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Real-world treatment persistence of golimumab in the management of immune-mediated rheumatic diseases in Europe: a systematic literature review

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ABSTRACT

Objectives To summarise real-world data from studies reporting golimumab persistence in European immune-mediated rheumatic disease (IMRD) populations and to report pooled estimates.

Design Systematic literature review.

Data sources Relevant literature was identified through searching Medline and Embase via Ovid as well as the conference databases of European League Against Rheumatism and American College of Rheumatology—Association of Rheumatology Health Professionals.

Eligibility criteria We screened records using predefined patients, interventions, comparators, outcomes and study design criteria. Eligible studies included reports of persistence among adult IMRD patients in Europe receiving treatment with subcutaneous golimumab. Clinical trials, randomised controlled trials, literature reviews, editorials, guidelines and studies with <20 patients receiving golimumab were excluded.

Data extraction and synthesis Following double screening by two independent reviewers, 27 studies out of 578 identified records were selected for inclusion and subsequent data extraction. Persistence was most commonly reported at 12and 24 months; hence, pooled persistence estimates were calculated for these two time points and reported according to indication.

Results Persistence ranged between 58.1% (psoriatic arthritis (PsA) patients regardless of treatment line) and 75.7% (biological-naïve rheumatoid arthritis patients) at 12 months; at 24 months, the range was 43% (axial spondyloarthritis (AxSpA) patients regardless of treatment line) and 69.6% (biological-naïve PsA patients). On the basis of data from 12 studies, persistence with golimumab treatment was either significantly higher or not significantly different from other tumour necrosis factor inhibitors (TNFi).

Conclusions Golimumab persistence at 24 months approximates 50%, with a lower persistence among AxSpA (43%) patients. However, as the number of studies in these populations was low, they warrant further research. In 12 studies comparing various TNFi treatments, golimumab was shown to have significantly better or equal persistence to its comparators.

Strengths and limitations of this study

► By excluding data from randomised controlled trials, this systematic literature review provides an up-to-date overview of real-world tumour necrosis factor inhibitors persistence in European immune-mediated rheumatic disease (IMRD) patient populations.

► Including different IMRD diagnoses, as opposed to limiting the scope to a single rheumatic disease, allows comparisons of treatment patterns across various disorders.

► The definition of persistence varied across included studies, thereby complicating the interpretation of any direct comparisons of results.

INTRODUCTION

The collective term immune-mediated rheumatic diseases (IMRD) encompasses a group of diagnoses, including axial spondyloarthritis (AxSpA), psoriatic arthritis (PsA) and rheumatoid arthritis (RA). Common to all types of IMRD is the presence of chronic inflammation, as evidenced by elevated synovial joint fluid levels of tumour necrosis factor alpha (TNF-α), which, in turn, stimulates the production of inflammatory cytokines, such as interleukin (IL)-1, IL-6, granulocyte macrophage colony stimulating factor (CSF) and granulocyte CSF.[1 2] The landscape for treatment of IMRD has evolved rapidly, and currently includes several TNF-α inhibitors (TNFi) in addition to the conventional synthetic disease-modifying antirheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) commonly used to treat IMRD. Other treatments, targeting IL-17 and Janus kinase pathways as well as the lymphocytes involved in propagating the inflammatory response, are also approved for clinical use or are still investigational.[3–5]

In Europe, the subcutaneously administered TNFi golimumab is indicated for the treatment of active RA, AxSpA and PsA.[6] Following the randomised controlled trials GO-FORWARD (RA patients),[7] GO-RAISE (ankylosing spondylitis (AS) patients),[8] GO-REVEAL (PsA patients)[9] and GO-AHEAD (non-radiographic AxSpA patients),[10] which established the efficacy and safety of golimumab, several open-label extension (OLE) studies were conducted.[11–13] The OLE studies followed patients for 5 years to obtain long-term outcome data, including persistence, defined as the proportion of patients not discontinuing treatment. OLE studies of golimumab in biological-naïve IMRD patients showed a 5-year persistence rate of 70%; among biological-experienced RA patients, the corresponding rate was approximately 40%.[11–15] However, patients enrolled in randomised controlled trials and subsequently, OLE studies are not always representative of patients in clinical practice. Thus, real-world data on drug utilisation, treatment patterns and outcomes are of great importance, as they provide information regarding the usage of available treatments outside of the strictly controlled environment of randomised controlled trials. Real-world persistence with treatment is particularly useful, as it has been considered a proxy marker not only for treatment safety and effectiveness, but also for patient satisfaction.[16–18] The definition of persistence is the 'duration of time from initiation to discontinuation of therapy', while two other commonly used terms, adherence and compliance, are related to patient behaviour and conformance with the prescribed dosing regimen.[19] Several systematic literature reviews (SLRs) focusing on real-world treatment patterns of golimumab and other TNFi in IMRD populations have been published.[20–24] However, many focus on a particular subset of IMRD patients—such as RA populations—and do not include patients with other IMRD indications that also receive TNFi treatment; in addition, recent years have seen a substantial increase in studies reporting real-world evidence of TNFi treatment patterns, warranting an updated overview of the field.

METHODS

In accordance with the study protocol (available on request), the literature search was performed in Medline and Embase via Ovid as well as in the American College of Rheumatology—Association of Rheumatology Health Professionals (ACR-ARHP) and European League Against Rheumatism (EULAR) conference abstract databases. The search was limited to include all studies indexed in Medline or Embase from 01 January 2009 to 30 April 2018. For EULAR abstracts, the search was limited to conference papers from 2017 to 2018, and for ACR-ARHP, only abstracts from the 2017 conference were considered. The search strings applied are listed in online supplementary tables 1–3. As golimumab is available as an intravenously administered formulation in non-European regions, with a label and dosage differing from the label approved by the European Medicines Agency (EMA), the literature search was limited to European studies including only the subcutaneous formulation and dosage approved by EMA.[6] The search was restricted to studies published in English.

