Review

Adherence and Persistence to Biological Drugs for Psoriasis: Systematic Review with Meta-Analysis

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Abstract: Despite the large number of biologics currently available for moderate-to-severe psoriasis, poor adherence and persistence to therapy represent the main issues for both the clinical and economic management of psoriasis. However, the data about adherence and persistence to biologics in psoriasis patients are conflicting. Our aim was to produce summary estimates of adherence and persistence to biologics in adult patients with psoriasis. We performed a systematic review and meta-analysis of observational studies, searching two databases (PubMed and Embase). Sixty-two records met the inclusion criteria, and a meta-analysis was conducted on fifty-five studies. Overall, the proportion of adherent and persistent patients to biological therapy was 0.61 (95% confidence interval: 0.48–0.73) and 0.63 (0.57–0.68), respectively. The highest proportions were found for ustekinumab, while the lowest ones were found for etanercept. The proportions of adherence and persistence to biological drugs in psoriasis patients are sub-optimal. Notably, both proportions largely differ between drugs, suggesting that a more rational use of biologics might ensure better management of psoriasis.

Keywords: psoriasis; biological drugs; anti-TNF-α; anti-IL-17; anti-IL-12/23; adherence; persistence

1. Introduction

Psoriasis affects about 30 million adults worldwide [1]. Genetic factors, as well as lifestyle (smoking, alcohol consumption, and diet), certain drugs, environmental factors, and various metabolic conditions, can promote the development and progression of psoriasis [2,3]. Although the etiopathogenesis of psoriasis is multifactorial, its clinical manifestation mainly results from both uncontrolled keratinocyte proliferation and the overproduction of inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-17, IL-12, and IL-23. In particular, the activation of these pro-inflammatory molecules triggers a vicious circle that progressively exacerbates psoriasis [2].

Due to its peculiar clinical manifestation, psoriasis has a negative psychological impact on patients, deeply affecting their quality of life [4]. Moreover, patients with psoriasis usually have several comorbidities that further aggravate their clinical condition [1]. Therefore, adequate pharmacological treatment might ameliorate both disease severity and, indirectly, the psychosocial sphere of the individual.

The therapeutic armamentarium currently available for the management of psoriasis is mainly represented by anti-inflammatory drugs and immunomodulators. In particular, topical (i.e., corticosteroids, vitamin D3 derivatives, and keratolytic products) and systemic drugs, such as methotrexate and retinoids, are commonly used in the mild-to-moderate forms of psoriasis, while targeted biological drugs are recommended for patients with severe forms who fail to respond to first-line therapy. TNF-α inhibitors were the first

biologics to obtain marketing authorization and reimbursement for psoriasis, and they include etanercept (ETN), infliximab (INF), and adalimumab (ADA) [5]. Other biologics are IL17A inhibitors (ixekizumab, IXE; secukinumab, SECU) [6] and ustekinumab (UST), which is an anti-IL12/23 human monoclonal antibody [7].

Despite the large number of therapeutic options for the clinical management of psoriasis, two key contributors to both treatment failure and scarce relapse control are poor adherence and persistence to therapy. Adherence reflects "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen", while persistence, also known as drug survival, is "the duration of time from initiation to discontinuation of therapy" [8]. In addition, suboptimal adherence and persistence deeply impact the economic management of psoriasis in healthcare systems [9], especially for the more expensive drugs (i.e., biologics). Therefore, improving medication-taking behaviors may help patients to better control therapy, as well as limiting the economic health expenditure. Currently, the data about adherence and persistence to biological therapy in psoriasis patients are scarce and conflicting, and previous systematic reviews, although quite recent [8,10], do not provide an exhaustive and quantitative synthesis of the literature. Moreover, real-world data about adherence and persistence to individual biologics are discordant, thus hindering the rational use of these drugs in clinical practice.

Hence, the aim of this systematic review and meta-analysis is to provide overall, updated adherence and persistence proportions to biologics, as well as reporting a stratification of results based on the individual biological drugs.

2. Materials and Methods

The protocol for this systematic review and meta-analysis was registered in the PROSPERO database (CRD42021245065).

