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ORIGINAL ARTICLE

Real-world effectiveness of anti-TNF switching in psoriatic arthritis: a systematic review of the literature

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Abstract Anti-tumor necrosis factors (Anti-TNFs) are a class of biologic disease-modifying anti-rheumatic drugs indicated for the treatment of moderate-to-severe psoriatic arthritis (PsA). Refractory patients are commonly managed by switching from one anti-TNF to another. To assess the evidence on the effectiveness of anti-TNF cycling in PsA patients, a systematic review of the literature was conducted. MEDLINE- and Embase-indexed English-language publications were systematically searched from 1995 to 2015 for studies assessing real-world effectiveness outcomes of anti-TNF cycling in PsA patients. Of 1086 citations identified, 18 studies were included; most conducted in Europe. Six of seven studies testing between lines found significant differences in effectiveness between earlier and subsequent lines of anti-TNF therapy. First-line therapy yielded better results compared with second-line therapy, and significant differences were observed between second- and third-line anti-TNF treatments. In the only study with multivariate regression testing for predictors of response, Danish registry patients were less likely to respond (American College of Rheumatology 20 % or 50 % response) to a second anti-TNF course if safety, rather than lack of effect, caused them to switch (odds ratio [OR] 0.04; $p = 0.003$ and OR 0.05; $p = 0.03$, respectively). Effectiveness of anti-TNFs at second line and later is reported in a small number of real-world studies of PsA patients. Subsequent treatment lines may be associated with less response in some measures. More research is needed to quantify the effectiveness of sequential anti-TNF lines in this progressive population, and to compare these effects with responses to drugs with different mechanisms of action.

Keywords Anti-TNF cycling · Psoriatic arthritis · Systematic literature review

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Introduction

Psoriatic arthritis (PsA) is a form of spondyloarthritis characterized by inflammatory arthritis and associated with skin psoriasis [1]. PsA is heterogeneous in nature and covers a wide range of manifestations that may involve peripheral arthritis, enthesitis, tenosynovitis, and the spine [2]. Affecting men and women equally, PsA has an estimated prevalence between 0.3 and 3 % in the general population [3, 4]. PsA can progress to an erosive and deforming disease, with approximately 40 % – 60 % of patients demonstrating joint damage at early stages after disease onset [5–7]. Moderate to severe forms of PsA are managed with conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs). Biologics, including tumor necrosis factor-α antagonists (Anti-TNFs), ustekinumab (used alone or combined with methotrexate), and secukinumab, are also approved for use in patients with active PsA.

Anti-TNFs are a class of biologic DMARDs that function by blocking TNF-α, a cytokine molecule active in the inflammatory response. The British Society of Rheumatology (BSR) [8] recommends anti-TNF therapy for PsA patients with active disease who have failed at least two conventional DMARDs. The European League Against Rheumatism (EULAR) [9] recommends anti-TNF use after failure of just one DMARD;

however, new 2015 guidelines suggest first-line treatment when there is axial involvement. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommends anti-TNFs as a possible option for first-line therapy (after failure of Non-steroidal Anti-inflammataory Drugs (NSAIDs)) in cases with axial disease and enthesitis, as rescue therapy for dactylitis, and in certain cases with peripheral arthritis or skin involvement [10].

Currently, licensed anti-TNF agents in the United States (US) and Europe [11–14] include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. These agents have been shown to lessen signs and symptoms of inflammation, enhance quality of life (QoL) and functional capacity, and some hinder the evolution of structural joint damage [15–17]. However, not all patients initially respond to anti-TNF treatment, and some may develop treatment resistance due to development of anti-drug antibody formation or compensatory changes in the inflammatory pathway. Side effects may also lead to discontinuation of anti-TNF treatment.

A plausible option to treat refractory PsA patients may be to switch their treatment from one TNF-α inhibitor to another. Prior to the published evidence on the effectiveness of anti-TNF switching in PsA populations, clinicians drew from the results seen in rheumatoid arthritis (RA) patients. Numerous studies have shown efficacy and tolerability in a significant percentage of patients with RA following treatment with a second or third anti-TNF, regardless of the order of subsequent therapies [18–20]. A recent meta-analysis on anti-TNF switching in RA patients suggested a treatment benefit to subsequent lines of treatment [21]. Conversely, analysis of Consortium of Rheumatology Researchers of North America (CORRONA) registry data reported RA patients with prior anti-TNF exposure who switched to rituximab, a drug with a different mechanism of action (MOA), had a higher likelihood of achieving low disease activity and remission compared with switching to a second anti-TNF [22]. However, because RA and PsA present with different joint patterns, radiographic changes, and other manifestations such as skin involvement unique to PsA, their distinct natural histories may result in differences in treatment response [23]. The synergy of anti-TNFs with methotrexate seen in RA has not been demonstrated in PsA, and not all drugs approved to treat PsA have RA indications.

