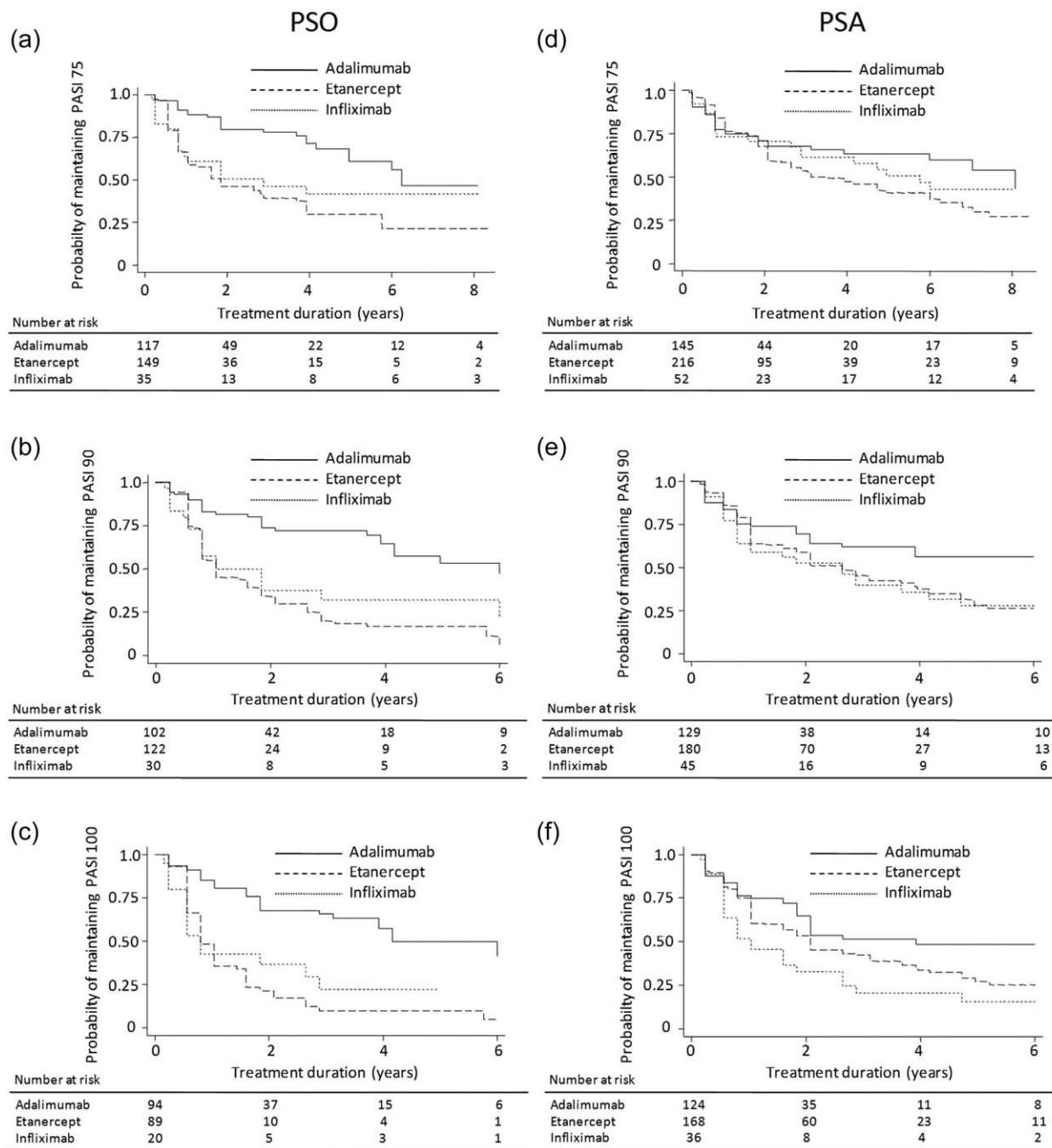


FIGURE 2 Probability of maintaining PASI 75, 90 and 100 in PsO and PsA patients

where a statistically significant difference was observed between adalimumab and etanercept ( $p = .050$ ) or infliximab ( $p < .01$ ) (Figure 2f).