2.1. Eligibility Criteria

We included prospective, retrospective, and cross-sectional observational studies evaluating adherence and persistence (or drug survival) to biologic drugs among participants aged 18 years or older with psoriasis. We considered studies irrespective of patient gender, comorbidities, or concomitant drugs. Biological drugs belonging to the following 3 classes were considered: TNF-α inhibitors (ETN, ADA, INF); IL17A inhibitors (IXE, SECU); and IL12/23 inhibitors (UST). The outcomes were adherence and persistence to biologics, as reported in the included studies.

2.2. Information Sources and Search Strategy

We searched Medline and EMBASE for studies published from inception to 18 January 2021. The search strategy (Supplementary Material S1) reports psoriasis as the first term; drug or therapy adherence, persistence, compliance, and switching as the second term; and the considered biologic drugs as the third term (etanercept, ustekinumab, adalimumab, infliximab, ixekizumab, and secukinumab). The three terms were combined using the Boolean operator "AND".

2.3. Selection Process

Titles and abstracts of papers identified by the search strategy were screened by two authors independently, E.P. and D.P. Each paper was categorized as not relevant or potentially included according to the eligibility criteria. Any disagreement was discussed with another author, E.L.

The full text of the potentially includible articles was retrieved or, if not available, directly requested from the authors of the study. Two authors (E.P. and D.P.) checked the full texts for the eligibility criteria and excluded studies not fitting them.

The selection process was managed using bibliographic management software Mendeley Desktop (v1.19.6, Mendeley Ltd., London, UK).

2.4. Data Extraction Process

We extracted the following information: study design, outcome (adherence or persistence), and objective; number and general characteristics of participants included in the studies, such as age, gender, comorbidities, and concomitant drugs (drugs used for the treatment of psoriasis, as well as other drugs); definition of adherence/persistence as reported in the study; number of adherent/persistent patients; and reasons for discontinuation/switching. Furthermore, the data relating to any stratifications were retrieved. The data extraction was carried out by two authors independently, E.P. and D.P., and any discrepancies were resolved through consultation with a third reviewer, E.L.

For the data collection, spreadsheet software Microsoft Excel was used (version 2102 build 13801.20864).

2.5. Study Risk of Bias Assessment

The methodological quality of included studies was assessed according to risk of bias in prevalence studies developed by Hoy et al. [11]. The tool considers ten domains concerning characteristics of prevalence studies, each rated in terms of risk of bias and applicability to research question. Risk of bias was judged from 0 (high risk) to 10 (low risk). The risk of bias was evaluated by two authors independently, E.P. and D.P., and any discrepancies were resolved through consultation with a third reviewer, E.L.

2.6. Effect Measures

We evaluated the study-specific prevalence of adherence or persistence (drug survival) to biologics by calculating the proportion of adherent or persistent subjects on the total number of participants for each study. Where the study provided adherence/persistence as a percentage or where the non-adherence/non-persistence was provided, appropriate calculations were performed.

2.7. Synthesis Methods

As adherence and persistence refer to two different concepts that cannot be matched and pooled, we separately analyzed these parameters, as previously reported by others [12]. In detail, three outcomes were evaluated in our meta-analysis: (1) adherence; (2) good adherence, generally reported as the medication possession ratio (MPR) or proportion of days covered (PDC) $\geq$ 80%; and (3) persistence.

Study-specific means of adherence were pooled using random effect models and the generic inverse variance method. Study-specific adherence/persistence proportions were pooled using random effect models with Freeman–Tukey transformation.

The heterogeneity for both methods was quantified through the Higgins heterogeneity index (I^2) and was tested through the chi-square test for mean adherence and Cochran's Q test for adherence/persistence proportion.

Subgroup analyses were conducted according to study design (retrospective observational, prospective observational, or cross-sectional), type of biologics, the type of biologic users (biological-naïve subjects, i.e., subjects who have never used a biological drug, and biological-experienced subjects, i.e., subjects who have already had experience with this type of treatment), and study quality (high quality, score $\geq$ 8, vs. low quality, score < 8). Differences between groups was considered statistically significant if the heterogeneity test was significant.

p-value < 0.10 was considered statistically significant.

The "metagen" and "metaprop" routines within the META package in R (version 4.12) was used for analyses [13].