Recently, the benefit of switching to later lines of anti-TNF in PsA patients, both in terms of efficacy testing in clinical trials [24] and, importantly, long-term drug persistence in observational study designs, has been published. Evidence on subsequent biologic use is sparse; however, it is compelling enough for the GRAPPA panel to recommend biologic switching across disease domains, including options of switching to another anti-TNF with the same MOA or to a biologic with a different MOA. To comprehensively assess the real-world evidence on the effectiveness of anti-TNF cycling in PsA patients, a systematic review of the literature was therefore conducted.

Materials and methods

Systematic literature searches were conducted in the MEDLINE (via PubMed) and Embase databases for English-language articles on the effectiveness of anti-TNF cycling in PsA patients published between January 1, 1995 and May 5, 2015. The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. Pre-defined Medical Subject Heading (MeSH) and free-text terms for PsA were paired with terms for anti-TNF treatment, including drug names of treatments labeled for PsA (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and ustekinumab) and observational study designs. The inclusion and exclusion criteria were determined per the PICOS criteria (participants, interventions, comparisons, outcomes, and study design) shown in Table 1. Eligible studies included those with at least 10 adult PsA patients who had failed at least one prior anti-TNF due to lack of efficacy or intolerance. Treatments of interest included anti-TNFs or other biologics that are currently approved for the treatment of PsA. In addition, observational or non-randomized comparative studies that examined any measure of treatment effectiveness were included. Conference proceedings from the 2013–2015 annual meetings of the American College of Rheumatology (ACR), EULAR, BSR, and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) were also searched.

Abstract and full-text screenings were each conducted by a single reviewer utilizing the PICOS study selection criteria. Every article excluded at the full-text level was validated by a second reviewer. Any discrepancies at each level of screening were resolved using a third, senior reviewer if a consensus could not be reached between reviewers. All articles accepted at the full-text level met none of the exclusion criteria and all of the inclusion criteria and were thus eligible for extraction.

Results

Literature search

In this review, 1086 unique citations were identified from MEDLINE and Embase for abstract screening. Using the previously described inclusion and exclusion criteria, 48 articles were selected for full-text review. Of those studies, a total of 33 articles were excluded. The primary reasons for exclusion were no prior anti-TNF failure ($n = 12$), followed by outcomes not separable by population of interest ($n = 6$). Fifteen studies were included after full-text screening. In addition, five studies were identified from the separate search of the conference proceedings, two of which were also identified in the database search. This resulted in a total of 18 studies [26–43] being included in the final review (Fig. 1).

Table 1 PICOS criteria for study selection

	Population	Interventions	Comparators	Outcomes	Study design
Inclusion	At least 10 adult patients with PsA who had failed at least one line of anti-TNF due to lack of efficacy or intolerance	Anti-TNF or other biologics currently approved for treatment of PsA	None[a]	Any measure of treatment effectiveness	▪ Observational studies: –Prospective –Retrospective ▪ Non-randomized comparative studies
Exclusion	▪ Study does not evaluate patients with PsA who failed prior anti-TNF ▪ <10 adult PsA patients ▪ Pediatric studies	Study does not evaluate treatment with an anti-TNF or other biologic that is currently approved for treatment of PsA		▪ Animal, *in vitro*, or genetic studies ▪ Study does not report outcomes of interest (treatment effectiveness)	▪ Randomized clinical trials, case reports, editorials, reviews, conference abstracts, commentary, or news

Abbreviations: PsA psoriatic arthritis, *TNF* tumor necrosis factor

[a] Outcome described across sequential anti-TNF lines within the same treatment arm NOT compared in parallel between treatment arms

Study characteristics

The included articles were published between 2007 and 2015, with half of the studies published since 2013. All but three studies were based in Europe, specifically, Austria [35], Denmark [32], France [38, 42], Italy [27, 29, 37, 39], Norway [30], Sweden [33, 34], and the United Kingdom (UK) [26, 28, 40]. One study each was conducted in the US [41] and Canada [31], and one meeting abstract did not report the geographic location [43]. Of the 17 studies that reported recruitment location, the most common were centers in Italy (4/17; 23.5 %) and the UK (3/17; 17.6 %). Per the study protocol, all studies were observational in design, and a majority of PsA cohorts were followed prospectively (10/18; 55.5 %) or retrospectively (6/18; 33.3 %). Two studies were uncontrolled clinical trials [27, 31]. Six registries were identified in this review: two prospective national registries from Sweden and Denmark (South Swedish Arthritis Treatment Group [SSATG] and DANBIO, respectively), a multicenter registry from Norway (Norwegian disease-modifying anti-