The identified publications were subsequently entered into an abstract screening sheet and duplicates were removed. Where several publications reported the results for the same patient population, only one was included.

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] Hence, all studies identified in the original literature search were assessed for inclusion eligibility using the patients, interventions, comparators, outcomes and study design (PICOS) approach, as outlined below:

Patients
Studies including adult patients (≥18 years of age) in Europe diagnosed with IMRD, including AxSpA (encompassing AS and non-radiographic AxSpA), PsA and RA, were eligible for inclusion. Studies reporting joint results for mixed IMRD populations were also included but are presented separately.

Interventions
Studies reporting data on golimumab, administered subcutaneously, were eligible for inclusion. Studies where the mode of administration was reported as intravenous, were excluded.

Comparators
No restrictions applied.

Outcomes
Studies reporting estimates of persistence were eligible for inclusion. This included data on the proportion of patients persistent with golimumab treatment at specific time points (persistence rates at different landmarks); mean or median time to golimumab treatment discontinuation (time to event); and/or mean or median time until 50% of the patient population are no longer persistent with golimumab treatment (treatment survival).

Study design
All studies reporting real-world evidence, prospective or retrospective, were eligible for inclusion. Pivotal registration clinical trials, literature reviews, editorials, guidelines and studies with <20 patients receiving golimumab were excluded.

Two independent reviewers using the PICOS criteria outlined above screened abstracts of the identified studies, and individual decisions on whether to include or exclude individual studies in the review were aligned until a consensus decision was reached. A second screening step was made based on the full-text version of the studies (where available), using the same approach as the one utilised in the abstract screening stage.
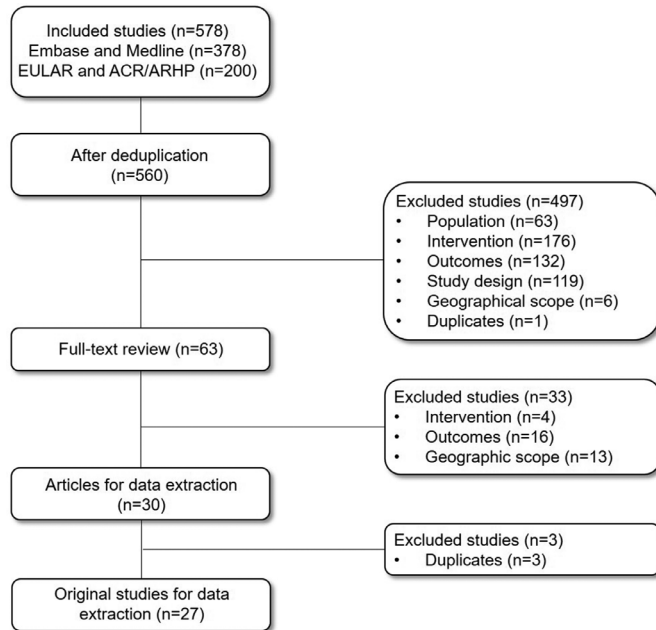
Figure 1 Selection process flowchart for identification of studies to be included in the literature review. ACR, American College of Rheumatology; ARHP, Association of Rheumatology Health Professionals; EULAR, European League Against Rheumatism.

Following the completion of the full-text screening, data were extracted from the studies included in the review. Information was extracted regarding (1) reference details; (2) study design; (3) patients; (4) treatments; (5) outcomes and (6) geographic scope. A full list of extracted variables is available in online supplementary table 4. Results were reported as pooled estimates of persistence by indication, weighted according to the number of patients in each subpopulation. For each subgroup analysis, it was noted which of the included studies had undertaken measures to minimise bias, and which had not. Studies that did not report the number of patients were not included in the pooled persistence estimates.

Risk of bias assessment
Studies included in the review were subjected to a risk of bias assessment using the Newcastle-Ottawa scale for cohort studies.[26] The scale was modified slightly so that the maximum score for selection was two points, since the categories 'selection of the non-exposed cohort' and 'demonstration that outcome of interest was not present at the start of the study' were set as 'not applicable' for all studies included in the current review. The results of the assessment are reported in online supplementary file S1. A meta-analysis was not deemed feasible based on the studies selected for inclusion, and hence, no assessment of systematic bias across studies was performed.

Patient and public involvement
Since the current study is an SLR, there was no involvement of patients and/or the public.

RESULTS
Identification and inclusion of studies
The Ovid search generated 378 hits, while the searches of the ACR-ARHP and EULAR database searches generated 16 and 184 hits, respectively. Duplicates were identified and removed, resulting in 560 full-text articles and conference abstracts that were included in the initial abstract screening. Sixty-three of these were included in a full-text screening, of which 30 records were selected for data extraction. Three studies were reported as both abstracts and full-texts; thus, only the estimates reported in the full-texts were included in the pooled results, resulting in 27 included studies. The selection process is shown in figure 1, using a PRISMA flowchart.