3. Results

3.1. Systematic Review

A flowchart of the search is presented in Figure 1. We identified 1285 records from the PUBMED search and 2698 from EMBASE. In total, 62 studies, including 169,371 par-

ticipants, met the inclusion criteria and were included in the qualitative synthesis. Three studies [14–16] did not show data on persistence or the number of persistent patients, while one did not show data on adherence [17]; two studies were conducted on patients not only affected by psoriasis [18,19] and did not report adherence data for psoriasis patients; one study [20] did not report the number of patients treated with each biological drug but only adherence as percentage. Fifty-five studies [21–75] on 161,748 participants were included in the quantitative synthesis (meta-analyses).
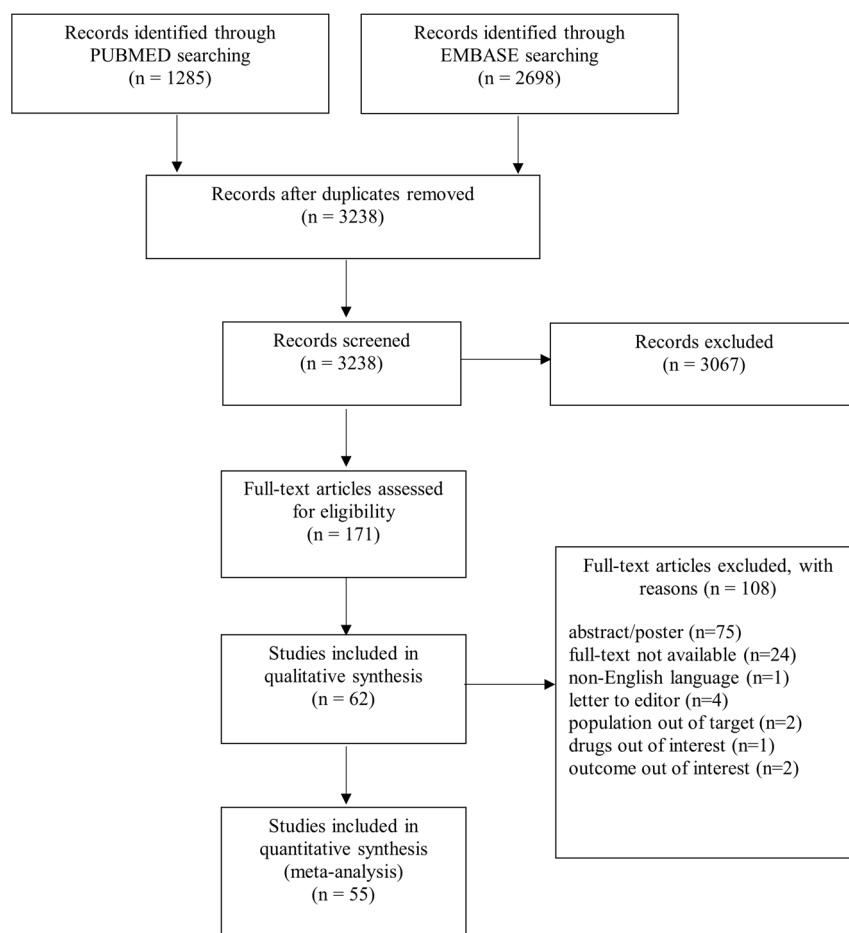
Figure 1. Flowchart of search.

In 13 studies [24,25,28,32,34,35,38,39,55,64,66,70,75], the sample was composed of patients with other chronic inflammatory autoimmune conditions, including osteoarticular diseases (such as ankylosing spondylitis and rheumatoid arthritis), bowel diseases (such as ulcerative colitis and Crohn's disease), and psoriatic arthritis. The extraction of data, in this case, focused on the cohorts of patients suffering from psoriasis regardless of other conditions.

Among the included studies (Table 1), 5 studies presented data on adherence [22,27, 33,44,53], 16 studies on good adherence [21,25–27,32,33,35,40,44,46,49,53,63,68,71,73], 46 studies on persistence data [21,23–25,27–31,33,34,36–39,41–45,47–62,64–70,72,74,75], and 8 studies reported data on both adherence and persistence [21,25,27,33,44,49,53,68]. Regarding study design (Table S1), 51 were retrospective cohort studies [15,18,19,21–49,51–57,59–62,64,66–68,70,72,74,75], 5 were prospective cohort studies [14,50,58,65,69], and 6 were cross-sectional studies [16,17,20,63,71,73]. The mean age of the participants was 47 years, of which about 45% were female. Thirty-two studies reported no use of concomitant drugs [14, 16–19,21,23–26,28–31,34,37,39,42,51,52,55,58,61,62,64,67,68,70,71,73,75]. Twenty-four studies presented data on biological-naïve patients [26–32,37–39,41,43,46,48,50,51,53,55,60,61,