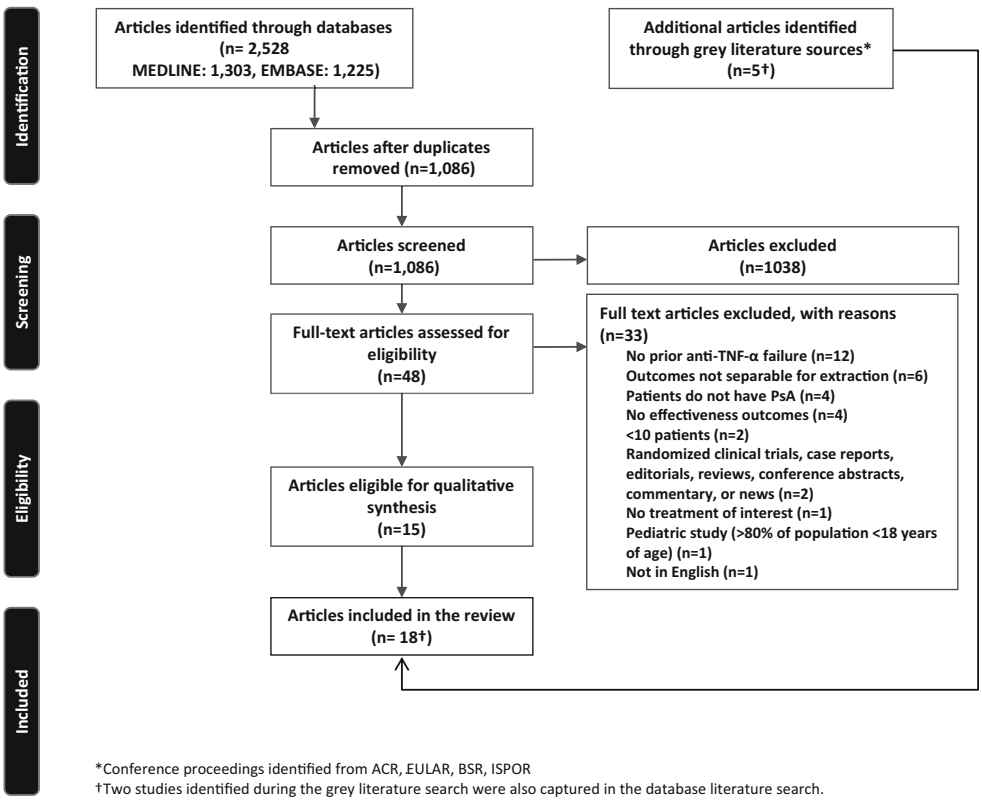

Fig. 1 Study attrition

rheumatic drug registry [NOR-DMARD]) that followed PsA patients longitudinally after initial anti-TNF treatment, and three single site registries in Italy, Norway, and the UK [28–30, 32–34, 36].

Patient characteristics

Across all studies, 5805 PsA patients were followed for effectiveness of subsequent therapies after anti-TNF exposure. Sample sizes ranged widely, from two patients to 1422, based on catchment area (single site compared to national) and line (fourth line compared to initial first anti- TNF line). In larger studies of 50 or more PsA patients, the median age was 47 years (range: 46–48) and seemed evenly distributed between genders (median percent of males: 51; range 41 %–62 %).

Case definition

Case definition was reported in 12 of 18 studies (66.7 %). Of these, the clinical judgment of the treating physician was sufficient to determine the case in half of the studies. Five studies required the initial PsA diagnosis to be further established per standard criteria: three per Moll and Wright [28, 29, 31], one per ClASsification criteria for Psoriatic ARthritis (CASPAR) [27], and one [42] that used either criteria. In a single hospital study in France, cases were identified using administrative database codes [38].

Treatment characteristics

Five studies [27, 30, 31, 37, 39] described PsA that was resistant to DMARDs and other biologics at baseline, and an additional three studies [33, 34, 41] followed populations exclusively after DMARD treatment. Per the study protocol, all patients were exposed to at least one line of anti-TNF. Fourteen studies [26–33, 37–39, 41–43] specified the anti-TNF given, specifically, adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab. PsA patients on anti-TNFs were followed for efficacy from first-line treatment to a second anti-TNF line in 16 studies [26, 28–38, 40–43], from second- to third-line treatment in 14 studies [26, 28, 30, 32–40, 42, 43], from third- to fourth-line treatment in nine studies [26, 28, 32–35, 39, 40, 42], and from fourth- to fifth-line treatment in one study [26]. All five of the currently approved anti-TNFs listed above were used as a first-line, second-line, or third-line rescue therapy in at least one study. Etanercept or adalimumab were most commonly reported: either or both of these anti-TNFs were listed in 100 % of first-line studies, 92.3 % of second-line, and 90 % of third line. Six studies [27–29, 31, 36, 41] reported efficacy after repeated anti-TNF exposure but did not further separate results by line. Use of a concomitant DMARD including methotrexate was reported in 10 studies [27–31, 33, 34, 37, 38, 41] (range 10 % to 100 %). No parallel comparison between a post-switch anti-TNF therapy and an alternative biologic treatment for real-world effectiveness was found.