Study and patient characteristics
Of the studies included in the literature review, 9 were full-text articles[27–35] while 18 were conference abstracts.[36–53] The years of data collection ranged from June 2003[43] to March 2016.[42] Seven studies did not report the period for data collection[45–48 50–52]; five of these were prospective studies.[47 48 50–52] The maximum number of months during which golimumab treatment persistence was reported ranged from 6[50] to 60 months,[43 45] the most common time points for reporting outcomes being 12 months (reported in 16 studies)[27–31 34–40 42 44 47] and 24 months (reported in 13 studies).[27–33 35 36 41 44–46] Ten studies reported golimumab persistence at more than one time point.[27–31 35 36 44 45 47] A minority (5/27) of the included studies reported data on mean/median persistence in months.[32 35 49 51 52] Four studies reported using methods to address selection bias,[29–31 53] while an additional five studies used Cox proportional hazards model to identify potential confounders.[27 28 33 34 52] The remaining 18 studies did not specify which methods, if any, that were used to address bias[32 35–51]; 16 of these were conference abstracts.[36–51]

Of the 19 studies that reported gender distribution in the patient cohort, the proportion of females ranged from 38.8% (AS patient subpopulation)[51] to 89.2% (RA patient subpopulation).[35] Eight studies did not report the proportion of female versus male patients[36–40 46 47 49]; these were all conference abstracts. The same eight studies did not report mean or median age of patients included in the cohorts. The reported mean age ranged between 39.8±10.1 years (nr-AxSpA patient subpopulation)[51] and 58.3±13.3 years (RA patient subpopulation).[35] Two studies reported median as opposed to mean age; one investigating PsA patients (median age 50 years (IQR 41–57)[27]) and one studying RA patients (median age 55 years (IQR 46–62)[28]).

One study reported exclusively on an AS population[38]; five reported exclusively on a PsA population[27 39 43 50 52] and six studies reported exclusively on an RA population.[28 31 34 40 41 46] Fourteen studies[29 30 32 33 35–37 42 44 45 47–49 52] included at least two different IMRD patient populations, and one study[53] did not provide any data on disease distribution within the cohort. Mean or median disease

duration was reported in 13 studies,[27 28 31–33 35 41 44–46 48 51 52] and ranged between a median of 6.1 years (IQR 1.7–13) among a cohort of PsA patients[27] and a mean of 18.8 years (SD 10.1) in a cohort of AS patients.[51] A total of 19 studies reported patient treatment history with regard to previous usage of biologic treatments; the proportion of biological-naïve patients ranged from 30% (AS patient subpopulation)[35] to 63% (IMRD patient population).[42] Four[30 34 37 43] and three studies[29 31 44] reported exclusively on naïve and experienced patient populations, respectively.

Table 1 provides an overview of selected patient characteristics of the cohorts included in the literature review; it also includes the concept of persistence used in each study, defined as the time period during which patients are required to fill their prescriptions before a specified number of days elapses (sometimes referred to as the 'gap size').

Pooled golimumab persistence estimates at 12 and 24 months

Figure 2 illustrates the proportion of patients persistent with golimumab treatment at specific time points by indication. The reporting time points ranged between 3 months[27–29 47] and 60 months,[43 45] the latter of which is comparable to the outcome reporting time point used in OLEs of the golimumab randomised controlled trials. As can be seen from figure 2, the most commonly reported time points were 12 and 24 months. At 12 months, the total number of studies reporting golimumab persistence ranged from five for AxSpA patients[35–38 44] to eight for IMRD patients[29 30 35 36 42 44 45 47]; at 24 months, the number of studies ranged between three and eight for AxSpA[35 36 44] and RA,[28 31–33 35 36 41 46] respectively. A detailed overview of the reporting time points is provided in online supplementary table 5. Pooled golimumab persistence data from 12 and 24 months, weighted according to relative sample size, are presented in figure 3A–D. The study by Favalli *et al*[41] was excluded from further analysis following quality assessment, and thus was not included in the pooled estimates. Note that since a different number of studies was used to calculate each pooled estimate, the number of patients used to weigh the sample size also varied between the pooled estimates.

Mixed IMRD populations

The persistence resulting from pooling estimates reported from overall IMRD patient populations treated with golimumab regardless of treatment line was 60.4% at 12 months[29 30 35 36 42 44 45 47] and 58.6% at 24 months.[29 30 32 35 44 45] For biological-naïve IMRD patients, the pooled persistence at 12 months was 63.8%; at 24 months, it was 52.2%.[30 45] Biological-experienced IMRD patients receiving golimumab in second and subsequent lines had a persistence rate of 71.7% and 58.7% at 12 and 24 months, respectively[29 44 45] (figure 3A).

RA populations

For RA, patients treated with golimumab had a pooled persistence across all therapy lines of 62.3% at 12

months[28 31 34–36] and 49.8% at 24 months[28 31–33 35 36 46] (figure 3B). Biological-naïve RA had a pooled 12-month persistence rate of 75.7%[28 34] and 62.5% at 24 months.[28 32 33] Biological-experienced RA patients had a pooled persistence rate of 71.3% at 12 months,[28 31] while at 24 months, the level of pooled persistence was 58.1%.[28 31–33]

AxSpA populations

When analysing AxSpA populations regardless of treatment line, the pooled persistence was 55.4% at 12 months[35 36] and 43% at 24 months[33 35 36] (figure 3C). Only two studies reported persistence by treatment line (one for biological-naïve patients and one for biological-experienced patients); therefore, no pooled persistence was calculated for these.

PsA populations

Regardless of treatment line, PsA patient populations had a pooled golimumab persistence of 58.1% at 12 months[27 35 36 44]; at 24 months, the pooled persistence was 48.7%.[27 32 33 35 36 44] While no pooled estimate for biological-naïve PsA patients could be calculated at 12 months since it was only reported in one study,[27] the persistence rate at 24 months was 69.6%.[27 33] For biological-experienced PsA patients, golimumab persistence was 74.7% at 12 months[27 44] and 63% at 24 months[27 33 44] (figure 3D).