66,68,74,75], while four studies [37,39,50,75] reported data on biological-experienced patients. Twenty-eight studies reported data on ADA adherence/persistence [26,27,29, 31–33,35,36,39,40,48–53,55,61,63–70,74,75], fifteen on INF [27,29,36,39,47,49,50,52,53,55,57, 64,67,70,75], twenty-five on ETN [22,26,27,29–32,36,39,40,48–53,55,56,63,66–68,70,74,75], four on IXE [28,33,44,54], ten on SECU [24,28,32,34,44,59,61,68–70], and twenty-one on UST [23,26,27,31,32,39,40,48,50,51,53,60,61,63,64,67–70,72,75]. Finally, forty-five studies were included in biological drug subgroup analysis [21,23,24,26–36,39,40,42–44,46–56,59–61,63–70,72–75] and twenty-eight in experienced/naïve subgroup analysis [26–32,35,37–39,41,43,46,48,50,51,53,55,60,61,66,68,74,75].

Table 1. Details of calculation methods in considered outcomes.

	No. of Studies (No. of Patients)
Adherence	
MPR/PDC mean	
during a period of 12 months	2 (4832) [27,53]
during a period of >12 months	3 (6297) [22,33,44]
Good adherence	
MPR/PDC $\geq$ 80%	
during a period of 12 months	6 (29,256) [25–27,49,53,68]
during a period of >12 months	5 (11,516) [32,33,35,40,44]
Other definitions during different or not-specified periods [a]	5 (4480) [21,46,63,71,73]
Persistence	
No discontinuation or gap [a] or switch	
during a period of <12 months	2 (1179) [23,72]
during a period of 12 months	24 (114,864) [24,27,28,31,37–39,43,45,48,49,51,53–55,60–62,64–66,68,74,75]
during a period of >12 months	11 (24,246) [29,33,34,41,42,44,50,56,58,59,67,69]
during a not-specified period	1 (84) [52]
Still on treatment	
after a period of <12 months	1 (378) [25]
after a period of 12 months or more	4 (2336) [30,36,47,57]
Other definitions during different or not-specified periods	2 (13,714) [21,70]

[a] different permissible gaps (from 7 to 150 days).

Table 1 shows details on adherence, good adherence, and persistence. The measures were highly heterogeneous: 5 studies gave the mean of adherence using MPR or PDC measures defined during different periods; 16 studies gave the proportion of adherent patients by mainly using (11 out of 16) the cut-off of 80% of MPR or PDC measures defined during different periods; 46 gave the proportion of persistent patients by mainly using (38 out of 64) discontinuation or switch or no gap (from 7 to 150 days) concepts defined during different periods.
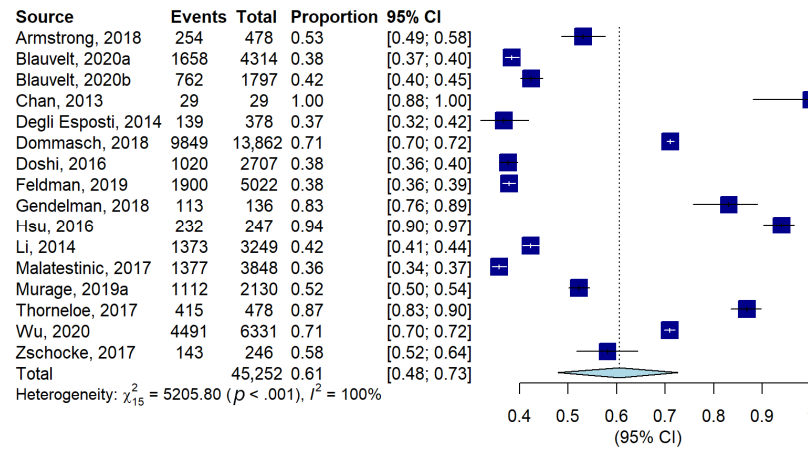
3.2. Risk of Bias in Studies

Seventeen studies [18,25–27,32,39,45,46,48,49,53,59,61,62,67–69] obtained a total score of 10 in quality assessment based on the scale of Hoy et al. [11], while three studies [34,42,73] scored less or equal than 6 points. Details on single domains can be found in Table S2.