Outcomes

In the 18 studies identified, 28 different measures of effectiveness were observed in PsA patients over a median follow-up of 5.6 months (range 0.5 months to 6 years) (Fig. 2). The most common of these were variations of the Health Assessment Questionnaire (HAQ) (7/18 studies, 38.9 %) [27, 30–32, 39, 42, 43] and changes in clinical signs, such as those listed per Psoriatic Arthritis Response Criteria (PsARC) [26, 29, 31, 40, 41, 43], as well as changes in swollen joints or C-reactive protein levels (6/18, 33.3 % each) [27, 28, 30–32, 41]. Anti-TNF drug survival, a proxy marker for efficacy, was also common (six studies) [32, 33, 36, 38, 42, 43]. Most measures (11/18, 61.1 %) were unique to a single study.

Although study results signaled changes over time with anti-TNF therapy, only four studies reported statistical testing for significant improvement from baseline to observation as shown in Table 2. Across all studies, an anti-TNF in the second or third line demonstrated effectiveness in at least one measure upon testing.

Nine studies [27, 30–32, 34, 36, 37, 41, 42] tested for differences in effectiveness between treatment lines. Of these, two compared mixed lines versus a referent line [31, 41]. The remainder stratified outcome by treatment lines and are detailed below, and individual study results are depicted in Table 3.

First to second line

Six studies [30, 32, 34, 36, 37, 42] compared first-line treatment effectiveness to second-line results (Table 3). Effectiveness was defined as a single measure (drug survival) in a single site study [36] and expanded to 18 measures in the NOR-DMARD registry [30]. Few outcomes overlapped among the included studies. Comparing across studies, first-line anti-TNF treatment demonstrated statistically greater improvement relative to a second-line anti-TNF in at least one outcome in four out of six studies. In the fifth study, no differences were detected between first and second TNF-treated Swedish PsA patients when measured as EQ-5D or with a utility based measure number needed per QALY adjusted year gained (NNQ) [34]. In the final study, a 12-year retrospective study in France, no difference between first- and second-line anti-TNF treatment was detected in either drug survival or in a composite response composed of (1) Assessment of SpondyloArthritis international Society (ASAS) and French Society for Rheumatology (SFR) guidelines, (2) a favorable expert opinion, (3) a 30 % joint improvement, and/or (4) at least a 2-point improvement of Bath Ankylosing Spondylitis Disease Activity Index (BASDI) [42].

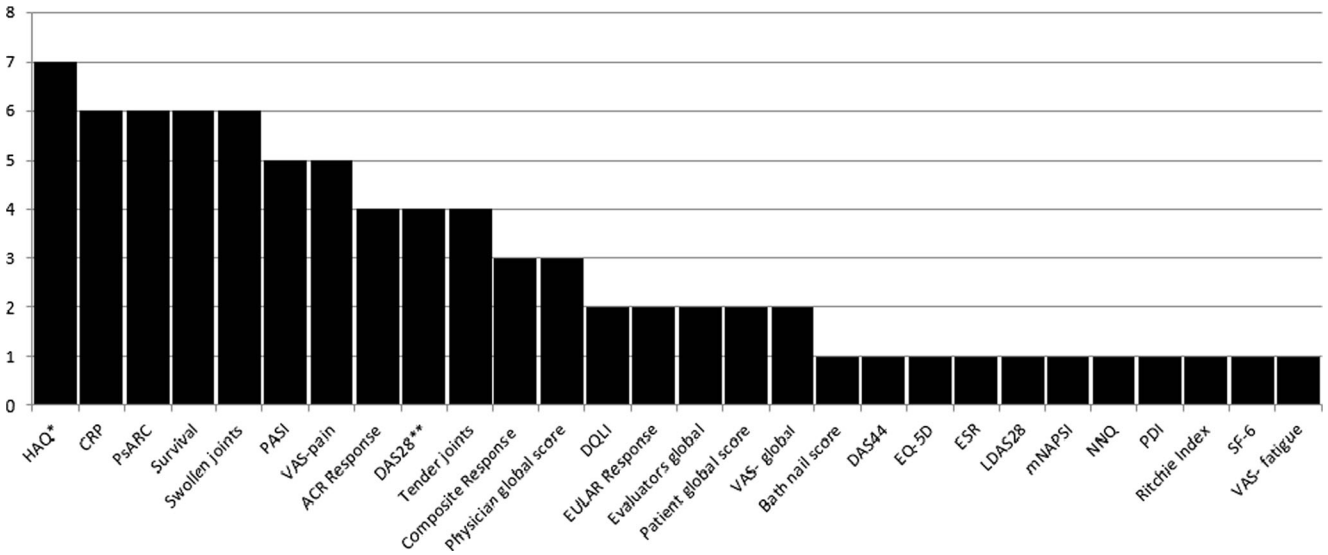

Fig. 2 Measures of effectiveness in PsA studies

Among the four studies detecting a difference between lines, statistically different outcomes included measurements of response, global and joint-specific clinical signs and symptoms, drug persistence, and survival. No obvious pattern by measurement type was found. In the four studies where multiple measures were reported, the effectiveness advantage of first-line relative to second-line was not consistently seen across all measurement types. Further, relative effectiveness also seemed sensitive to how a measurement was summarized. For example, improvement in DAS28, expressed as a mean change, was significantly greater for first-line relative to second ($p = 0.005$), but not when summarized as a mean ($p = 0.14$) or category cutoff ($p = 0.07$) in 344 registry patients at three months [30]. Finally, relative effectiveness varied by time. Measured as Psoriasis Area Severity Index [PASI] 50 and 75, relative superiority of first line was demonstrated in 110 etanercept-treated patients at 24 weeks but not at 12 weeks [37].