Persistence expressed as mean number of months

For mean golimumab persistence expressed as mean number of months until discontinuation, pooled data were only available for PsA and RA populations with mixed or unknown treatment history. For IMRD and AxSpA, as well as for subpopulations with specified treatment history, only one study reported mean survival time. The pooled mean survival time is shown in figure 4. For PsA, mean survival time in months equalled 26.3 (±2.6) (three studies)[32 35 52] (figure 4A); for RA, it was determined as 33 months (±1.8) (two studies)[32 35] (figure 4B).

Comparative persistence

In total, 12 studies reported persistence of golimumab and other biological treatments.[27–31 37–41 43 53] All of these studies included data on adalimumab and etanercept, while nine studies included data on certolizumab pegol[28–30 37–41 53] and three on infliximab.[27 28 43] Four studies reported effect size of the difference in persistence, formulated as hazard ratios (HRs), using golimumab as the reference treatment.[28 38–40] Of these, golimumab persistence was significantly higher in two,[38 40] four,[28 38–40] three[38–40] and one[28] study when compared with adalimumab, certolizumab pegol, etanercept and infliximab, respectively. An overview of studies reporting differences in effect size HR is provided in figure 5, in which an HR>1 indicates that golimumab persistence is significantly higher than that of its comparator. The results shown in figure 5 were further confirmed in studies reporting significant differences in persistence compared with golimumab as p values only; for adalimumab,[29–31 53] etanercept[30] and infliximab,[43]

Table 1 Patient characteristics

Reference, year	Country	Years of data collection	Data source	Diagnosis (n (%))	Number of patients on golimumab	Mean age, years, (SD)	Female, n (%)	Mean disease duration, years, (SD)	Naïve to biologics, n (%)	Gap before classified as non-persistent (days)
Aaltonen et al, 2017[27]	Finland	2004–2014	ROB-FIN	PsA (515 (100))	87	50 (41–57)*†	NR (48)†	6.1 (1.7–13)*†	36 (41.4)	N/A
Flipo, 2017[42]	France	2015–2016	GO-PRACTICE	AS (NR (22))‡ PsA (NR (13))‡ RA (NR (22))‡	163	46 (13)‡	NR (61)‡	NR	NR (63)‡	N/A
Manara et al, 2017[33]	Italy	2010–2015	LORHEN	RA (180 (43.9)) AS (120 (29.3)) PsA (110 (26.8))	410	54.6 (13.6) 45.2 (12.2) 47.9 (12.8)	147 (81.7) 52 (43.3) 55 (50)	6.3 (3–13.4)* 6.4 (1.9–13.3)* 6.6 (2.5–11.3)*	85 (47.2) 51 (42.5) 47 (42.7)	NR
Dalén et al, 2017[29]	Sweden	2010–2013	National registry data	RA (92 (49.2)) AS (54 (28.9)) PsA (31 (16.6))	187	52.3 (13.18)	113 (60.4)	NR	0 (0)	60
Favalli et al, 2018[31]	Italy	2010–2015	LORHEN	RA (51 (100))	51	54.9 (15.3)	45 (88.2)	9.5 (7.8)	0 (0)	NR
Aaltonen et al, 2017[28]	Finland	2004–2014	ROB-FIN	RA (887 (100))	200	55 (46–62)*†	2556 (74)†	9.5 (3.3–18)*†	109 (54.5)	NR
Iannone et al, 2017[32]	Italy	2013–2015	GOAREL	RA (88 (21.2)) PsA (181 (43.5)) SpA (147 (35.3))	416	56 (13) 53 (10) 48 (11)	71 (81) 128 (70) 75 (51)	8.1 (8) 6.9 (6) 7.4 (7)	41 (47) 74 (41) 56 (38)	30
Dalén et al, 2016[30]	Sweden	2010–2012	National registry data	RA (352 (46.7)) AS (205 (27.2)) PsA (155 (20.6))	754	49.75 (15.57)	440 (58.4)	NR	754 (100)	60
Belhassen, 2016[37]	France	2012–2013	SNIIR-AM	RA (4750 (40.5))† AS (5735 (48.9))† PsA (1244 (10.6))	NR	NR	NR	NR	100%	NR
Belhassen et al, 2016[36]	France	2012–2013	SNIIR-AM	RA (1315 (29.3)) AS (2656 (59.2)) PsA (514 (11.5))	4485	NR	NR	NR	NR	NR
Favalli et al, 2016[41]	Italy	2010–2015	LORHEN	RA (677 (100))	136	54.3 (13.5)†	NR (79.7)†	8.9 (8.8)†	85 (62.5)	NR
Svedborn et al, 2015[53]	Sweden	2010–2012	National registry data	NR	754	52 (15)†	NR (62)†	NR	NR	60
Mourão et al, 2017[34]	Portugal	2011–2015	Reuma.pt	RA (109 (100))	109	55.5 (13.2)	94 (86.2)	NR	109 (100)	90