### 3.4 | PASI clinical response rate

The clinical response was evaluated as the rate of patients attaining PASI 75, 90, or 100 over the 7 year follow up period. Figure 3 shows the rate of PsO and PsA patients with PASI 75, 90, and 100 response stratified by anti-TNF treatment. The proportion of PsO patients with PASI 75 over the follow up period was higher for adalimumab vs. etanercept and infliximab (Figure 3a). Similarly, a higher proportion of patients attained PASI 90 treated with adalimumab compared to

etanercept or infliximab as well as those patients with PASI 100 (Figure 3b,c). In contrast, in PsA patients, no differences in terms of PASI 75 response rate were observed among the three treatments (Figure 3d). PASI 90 and PASI 100 responses were markedly higher in patients treated with adalimumab compared with patients treated with etanercept (Figure 3e,f). A higher PASI 100 response rate was observed for adalimumab vs. infliximab (Figure 3f).

### 3.5 | Impact of predictor variables on PASI 75 loss

Logistic regression analysis was used to evaluate the impact of independent variables on the probability of PASI 75 loss in the PsO

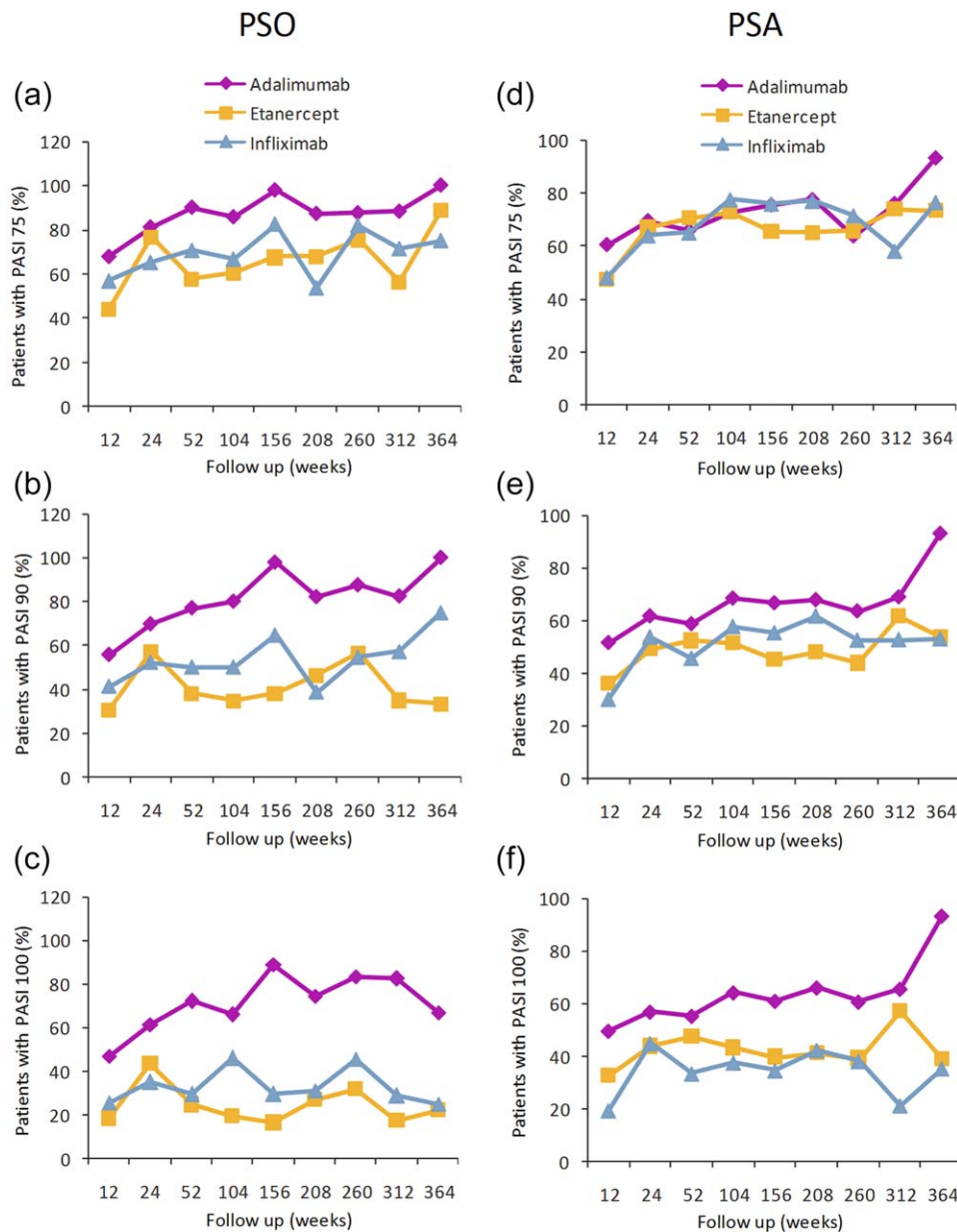


FIGURE 3 PASI clinical response rate in PsO and PsA patients

and PsA groups (Supporting Information Table S2, upper panel). In PsO patients, univariate analysis revealed that etanercept and infliximab compared to adalimumab treatment increased the odds of PASI loss by 8.9- (95% CI: 14.7–16.9) and 6.6-fold (95% CI: 2.78–15.7), respectively. The presence of 1 or > 1 previous therapies were associated with a protective effect against PASI 75 loss as was baseline PASI, where every 1 unit increase in baseline PASI was associated with a 5% reduction in odds of PASI 75 loss. Multivariate logistic analysis was performed excluding variables that had a *p* value  $\geq .2$  following univariate analysis. In addition to baseline PASI having a protective effect on PASI 75 loss, etanercept (Odds ratio: 8.1, 95% CI: 4.2–15.6, *p* < .001) and infliximab (Odds ratio: 6.6, 95% CI: 2.6–16.3, *p* < .001) compared to adalimumab treatment still emerged as strong predictors of PASI 75 loss. The effect of biologic therapy had less of an impact on PASI 75 loss in PsA patients (Supporting