Second to third line

Second-line anti-TNF treatment was statistically compared to later lines of treatment in four studies [27, 32, 34, 42]. Compared with first-/second-line comparisons, which favored initial treatment in 66.0 % of studies, second-line anti-TNF patients showed statistically significant improvement in only half of studies (50 %) relative to the subsequent third line. In one study, a Danish registry, drug survival proved to be significantly longer in second- compared to third-line exposures ($p < 0.0001$) [32]. In a large Swedish study, an EQ-5D gain of 0.20 was calculated for time elapsed during second-line anti-TNF. No change in this measure was detected at third line [34].

Second to fourth line

Second-line anti-TNF treatment was compared to fourth line in a single hospital study of 34 PsA patients treated with golimumab [27]. No improvement was found at 24 weeks when effectiveness was measured as change in PASI, change in visual analog scale (VAS), change in DAS44, and change in CRP values (raw data not reported by measure).

Third to fourth line

From the same small study in Italy [27], patients were followed further to compare the effectiveness of a third line of treatment relative to a fourth line. Results were mixed, with no difference detected between lines for DAS44 and CRP levels. Third-line treatment was favored relative to fourth line in a VAS, and fourth-line treatment was favored relative to the earlier third line in change in PASI scores ($p < 0.05$).

Eleven studies (61.1 %) [26, 28–30, 32, 35, 39–43] reported why PsA patients switched from a prior anti-TNF therapy (Table 4). Of these, the anti-TNF given was mixed or unspecified in the majority of studies, and 10 each reported the reason for switching from first-line to second, and from second- to third-line, with seven studies specifying the reason for discontinuing third-line anti-TNF. Safety or tolerance was the most common reason for switching and was reported in all studies. The proportion of patients who switched due to inefficacy seemed to increase after repeated anti-TNF exposure, while loss of efficacy as a reason for switching or discontinuing therapy remained stable, regardless of therapy line. Intolerability was reported less frequently as a reason for switching in subsequent lines. This may be expected, as patients who experience serious adverse events while receiving an anti-TNF would not be given another anti-TNF.

Table 2 Summary of studies that performed effectiveness testing compared to baseline results

Author, year, location	Accrual years	Sample size	Setting	Study summary	Effectiveness testing results from baseline
Mazzotta, 2009 [37] Italy	2004–2005	110	Single center, hospital	PsA patients with an unsatisfactory clinical response of resistance to systemic treatments were treated with etanercept and followed for efficacy and safety over 12 and 24 weeks.	**Second-line** anti-TNF patients' **PASI** improved significantly from baseline (8.0) to week 12 and baseline to week 24 (2.9 and 3.0; $p = 0.0004$ and 0.0006, respectively). No difference was detected between week 12 and 24.
Gulfe, 2010 [34] Sweden	2002–2008	574	Multicenter registry	PsA patients were stratified by anti-TNF line, and followed for health utility and drug survival from baseline to 60 months.	**Second-line** anti-TNF patients posted a positive utility gain (Delta **EQ-5D**: 0.20) relative to baseline. **Third-line** anti-TNF patients had no utility gain relative to baseline.
Glintborg, 2013 [32] Denmark	2000–2012	1,422	Multicenter registry	First-time anti-TNF PsA patients registered in the nationwide DANBIO registry were followed for efficacy, switching patterns, and discontinuation reasons over a median follow-up of 2.3 years.	**Second-line** anti-TNF patients significantly improved from baseline to 3 and 6 months in the following measures: **CRP mg/liter** (6 to 5 and 4); $p = 0.0001$ at 3 months, $p = 0.001$ at 6 months **Fatigue score** (67 to 48 and 51); $p = 0.0001$ at 3 months, $p = 0.01$ at 6 months **Pain score** (65 to 38 and 40); $p = 0.0001$ for 3 and 6 months **Global analog score** (69 to 46 and 43) **DAS28** (4.6 to 3.2 and 3.0); $p = 0.0001$ for 3 and 6 months **HAQ** (1.1 to 0.9 and 0.9); $p = 0.0001$ for 3 and 6 months **Third-line** anti-TNF patients significantly improved from baseline to 3 and 6 months in the following measures: **CRP mg/liter** (6 to 6 and 4); $p = 0.003$ at 3 months, $p = 0.02$ at 6 months **Fatigue score** (78 to 62 and 58); $p = 0.03$ at 3 months, $p = 0.0001$ at 6 months **Pain score** (72 to 48 and 51); $p = 0.0001$ for 3 and 6 months Global analog score (77 to 53 and 59) $p = 0.0001$ for 3 and 6 months **DAS28** (5.0 to 3.7 and 3.2); $p = 0.0001$ for 3 and 6 months **HAQ** (1.4 to 1.0 and 1.3); $p = 0.02$ at 3 months, $p = 0.003$ at 6 months
Conti, 2007 [29] Italy	2001–2006	15	Single center, hospital	PsA patients who initiated an anti-TNF and had at least 6 months of records were prospectively followed for response, switching, and reason for switching.	Anti-TNF patients who switched from **infliximab** to **second-line etanercept** showed improvements from baseline in **patient** ($p < 0.0001$) **and physician assessment** scores ($p < 0.01$) and **PsARC** (10 % to 70 %; $p < 0.01$). Differences in tender joint count and swollen joint count between lines were both non-significant at 3 months. Patients switching from **etanercept to adalimumab as second- or third-line treatment** did not show significant gains in any study measure.