Continued

Table 1 Continued

Reference, year	Country	Years of data collection	Data source	Diagnosis (n (%))	Number of patients on golimumab	Mean age, years, (SD)	Female, n (%)	Mean disease duration, years, (SD)	Naïve to biologics, n (%)	Gap before classified as non-persistent (days)
Fautrel, 2017[38]	France	2012–2013	National health insurance database	AS (9098 (100))	NR	NR	NR	NR	NR	>90
Fautrel, 2017[39]	France	2012–2013	National health insurance database	PsA (2011 (100))	NR	NR	NR	NR	NR	>90
Fautrel, 2017[40]	France	2012–2013	National health insurance database	RA (7204 (100))	NR	NR	NR	NR	NR	>90
Thomas et al, 2018[35]	Greece	2010–2014	Four academic centres	RA (166 (50.6)), PsA (82 (25)), AS (80 (24.4))	328	58.3 (13.3), 52.1 (11.9), 45.7 (11.3)	148 (89.2), 55 (67), 41 (50)	9.9 (8.7), 9.3 (6.6), 10.4 (7.6)	75 (45), 33 (40), 24 (30)	NR
Michelsen et al, 2018[48]	Norway	NR	NOR-DMARD	RA (163 (20.1)), PsA (267 (32.9)), AxSpA (382 (47))	812	51.2 (14.1), 48.1 (11.7), 41.8 (11.1)	NR (76.1), NR (55.1), NR (44.1)	11.3 (10.0), 8.7 (9.0), 10.6 (11.2)	NR	N/A
González Fernández et al, 2018[44]	Spain	2013–2015	GO-BEYOND	AxSpa (131 (62.4)), PsA (79 (37.6))	210	49 (12)	NR (40)	6.71*	0 (0)	NR
Klaudius, 2018[47]	Germany	NR	NR	RA (237)§, PsA (235)§, AS (228)§	748	NR	NR	NR	NR	N/A
García-Porrúa, 2018[43]	Spain	2003–2015	Multicentre cohort	PsA (468 (100))	31	53.3 (12.6)†	NR (44.8)†	NR	31 (100)	N/A
Serrano-Benavente, 2018[51]	Spain	NR	Monocentric cohort	AS (49 (46.7)), nr-AxSpA (40 (38.1)), All (axial and peripheral SpA) (NR (NR))	105	51.1 (10.8), 39.8 (10.1), 45.1 (13.2)	19 (38.8), 21 (52.5), 53 (50.5)	18.8 (10.1), 7.3 (10.3), 11.8 (12.3)	15 (30.6), 24 (60), 48 (45.7)	N/A
Scrivo, 2018[50]	Italy	NR	NR	PsA (149 (100))	149	49 (11)	NR (46.3)	NR	NR	N/A
Iannone et al, 2018[46]	Italy	NR	GISEA	RA (345 (100))	345	NR	NR	RF/ACPA-positive: 10.6 RF/ACPA-negative: 8.2 (6)	NR	NR

Continued

Reference, year	Country	Years of data collection	Data source	Diagnosis (n (%))	Number of patients on golimumab	Mean age, years, (SD)	Female, n (%)	Mean disease duration, years, (SD)	Naïve to biologics, n (%)	Gap before classified as non-persistent (days)
Serrano-Benavente, 2018[52]	Spain	NR	Monocentric cohort	PsA (48 (100))	48	48.3 (11.1)	25 (52.1)	8.4 (7.9)	25 (52.1)	N/A
Hernández, 2018[45]	Spain	NR	BIODABASER	RA (105 (29.8)) AxSpA (147 (30.6)) PsA (101 (28.6))	353	52 (11)	NR (55)	8 (2.8–15)*	NR (40.1)	NR
Santo, 2017[49]	Italy	2013–NR	GOAREL	RA (73 (19.8)) PsA (168 (45.7)) AxSpA (127 (34.5))	368	NR	NR	NR	206 (56)	N/A

Table 1 Continued

*Median (IQR).
†Data not specific to patients receiving GLM.
‡Data for the entire cohort, including those lacking follow-up data.
§Modified intention-to-treat population; not full data set (n=70).
ACPA, anticitrullinated protein antibody; AS, ankylosing spondylitis; AxSpA, axial spondyloarthritis; GLM, golimumab; N/A, not applicable; NR, not reported; nr-AxSpA, non-radiographic-AxSpA; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.
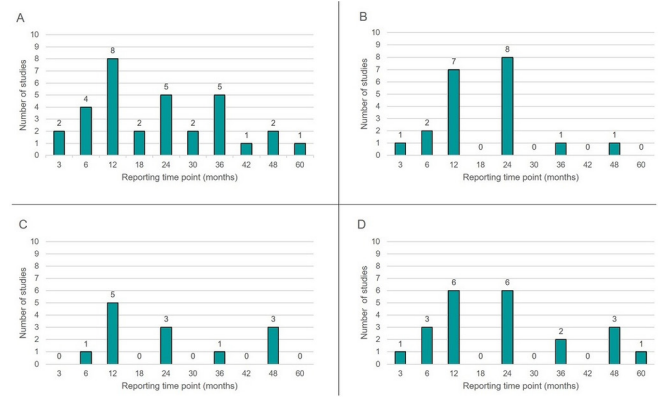

Figure 2 Number of studies reporting persistence at various time points. Results are reported by indication. (A) Immune-mediated rheumatic disease; (B) rheumatoid arthritis; (C) axial spondyloarthritis and (D) psoriatic arthritis.

respectively. Remaining comparisons in persistence between golimumab and adalimumab, certolizumab pegol, etanercept or infliximab showed no significant differences.[27–31 39 41 53] A detailed summary of comparative persistence data can be found in online supplementary table 6.

Compared with adalimumab, golimumab was reported to have significantly higher persistence in seven studies,[29–31 38 40 41 53] while two studies found no significant difference between the two comparators[28 39]; three studies reported persistence for adalimumab and golimumab, but did not provide any p values or results from statistical tests between them.[27 37 43] Compared with certolizumab pegol, four studies found no significant difference in persistence,[29 30 41 53] while four other studies found that golimumab had a significantly higher persistence[28 38–40]; one study did not provide any information on statistical significance between patients receiving certolizumab pegol or golimumab.[37] Compared with etanercept,
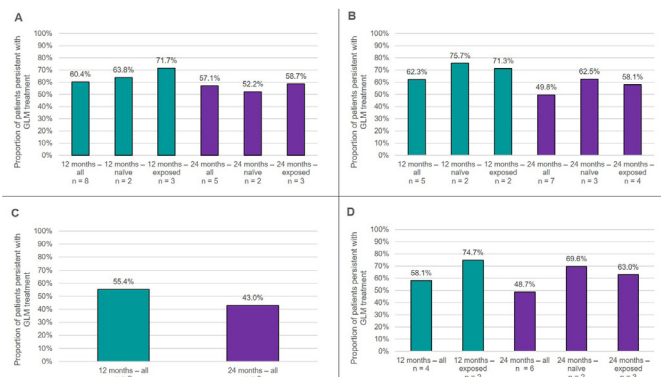