3.3. Results of Synthesis

3.3.1. Adherence

The meta-analysis conducted on five studies including 11,129 patients showed a mean adherence of 65% (95% confidence interval, CI: 61–70%, Figure S1) with considerable heterogeneity (I^2 = 99%). Among 16 studies including 45,252 patients, the proportion of good adherence was 61% (48–73, Figure 2), with considerable heterogeneity (I^2 = 100.0%). Only 2 out of 16 studies reported the reasons for non-adherence, which were loss of efficacy and adverse events. Qualitative descriptions of the reasons are shown in Table S3.

Source	Events	Total	Proportion	95% CI
Armstrong, 2018	254	478	0.53	[0.49; 0.58]
Blauvelt, 2020a	1658	4314	0.38	[0.37; 0.40]
Blauvelt, 2020b	762	1797	0.42	[0.40; 0.45]
Chan, 2013	29	29	1.00	[0.88; 1.00]
Degli Esposti, 2014	139	378	0.37	[0.32; 0.42]
Dommasch, 2018	9849	13,862	0.71	[0.70; 0.72]
Doshi, 2016	1020	2707	0.38	[0.36; 0.40]
Feldman, 2019	1900	5022	0.38	[0.36; 0.39]
Gendelman, 2018	113	136	0.83	[0.76; 0.89]
Hsu, 2016	232	247	0.94	[0.90; 0.97]
Li, 2014	1373	3249	0.42	[0.41; 0.44]
Malatestinic, 2017	1377	3848	0.36	[0.34; 0.37]
Murage, 2019a	1112	2130	0.52	[0.50; 0.54]
Thorneloe, 2017	415	478	0.87	[0.83; 0.90]
Wu, 2020	4491	6331	0.71	[0.70; 0.72]
Zschocke, 2017	143	246	0.58	[0.52; 0.64]
Total		45,252	0.61	[0.48; 0.73]

Heterogeneity: χ^2_{15} = 5205.80 (*p* < .001), I^2 = 100%

Figure 2. Forest plot of proportions, and their 95% confidence intervals, of adherent patients.

Regarding the stratification according to the type of biologic drug, the highest adherence proportion (Table 2, Figures 3 and 4) was observed for UST (72%, 48–91), followed by INF (63%, 44–80), ADA (62%, 47–76), SECU (52%, 35–68), ETN (50%, 36–65), and, finally, IXE (46%, 43–48). The difference between groups was statistically significant (*p*-value = 0.04). ADA, ETN, and UST represent the three biological drugs most considered in the included studies, as the use of each of them was evaluated in a considerable number of studies compared to the others: 10 studies for the first drug [26,27,32,33,35,40,49,53,63,68], 8 for the second [26,27,32,40,49,53,63,68], and 7 for the third [26,27,32,40,53,63,68].

Table 2. Pooled proportions of adherent patients stratified according to study design, type of biological drug, and type of patient.

	No. of Studies	No. of Patients	Adherence, %, [CI 95%]	I^2	Q	*p*-Value for Heterogeneity within Strata	*p*-Value for Heterogeneity between Strata
Overall	16	45,252	61 [48; 73]	99.7%	5205.80	0	
Study design							
Cross-sectional	3	753	85 [55; 100]	98%	89.03	<0.0001	0.06
Retrospective cohort	13	44,499	54 [43; 66]	100%	4905.70	<0.0001	
Biological drug							
ADA	10	19,340	62 [47; 76]	100.0%	2263.54	0	
ETN	8	11,376	50 [36; 65]	100.0%	1444.93	<0.0001	
INF	3	650	63 [44; 80]	94.0%	33.15	<0.0001	
UST	7	6179	72 [48; 91]	99.0%	1087.17	<0.0001	0.04
IXE	2	1291	46 [43; 48]	0.0%	0.28	0.5976	
SECU	3	2036	52 [35; 68]	98.0%	128.11	<0.0001	
Not specified	5	4380	61 [33; 85]	97.0%	129.88	<0.0001	
Type of patient							
Biological naïve	6	33,301	52 [39; 65]	99.8%	3107.32	0	0.29
Not specified	12	12,912	63 [47; 78]	99.1%	1198.03	<0.0001	