Information Table S2, lower panel). Univariate analysis showed that etanercept and infliximab compared to adalimumab treatment increased the odds of PASI 75 loss by 2.33- (95% CI: 1.4–3.8, *p* = .001) and 2.32-fold (95% CI: 1.14–4.1, *p* = .01), respectively. Baseline PASI was not associated with PASI 75 loss. Etanercept (Odds ratio: 2.29, 95% CI: 1.4–3.77, *p* = .001) and infliximab (Odds ratio: 2.19, 95% CI: 1.14–4.14, *p* = .018) compared to adalimumab treatment still emerged as significant predictors of PASI 75 loss following multivariate logistic analysis.

#### 4 | DISCUSSION

The main outcome measure examined in this retrospective study, carried out in a routine clinical setting using the data of a clinical database of PsO/PsA patients treated with biological drugs in 6 Italian centers,

was the drug survival, which reflects a drug's effectiveness, safety and tolerability. Drug survival is based on several factors such as dosage, effectiveness, improvement of the quality of life, safety and compliance and could be considered an overall marker for treatment success.

Gisoni et al. recently demonstrated that the retention rate (the number of patients who maintain the same therapy during a given period of treatment) of TNF-alpha inhibitors was significantly higher compared with conventional systemic treatment (DMARDs), due to a better tolerability (Gisoni, Tessari, Di Mercurio, Del Giglio, & Girolomoni, 2013). In fact, the number of patients who discontinued TNF-alpha inhibitors was lower than that of DMARDs. No differences were noted among TNF-alpha inhibitors (Gisoni, Tessari, & Di Mercurio, 2013). An Italian experience (BEETLE study) evaluated 1,219 patients included in administrative databases of five Italian local health units (LHU) in Emilia-Romagna, Lazio, Tuscany, Campania, and Lombardy. Patients were affected by rheumatoid arthritis (36%), PsO (31%), Crohn's disease (10%) and other immune-mediated inflammatory diseases and treated with etanercept ( $n = 615$ ), adalimumab ( $n = 420$ ), and infliximab ( $n = 184$ ). Among the group of patients who did not switch to another drug (94%), the rate of adherence across all indications was higher for infliximab (51%) compared to etanercept (27%) or adalimumab (23%) (Degli Esposti, Sangiorgi, & Perrone, 2014).