Abbreviations: *CRP* C-reactive protein, *DAS* disease activity score, *EQ-5D* EuroQol – Five Dimensions, *HAQ* health assessment questionnaire, *mg* milligram, *PASI* psoriasis area severity index, *PsA* psoriatic arthritis, *PsARC* psoriatic arthritis response criteria

Table 3 Summary of studies that performed effectiveness testing comparing treatment lines

Study details	Line 1 vs. Line 2	Line 1 vs. Line3	Line 2 vs. Line 3	Line 2 vs. Line 4	Line 3 vs. Line 4
Gulfe, 2010 [34] Sweden 2002–2008 $n = 574$ PsA patients were followed for health utility and drug survival from baseline to 60 months.	Time-corrected NNQ yielded very similar results as the NNQ across treatment courses had overlapping 95 % CIs in first- and second-line estimates: it would take about five TNF patients (4.8 and 4.7 respectively) to be treated in order to gain one QALY. Similarly, a point estimate of 0.20 was calculated for time elapsed during first- and second-line anti-TNF. Intervals of earlier lines do not overlap with the null change at third line			–	–
	Line 1: Change in EQ-5D ($n = 241$) 0.20 (95 % CI: 0.16, 0.24)	Line 2: Change in EQ-5D ($n = 86$) 0.20 (95 % CI: 0.14, 0.27)	Line 3: change in EQ-5D ($n = 17$) −0.0 (95 % CI: -0.1, 0.11)	–	–
Soubrier, 2015 [42] France 2001–2012 $n = 193$ PsA patients were followed for efficacy and safety at three months and for extended treatment history over 12 years.	Composite response rates* First line ($n = 174$) vs. second line ($n = 65$): 82 % vs. 90 % $p = 0.07$) No difference in drug survival	Composite response rates* First line ($n = 174$) vs. third line ($n = 24$): 83 % vs. 90 %; $p = 0.23$) No difference in drug survival	"No statistically significant difference in survival was observed between first-, second- and third-line anti-TNF therapy ($p > 0.05$)."	–	–
Glintborg, 2013 [32] Denmark (DANBIO Registry) 2000–2012 $n = 1,422$ PsA patients were followed for efficacy, switching patterns, and discontinuation reasons over a median follow-up of 2.3 years.	K-M drug survival was significantly different between treatment courses ($p < 0.0001$) Measurements for first line ($n = 1,422$) vs. second line ($n = 548$) (NNT) favored first (all $p < 0.05$) ACR 20: 47 % (2.2) vs. 22 % (4.5) ACR 50: 33 % (3.1) vs. 13 % (7.9) ACR 70: 17 % (5.9) vs. 5 % (20) EULAR: 45 % (2.3) vs. 19 % (5.3) DAS28: 43 % (2.3) vs. 34 % (2.9)	K-M drug survival was significantly different between treatment courses ($p < 0.0001$) Measurements for first line ($n = 1,422$) vs. second line ($n = 189$) (NNT) favored first (all $p < 0.05$) ACR 20: 47 % (2.2) vs. 18 % (5.3) ACR 50: 33 % (3.1) vs. 6 % (16) ACR 70: 17 % (5.9) vs. 2 % (48) EULAR: 45 % (2.3) vs. 17 % (5.8)	K-M drug survival was significantly different between treatment courses ($p < 0.0001$)	–	–

Table 3 (continued)