Figure 3 Pooled persistence data at 12 and 24 months, by treatment line (where available). Results are reported by disease. (A) IMRD populations (persistence data not reported for individual diagnoses)[29 30 35 36 42 44 45 47], (B) rheumatoid arthritis populations[28 31–36 46]; (C) axial spondyloarthritis populations[33 35 36] and (D) psoriatic arthritis populations.[27 32 33 35 36 44] IMRD, immune-mediated rheumatic disease; GLM, golimumab; n, number of studies included.
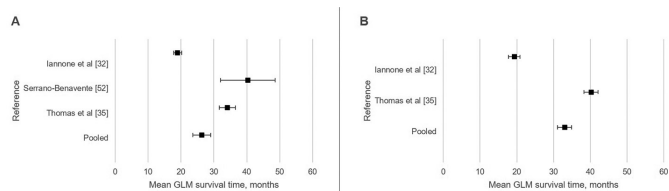
Figure 4 Pooled mean survival time (months) for patients with mixed or unknown treatment history receiving golimumab (GLM) treatment. (A) Psoriatic arthritis patient populations[32 35 52] and (B) rheumatoid arthritis patient populations.[32 35]

golimumab was found to have higher persistence in five studies[30 38–40 53]; four studies could not detect any significant difference between the two comparators[28 29 31 41] and three studies did not provide any information on statistical significance between patients receiving etanercept or golimumab.[27 37 43] Compared with infliximab, golimumab was found to have significantly higher persistence in one study[28]; no significant difference in persistence in another[27] and numerically higher persistence in a third study, which did not report any information on statistical significance.[43] Overall, golimumab shows statistically higher persistence or at least numerically higher persistence when compared with other TNFi treatments based on reported HR and p-values.

Predictors of persistence

Thirteen studies reported on the predictors of persistence among patients taking golimumab.[32 34 35 38–40 43 45 46 48 49 51 52] Eight studies found females to be significantly less persistent.[32 34 38–40 43 48 49] Biological-experienced patients were significantly less persistent in six studies[38–40 45 46 52] while four studies found no difference between biological-naïve and biological-experienced patients.[34 35 46 51] 'No concomitant DMARDs' were found to be a predictor of low persistence in three
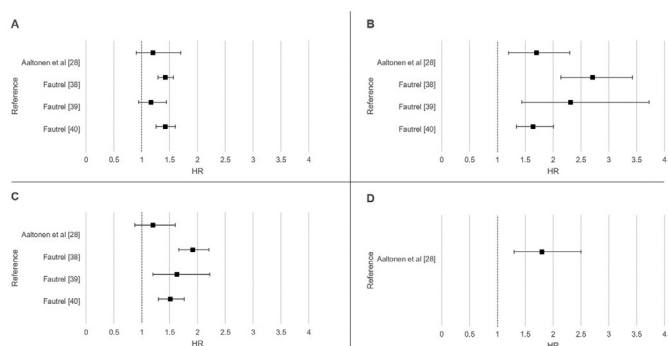

Figure 5 Effect size of differences in persistence between golimumab (GLM) and comparators, expressed as HRs. All HR calculations were made using GLM persistence data as reference. (A) GLM versus adalimumab; (B) GLM versus certolizumab pegol; (C) GLM versus etanercept and (D) GLM versus infliximab. HR>1 indicates that comparator persistence is lower than reference (GLM) treatment persistence.

studies.[32 43 48] A summary of the reported predictors of persistence across studies is presented in table 2.

DISCUSSION

This study provides an up-to-date overview of persistence with golimumab among IMRD patients in Europe. By excluding randomised controlled trial data, the included studies provide valuable information on the real-world persistence of golimumab, as well as information on comparative persistence between golimumab and other TNFi treatments. Hence, the current study offers opportunities for understanding the treatment landscape and improving disease management among IMRD patients.

From a clinical perspective, a high level of persistence with treatment is desirable as it may serve as a proxy for treatment efficacy, safety and patient satisfaction.[16–18] Furthermore, increased persistence is of interest from a payer perspective, as non-persistent RA patients have been found to incur higher healthcare costs 12 months after switching treatment, compared with patients who are persistent with their index treatment.[54]

The pooled persistence at 12 months ranged between 58.1% (PsA patients regardless of treatment history) and 75.7% (biological-naïve RA patients); at 24 months, persistence ranged between 43% (AS patients regardless of treatment history) and 69.6% (biological-naïve PsA patients).

Several studies found that the persistence rate of golimumab was higher than that of adalimumab, certolizumab pegol, etanercept and/or infliximab, and no study found golimumab to have a significantly lower persistence than its comparators. Taken together, this overview suggests that golimumab offers a good balance of efficacy, safety and patient satisfaction regardless of current treatment line.

When looking at differences in persistence by indication, golimumab persistence appears to be somewhat higher among RA and PsA patients compared with AxSpA patients; however, as the number of studies is low (particularly for AxSpA), comparisons should be interpreted with caution. In fact, several studies found no differences in persistence between patients with different indications.[35 45 48] Similarly, although the current SLR did not allow for any statistical comparisons to be made, the data appear to indicate that golimumab persistence does not differ substantially between biological-naïve and biological-experienced IMRD patients.