Our results show that in PsO patients, adalimumab has the highest survival rate, statistically superior to that of etanercept and infliximab. These results are partially in contrast with other recent epidemiological surveys (Esposito, Gisoni, & Cassano, 2013; Gniadecki, Kragballe, Dam, & Skov, 2011; Gniadecki, Bang, and Bryld, 2015).

The retrospective study Outcome and Survival Rate Concerning Anti-TNF Routine treatment (OSCAR) showed that etanercept had a longer survival (mean 51.4 months,  $p < .001$ ) compared with infliximab (36.8 months) and adalimumab (34.7 months) (Esposito et al., 2013). Gniadecki et al. evaluated the data of the Danish prospective nationwide database DERMBIO (registry for PsO patients showing that in the group of anti-TNF-a-naive patients, the longest drug survival was observed for infliximab, followed by adalimumab and etanercept (Gniadecki, Kragballe, & Dam, 2011). A recently published update of this study included 1,867 treatment series over a period of 10 years. In this study, drug survival was significantly longer for ustekinumab than for the anti-TNF-alpha inhibitors ( $p < .001$ ). In particular, adalimumab and infliximab had comparable median survival rates and etanercept had the shortest survival time (Gniadecki et al., 2015).

Our data confirmed previously reported data from several registry-based studies (Brunasso, Puntoni, & Massone, 2012; Iskandar, et al. 2015May18; Menting, Sitaram, & Bonnerjee-van der Stok, 2014; van den Reek et al., 2014; Warren et al., 2015). In a retrospective cohort study evaluating tolerability and safety of biological drugs (adalimumab, efalizumab, etanercept, and infliximab) in 108 PsO patients infliximab was significantly associated with a shorter adherence to therapy compared with adalimumab, etanercept, and efalizumab (Brunasso et al., 2012). The British Association of Dermatologists Biologic Interventions Register (BADBIR) is a prospective, observational database designed to evaluate the long-term safety of biologic and conventional systemic treatments for adults with moderate-to-severe PsO in the U.K. and

Republic of Ireland. 5,065 (60%) out of 8,399 patients included in BADBIR received a biologic drug: 52.8% adalimumab, 24.6% etanercept, 18.7% ustekinumab, and 3.9% infliximab (Iskandar et al., 2015). Warren et al. calculated the survival rates of the first course of biologics for 3523 biologic-naïve patients with chronic plaque PsO enrolled in BADBIR database. The overall survival rate in the first year was 77% and 53% in the third year. In particular, patients treated with etanercept or infliximab were more likely to discontinue therapy compared with adalimumab or ustekinumab (Warren et al., 2015). Similar results were observed in Bio-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with biologics) registry, implemented by the department of Dermatology of the Radboud University Medical Center, Nijmegen in 2005. The results of these trials showed that the 1-year drug survival rates for ustekinumab, adalimumab, and etanercept were 85%, 74%, and 68%, respectively (van den Reek et al., 2014). Finally, a single center database analysis performed in the Academic Medical Center, Amsterdam, the Netherlands, on 221 PsO patients treated with biological drugs showed no statistically significant differences in terms of drug survival, either in naïve episodes (etanercept 82–52%, adalimumab 75–80%, infliximab 73–57% after year 1–4), or in non-naïve episodes (etanercept 77–31%, adalimumab 75–44%, infliximab 65–43% after year 1–4, ustekinumab 80–25% after year 1–3) (Menting et al., 2014).

According to our data, in PsA patients the probability of remaining in treatment was higher for adalimumab, significantly lower for etanercept, followed by infliximab. Our findings contrast with those in other reports. The retrospective study by Fabbroni et al. evaluated treatment persistence rates and causes of discontinuation in 268 PsA and ankylosing spondylitis patients treated with biological drugs in clinical practice (Fabbroni, Cantarini, & Caso, 2014). The comparison among the 3 anti-TNF drugs showed a difference in terms of drug survival: a withdrawal was required in 28.9% of patients treated with adalimumab, 22.8% of patients treated with etanercept and in 38.2% of those treated with infliximab; the difference between etanercept and infliximab was statistically significant ( $p = .0058$ ) (Fabbroni et al., 2014). An epidemiological observational cohort study from The Danish biologics registry DANBIO evaluated the patients' clinical response and drug survival to anti-TNF-alpha inhibitors of 764 PsA patients (Glintborg, Østergaard, & Dreyer, 2011). The results showed that the median drug survival was 2.9 years, and 1-year and 2-year drug survival rates were 70% and 57%, respectively. In particular, no differences were observed in terms of retention rates, which were similar among patients receiving infliximab, adalimumab and etanercept (Glintborg et al., 2011).