Study details	Line 1 vs. Line 2	Line 1 vs. Line3	Line 2 vs. Line 3	Line 2 vs. Line 4	Line 3 vs. Line 4
		DAS28: 43 % (2.3) vs. 22 % (4.4)			
Fagerli, 2013 [30] Norway (NOR-DMARD) 2001–2011 $n = 344$ PsA patients followed from first anti-TNF for three-month response and three-year drug survival	Measures where first line ($n = 344$) was found to have significantly greater improvements than second line ($n = 95$) at three months Mean change CRP: 0 vs. 0; $p = 0.001$ ACR 70: 23.7 % vs. 12.5 %; $p = 0.04$ EULAR good response: 45.7 % vs. 20.0 %; $p = 0.021$ Mean change DAS28: −1.3 vs. −0.7; $p = 0.005$ Outcomes where no statistically significant difference was found between first and second line ACR 20: 45.8 % vs. 40.0 %; $p = 1.0$ ACR 50: 30.5 % vs. 22.5 %; $p = 0.34$ DAS28 remission: 35.8 % vs. 28.2 %; $p = 0.22$ LDAS28: 54.7 % vs. 35.9 %; $p < 0.07$ Mean DAS28: 3.3 vs. 3.6; $p = 0.14$ Physician global: 23.5 vs. 22.0; $p = 0.77$ Mean change physician global: -16.9 vs. 114.3; p = 0.87 Patient global: 34.2 vs. 38.2; p = 0.05 Mean change patient global: -20.8 vs. -14.9; $p = 0.05$ Median mHAQ: 0.38 vs. 0.50 $p = 0.45$ Mean change mHAQ: -0.27 vs. -0.23; $p = 0.45$ Mean SF-6D: 0.66 vs. 0.65 $p = 0.22$ Mean change SF-6D: 0.07 vs. 0.06; p = 0.27 Median CRP: 4 vs. 5; $p = 0.06$	–	–	–	–
Chimenti, 2013 [27] Italy 2011–2012 $n = 32$ PsA patients followed for efficacy and safety over 24 weeks		At 24 weeks (no raw numbers reported by treatment line) PASI change: $p = NS$ VAS change $p = NS$ DAS44 change	At 24 weeks (no raw numbers reported by treatment line) PASI change: $p = NS$ VAS change $p = NS$	At 24 weeks (no raw numbers reported by treatment line) PASI change (4 > 3) $p < 0.05$ VAS change (3 > 4) $p < 0.05$	

Table 3 (continued)

Study details	Line 1 vs. Line 2	Line 1 vs. Line3	Line 2 vs. Line 3	Line 2 vs. Line 4	Line 3 vs. Line 4
			p = NS CRP change p = NS	DAS44 change p = NS CRP change p = NS	DAS44 change p = NS CRP change p = NS
Mazzotta, 2009 [37] Italy 2004–2005 n = 110 PsA patients treated with etanercept and followed for efficacy and safety over 12 and 24 weeks	PASI response First line (n = 80) vs. Second line (n = 30) 12 weeks PASI 50: 65.7 % vs. 59.3 %; p = NS PASI 75: 45.2 % vs. 37.0 %; p = NS 24 weeks PASI 50: 92.3 % vs. 45.8 %; p < 0.0001 PASI 75: 73.8 % vs. 29.2 %; p < 0.0001	–	–	–	–
Haugeberg, 2013 [36] Norway 2002–2012 n = 148 PsA patients were followed for drug survival to three or more anti-TNFs	Overall drug survival was significantly higher for the first-line anti-TNF compared to the second-line anti-TNF (p < 0.001)	–	–	–	–

Abbreviations: ACR 20 American College of Rheumatology 20 % response, *ACR 50* American College of Rheumatology 50 % response, *ACR 70* American College of Rheumatology 70 % response, *CI* confidence interval, *CRP* C-reactive protein, *DAS* disease activity score, *EQ-5D* EuroQol – Five Dimensions, *EULAR* European league against rheumatism, *HAQ* health assessment questionnaire, *K-M* Kaplan-Meier, *LDAS28* low disease activity score, *mHAQ* modified health assessment questionnaire, *NNQ* number needed per QALY adjusted year gained, *NNT* number needed to treat, *NOR-DMARD* Norwegian disease-modifying anti-rheumatic drug registry, *NS* not significant, *PASI* psoriasis area severity index, *PsA* psoriatic arthritis, *PsARC* psoriatic arthritis response criteria, *QALY* quality-adjusted life-year, *SF-6D* short form – six dimensions, *TNF* tumor necrosis factor, *VAS* visual analog scale

Table 4 Reason for anti-TNF switching from current line

	Number of studies	Inefficacy[a, *]	Loss of efficacy[b, *]	Tolerability (AEs)[*]
First line	10	5.9 % (1–51.6)	21.0 % (8.4–60)	9.4 % (3.0–40)
Second line	10	20.0 % (5.3–56.7)	10.0 % (2.4–42.1)	8.8 % (0.5–36.7)
Third line	7	16.9 % (7–42)	21.3 % (14–33)	4.9 % (0–17.2)

Abbreviation: AE adverse event

*All data are presented as median (range)

[a] Inefficacy includes data reported as primary non-response

[b] Loss of efficacy includes data reported as secondary non-response

Only four studies [32, 39, 41, 43] reported outcomes stratified by reason for switching. Of these, one study [32] tested this variable as a predictor of clinical response. In a multiple-regression, backward-selection model, patients from the Danish registry, DANBIO [32], were less likely to respond to a second-line anti-TNF course if the reason for switching was safety, rather than ineffectiveness. American College of Rheumatology, 20 % response (ACR 20) and ACR 50 responses were shown to be less often achieved (OR 0.04; 95 % confidence interval [CI]: 0.004, 0.3; $p = 0.003$ and OR 0.05; 95 % CI: 0.03, 0.7; $p = 0.03$) in patients who switched due to intolerability. No difference in ACR 70 or EULAR good response was detected when outcomes were stratified by reason for switching.