The most common predictor of non-persistence was being female, resulting in a risk of lower persistence. While being biological-experienced was the second most reported predictor of non-persistence, several studies found no difference in the risk of non-persistence when comparing biological-naïve and biological-experienced, a finding that may further support comparable golimumab persistence in IMRD patients with or without previous exposure to a biological anti-TNF agent.

Table 2 Summary of predictors of persistence reported

Author	Disease	Time	Predictors of persistence
Iannone et al, 2017[32]	Mixed IMRD	24 months	*Risk of non-persistence* *SpA* Female—HR=4.1, 95% CI 1.35 to 12.77 (reference category: male) Without extra-articular manifestations—HR=4.6, 95% CI 1.03 to 20.49 (reference category: with extra-articular manifestations) *RA* Failing to achieve a good EULAR response at 3months—HR=3.0, 95% CI 1.26 to 7.30 (reference category: achieving good EULAR response at 3months) *PsA* Duration of disease—HR=0.9, 95% CI 0.95 to 1.00 (reference category: NR) Golimumab monotherapy without combination with cDMARDs—HR=2.2, 95% CI 1.13 to 4.30 (reference category: golimumab monotherapy with combination with cDMARDs)
Mourão et al, 2017[34]	RA	12 months	*Risk of persistence* Female—HR=0.34, 95% CI 0.13 to 0.85, p value=0.021 (reference category: male) Age at the beginning of treatment with biologics (GLM)—HR=0.95, 95% CI 0.95 to 1.02, p value=0.355 (reference category: NR) Years of disease until treatment with biologics (GLM)—HR=1.00, 95% CI 0.93 to 1.08, p value=0.977 (reference category: NR)
Fautrel, 2017[38]	AS	12 months	*Risk of non-persistence* Female—HR=1.377 (1.300 to 1.458) p<0.0001 (reference category: male) Age—HR=0.995 (0.993 to 0.997) p<0.0001 (reference category: NR) Deprived socioeconomic status—HR=1.543 (1.288 to 1.849) p<0.0001 (reference category: non-deprived socioeconomic status) Number of comorbid conditions (per additional condition)—HR=1.150 (1.113 to 1.187) p<0.0001 Biotherapy line (per additional line)—HR=1.176 (1.124 to 1.231) p<0.0001 Hospital admission for IMRD—HR=0.883 (0.792 to 0.984) p=0.0249 (reference category: NR)
Fautrel, 2017[39]	PsA	12 months	*Risk of non-persistence* Female—HR=1.480 (1.301 to 1.684) p<0.0001 (reference category: male) Deprived socioeconomic status—HR=1.486 (1.197 to 1.843) p=0.0003 (reference category: non-deprived socioeconomic status) Biotherapy line (per additional line)—HR=1.422 (1.188 to 1.702) p=0.0001
Fautrel, 2017[40]	RA	12 months	*Risk of non-persistence* Female—HR=1.610 (1.367 to 1.897) p<0.0001 (reference category: male) Number of comorbid conditions (per additional condition)—HR=1.122 (1.086 to 1.160) p<0.0001 Biotherapy line (per additional line)—HR=1.364 (1.296 to 1.432) p<0.0001 Hospital admission for IMRD—HR=0.932 (0.871 to 0.997) p=0.0419 (reference category: NR) Visits to rheumatologist 1–4—HR=0.681 (0.578 to 0.803) p<0.0001 (reference category: 0 visits) Visits to rheumatologist>4—HR=0.704 (0.599 to 0.828) p<0.0001 (reference category: 0 visits)

Continued

Table 2 Continued

Author	Disease	Time	Predictors of persistence
Thomas et al, 2018[35]	Mixed IMRD	36 months	*Risk of non-persistence* RA VAS global (per 10mm)—HR=1.23 (1.01 to 1.50) p=0.04 PsA Swollen joint count—HR=1.10 (1.00 to 1.21) p=0.04 (reference category: NR) ESR—HR=0.98 (0.96 to 0.99) p=0.02 (reference category: NR) AS VAS (per 10mm)—HR=2.2 (1.05 to 4.61) p=0.04
Michelsen et al, 2018[48]	Mixed IMRD	48 months	*Risk of non-persistence* RA—none PsA Female—HR 1.63 (1.18 to 2.25) p=0.003 (reference category: male) No concomitant sDMARDs—HR=1.39 (1.01 to 1.90) p=0.04 (reference category: concomitant sDMARDs) AxSpA Female—HR 1.97 (1.50 to 2.60) p<0.001 (reference category: male)
García-Porrúa, 2018[43]	PsA	60 months	Risk of non-persistence—lack of concomitant MTX and gender female—not GLM specific
Serrano-Benavente, 2018[51]	Mixed IMRD	48 months	Patients with nr-AxSpA without objective inflammation had worse persistence compared with AS patients (HR=2.47, 95% CI 1.09 to 5.57, p<0.03)
Iannone et al, 2018[46]	RA	24 months	*Risk of non-persistence*—lack of MTX at baseline (HR=1.62, 95 CI 1.07 to 2.46, p=0.02) (reference category: MTX at baseline) GLM-naïve status (HR=0.62, 95 CI 0.39 to 0.99, p=0.04) (reference category: GLM-experienced status)
Serrano-Benavente, 2018[52]	PsA	48 months	*Risk of non-persistence* Age, mean evolution time and previous biological
Hernández, 2018[45]	Mixed IMRD	60 months	*Risk of non-persistence* Second biological drug—HR=2.30 (95% CI 1.16 to 4.55) p=0.02 (reference category: first biological drug) Third biological drug—HR=3.92 (2.07 to 7.39)p<0.01 (reference category: first biological drug) Concomitant MTX—HR=0.55 (0.33 to 0.91) p=0.02 (reference category: no concomitant MTX) Corticosteroids—HR=2.83 (1.72 to 4.66)p<0.01 (reference category: no corticosteroids)
Santo, 2017[49]	Mixed IMRD	24 months	*Risk of non-persistence* Female—HR=2.5, 95% CI 1.5 to 4.2, p=0.0001 (reference category: male)

AS, ankylosing spondylitis; AxSpA, axial spondyloarthritis; cDMARDs, conventional disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GLM, golimumab; IMRD, immune-mediated rheumatic disease; MTX, methotrexate; NR, not reported; nr-AxSpA, non-radiographic-AxSpA; PsA, psoriatic arthritis; RA, rheumatoid arthritis; sDMARDs, synthetic DMARDs; VAS, visual analogue scale.