Considering the efficacy outcome based on PASI response and the survival rate, in our experience adalimumab was the most effective treatment both in PsO and in PsA patients. These efficacy results are similar to or even higher than those reported in clinical trials (Armesto, Coto-Segura, Mayorga, Illaro, & Santo-Juanes, 2015; Esposito, Giunta, and Mazzotta, 2012; Gordon et al., 2012; Lopez-Ferrer, Vilarrasa, Gich, & Puig, 2013; Menter et al., 2008; Papp, Ho, and Teixeira, 2012; Papp, et al. 2009September–October). Some recent meta-analyses and direct/indirect comparisons evaluated the effectiveness of available biological drugs in PsO and PsA patients. Overall, the results showed that there were no significant differences between the drugs in relation to the

efficacy outcomes, except for a superiority of ustekinumab, adalimumab and infliximab versus etanercept in terms of PASI response in PsO patients (Galvan-Banqueri, Marín Gil, Santos Ramos, & Bautista Paloma, 2013; Puig, Lopez, Vilarrasa, & García, 2014; Reich, Burden, Eaton, & Hawkins, 2012; Schmitt, Rosumeck, and Thomaschewski, 2014).

Taken together, these results confirm that adalimumab is a valid therapeutic options for the long term management of severe-to-moderate PsO and PsA patients, as recommended by International and National guidelines. Furthermore, adalimumab is the only anti-TNF agent approved for first line treatment of moderate to severe chronic plaque psoriasis in adult patients (16). It is noteworthy that biological drugs are often combined with traditional therapies in daily clinical practice: this aspect should be further evaluated in clinical trials, as well as the clinical response in PsO and PsA biologic experienced vs. naïve patients.

#### 4.1 | Study strengths and limitations

This study is of particular value as it provides longitudinal data (collected retrospectively) from 1,235 patients, (577 in the PsO group and 658 in the PsA group) from 6 centers with follow-up times ranging from 6 months to 8 years. To date, few studies are available that report data on this Italian population. However, there are some potential limitations that need to be addressed. Weaknesses of observational registries such as the reliability of results and incompleteness of data have previously been highlighted (Vandenbroucke, von Elm, and Altman, 2007; von Elm, Altman, and Egger, 2007). Furthermore, the lack of randomization may also introduce selection bias, and the presence of unmeasured confounders cannot always be ruled out. However, we did not observe any marked changes in clinical characteristics among treatment groups attributed to loss during follow-up. This potential limitation was also addressed by including potential confounding variables in logistic regression models. It is recognized that efficacy and retention in therapy for biologics is correlated with line of treatment. Although the proportion of naïve patients was not markedly different in the PsO (50–65%) and PsA groups (30–55%), our analysis did not specifically examine efficacy by line of treatment, which was not feasible due to the low sample sizes for this sub-analysis. Last, our analysis was limited to the comparison of adalimumab, etanercept, and infliximab for the treatment of PsO and PsA patients. Few patients were treated with golimumab ( $N = 47$ ) to permit further analysis and certolizumab was not available in Italy at the time this study was undertaken.

## 5 | CONCLUSIONS

Real-life data, typically collected by national registers and non-interventional studies, represent an important source of information on long-term treatment, efficacy and safety in day-to-day conditions of clinical practice and among heterogeneous groups of patients, such as elderly subjects or patients with comorbidities or co-medications, usually excluded from randomized controlled trials.

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## CONFLICT OF INTEREST

AC served as speaker for Janssen, Abbvie, Pfizer, Celgene, Lilly, Novartis.

## ORCID

Antonio Costanzo  <http://orcid.org/0000-0001-9697-2557>

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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