Discussion

This is the first systematic review to evaluate the real-world effectiveness of repeated anti-TNF treatment in PsA patients who have failed previous anti-TNF therapy. Eighteen studies were identified. In these studies, PsA populations were most often recruited in Europe, and only one study was based in the US. The lack of US-based publications is surprising since the disease prevalence of PsA has been estimated at 0.16 % in this geographic location [44]. Effectiveness was reported from the second line as far as the fifth line of anti-TNF treatment, and patients were often followed longitudinally from initial first-line exposure. The measures used to evaluate effectiveness in the real-world setting varied widely, limiting the ability to make comparisons across many of the studies; this also indicates the lack of standard instruments used in PsA patients.

A simple summary of the outcomes from this dataset was hampered by a lack of standardization of outcomes, a wide range of observation times (12 weeks to five years), and inconsistent reporting by individual anti-TNF or by treatment line. However, trends were identified in the 44 % of studies that tested for statistical differences from baseline to observation, or tested for differences in effectiveness between lines. Treatment with anti-TNF in the second line and beyond showed statistical improvement in PsA outcomes from baseline, but not compared to previous lines for some measures. In three studies [29, 32, 37], statistically significant improvements were found for PASI, CRP, fatigue, pain, global analog score, DAS28, HAQ, and PsARC measures at time points between three and six months for patients receiving second- and third-line therapy. Comparable findings were reported in a 2016 prospective cohort study of peripheral 274 PsA patients registered from 2003 to 2012 in a Swedish database [45]. Response rates and drug survival time dropped steeply with repeated switching, but at least one measurable improvement was observed (EQ-5D gain, DAS28-CRP, or CRP) compared to baseline measures.

In studies that tested differences between lines, first-line anti-TNF therapy performed significantly better than second-line treatment in at least one measure in four of six studies. Still, the effectiveness of second-line therapy was often similar or attenuated compared to initial anti-TNF results.

As before, drawing definitive conclusions across studies (even those that offered statistical evidence of effectiveness) was made difficult due to the variation in anti-TNF drugs, outcomes, and the lack of a definition or stratification by drug or line. Importantly, inherent to studies of less common diseases followed longitudinally, many of the populations described in observational studies were modest in size and often retrospectively identified from a single site. Eight of the nine studies that reported effectiveness across lines enrolled fewer than 100 patients per line of anti-TNF treatment, with sample sizes decreasing with each line of therapy. By third-line anti-TNF treatment, fewer than 20 patients were included in studies evaluating this later line of therapy. Testing for loss of effectiveness relative to earlier lines would be difficult in these progressively smaller groups, since statistical power to detect difference will be lost with diminishing sample sizes. Further, results would be confounded by patient channeling bias, since patients with more refractory disease or those more intolerant to anti-TNF would be more likely to switch. Additionally, PsA as a chronic progressive disease may be expected to worsen in regards to disability as a result of cumulative joint damage over time.

This review highlights several gaps in the current research on anti-TNF switching in PsA. Using a systematic review method, we found that there is limited high-quality, real-world evidence evaluating effectiveness of repeated anti-TNF therapy, with only 18 papers found. Interpreting the

utility of repeated anti-TNF therapy in PsA patients within individual papers was difficult due to the lack of standardized definitions, stratification, or statistical testing. In addition, a lack of standardization across papers precluded qualitative analysis. Importantly, no studies directly compared two biologics head to head beyond first-line failure; therefore, this study cannot make any conclusions on the superiority of specific anti-TNF therapies. Likewise, no studies comparing later lines of anti-TNF to treatments with other MOAs have been published to date. Additional research in an observational, real-world setting is needed to evaluate the performance of individual anti-TNFs after initial failure, as well as to compare their effectiveness to that of drugs with alternative MOA in refractory PsA patients.

This study shares the same limitations of any review of the published literature, including index bias and publication bias. However, since the search was broad and the study attrition was protocol-driven with objective criteria, the results presented here are a fair, independent, and reproducible dataset from which to draw field-wide conclusions.

Our study provides evidence to support the current practice of TNF switching in the treatment of PsA, but further well-defined studies are needed to establish the true efficacy of this approach in real-world PsA patients. Future studies to evaluate efficacy of switching to biologics with other MOAs after anti-TNF failure in routine practice are also warranted given the expanding therapeutic options in PsA.

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Compliance with ethical standards

Conflict of interest Sheila Crean, Amber L. Martin, and Meghan D. Burns are employees of Evidera, which received funding from Novartis Pharmaceuticals Corporation in connection with the study on which the manuscript is based. Jacqueline Palmer is employed by Novartis Pharmaceuticals Corporation, which funded this study. Soumya Reddy is a consultant to Novartis Pharmaceuticals Corporation and received honoraria for her work.

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