The current study has a few limitations. First, the search string did not include the golimumab brand name Simponi, which may have affected the number of studies identified as part of the Ovid and conference database search. Also, while eligible abstracts from choice conferences were included, other grey literature was not searched since the focus of the current review was directed towards peer-reviewed literature and findings reported in a conference setting. Second, studies included in this SLR did not allow for a meta-analysis to be performed, as there were too few studies reporting persistence by indication for any particular time point. Because no meta-analysis was performed, no formal assessment of selection bias was done; however, study quality was assessed using the Newcastle-Ottawa scale for cohort studies,[26] the results of which are provided in online supplementary file S1. Overall, study quality did not vary significantly across included studies. Compared with RA and PsA patient populations, the paucity of studies was particularly pronounced for AxSpA, highlighting the need for further research. As several of the included studies were conference abstracts, the amount of available information was, at times, limited. Notably, both Belhassen *et al*[36] and Fautrel[39] report the same persistence rate at 12 months among PsA patients (50.8%); however, since it could not be determined whether the same population was used, both studies were included in the current review. The sparsity of information regarding the definition of persistence used in the included studies is also worth noting. A minority of studies (8/27) provide information on the number of days allowed to elapse without re-filling a previously finished prescription before a patient is considered non-persistent; however, the majority (19/27) do not state what gap size was allowed before patients were deemed to have discontinued treatment. Furthermore, known gap size ranged from 30 days[32] to 91 days,[38–40] complicating the interpretation of interstudy persistence comparisons.

In addition, since no statistical comparison of baseline characteristics was made between populations included in the pooled persistence estimate, the estimates are potentially exposed to bias provided that baseline characteristics, such as gender, age, comorbidity profile, disease activity and duration, and so on, affect persistence. In addition, since pooled persistence estimates were calculated based on relative sample size, studies not reporting the number of golimumab patients were not included in the weighted average. Similarly, pooled estimates were only calculated for studies that reported persistence at 12 and 24 months.

Finally, patient populations eligible for inclusion were further restricted to studies performed in Europe; while this increases the likelihood that drug administration and dosing is homogenous and in accordance with EMA-approved drug use, it is not possible to extrapolate the findings to non-European patient populations. Also, there are local variations in healthcare systems across Europe with regard to out-of-pocket payments, and so on, which may

have had an impact on treatment persistence. Indeed, Giacomelli *et al* show differences in the use of golimumab when comparing Italian RA patients to patients from other countries.[55] Similarly, the language restriction (English only) confers an element of publication bias.

The study also has a number of strengths. By restricting the included studies to those reporting real-world data, as opposed to findings made in randomised controlled trials, this review offers an overview of persistence data obtained from actual clinical practice. In a real-world setting, a number of factors interact to determine treatment persistence, for example, adverse effects, loss of efficacy and patient preference. By using persistence as the outcome of interest, this review captures all of the aforementioned factors, regardless of the underlying reason behind treatment switch or cessation. The concept of persistence is, therefore, a simple and useful way of investigating various reasons for treatment switch and discontinuation simultaneously. Furthermore, by grouping persistence data by indication and by investigating differences in persistence between different types of TNFi, the current review highlights differences in persistence between various patient groups and TNFi treatments. Finally, this study adds to previous studies of similar design by expanding the number of included studies, and thereby the available data, detailing real-world persistence among IMRD patients receiving golimumab treatment. As TNFi treatments are increasingly used in clinical practice, the amount of real-world data will continue to grow and provide valuable information regarding relevant aspects of routine care.

While information regarding statistical predictors of persistence was extracted and summarised as part of the current review, underlying reasons for treatment switch or discontinuation as noted by a healthcare professional were not. Hence, it would be of interest to investigate reasons for the observed differences in persistence as part of future studies. Adverse effects, treatment efficacy and dose, out-of-pocket payments, patient characteristics (including, but not restricted to, the presence or absence of comorbidities) and patient preference with regard to eg, mode of administration have all been shown to impact the likelihood of treatment switch and/or discontinuation.[56–58] Similarly, varying dosing intervals among subcutaneously administered TNFi treatments are relevant to consider. In the context of this review, golimumab is injected once monthly; adalimumab, every 2 weeks; certolizumab pegol, every 2–4 weeks; and etanercept, once or twice weekly. As patients have been shown to prefer less frequent injections,[56 59] this difference might be expected to have an impact on patient preference and hence, persistence with treatment. The interaction between patient characteristics and reasons for differences in persistence would similarly be of interest to investigate, as it may yield valuable information regarding potential variations in the probability of remaining persistent with treatment between subgroups of patients. This type of information would be useful to healthcare

practitioners, as it might be an initial step towards using different preventative measures directed at different patient groups for increasing treatment persistence.

CONCLUSIONS

In conclusion, the data from the studies included in this SLR indicate that in European routine clinical practice, golimumab has a high persistence at 12 and 24 months across different IMRD indications regardless of the treatment line.

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