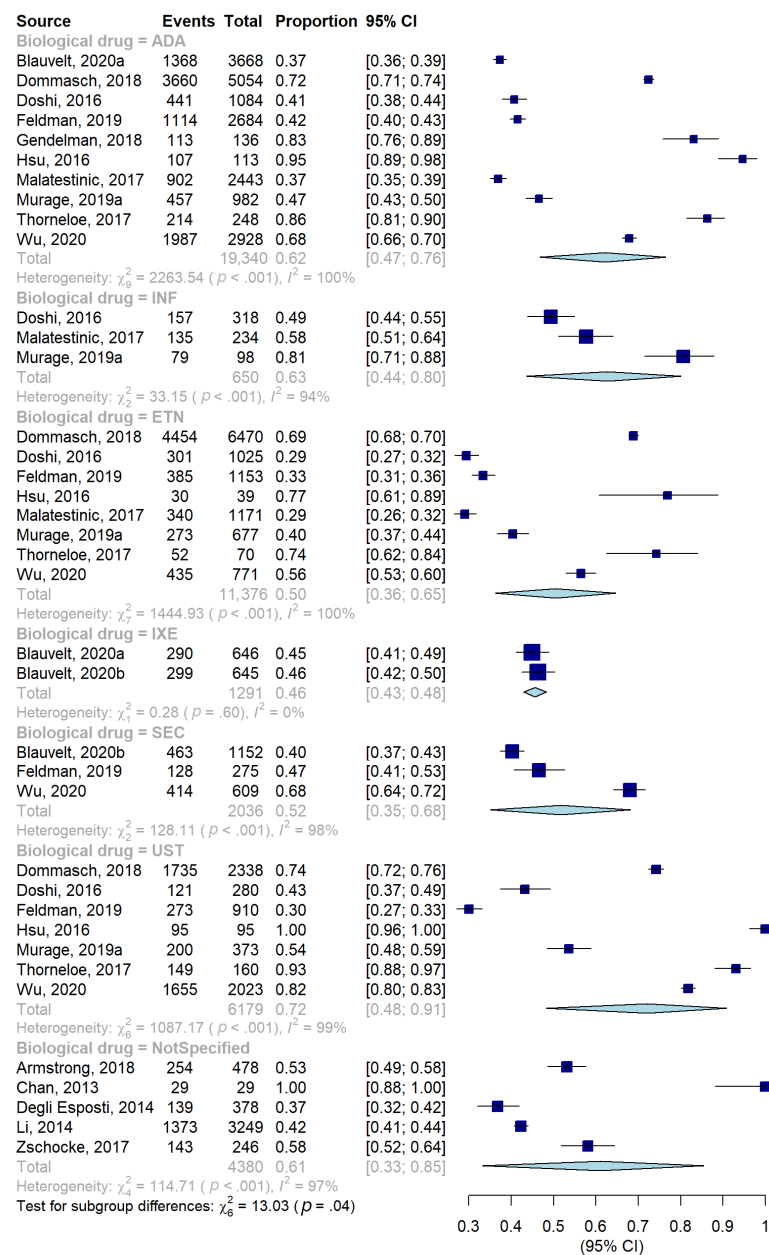| Source	Events	Total	Proportion	95% CI
Biological drug = ADA				
Blauvelt, 2020a	1368	3668	0.37	[0.36; 0.39]
Dommasch, 2018	3660	5054	0.72	[0.71; 0.74]
Doshi, 2016	441	1084	0.41	[0.38; 0.44]
Feldman, 2019	1114	2684	0.42	[0.40; 0.43]
Gendelman, 2018	113	136	0.83	[0.76; 0.89]
Hsu, 2016	107	113	0.95	[0.89; 0.98]
Malatestinic, 2017	902	2443	0.37	[0.35; 0.39]
Murage, 2019a	457	982	0.47	[0.43; 0.50]
Thorneloe, 2017	214	248	0.86	[0.81; 0.90]
Wu, 2020	1987	2928	0.68	[0.66; 0.70]
Total		19,340	0.62	[0.47; 0.76]
Heterogeneity: $\chi_9^2 = 2263.54$ ($p < .001$), $I^2 = 100\%$				
Biological drug = INF				
Doshi, 2016	157	318	0.49	[0.44; 0.55]
Malatestinic, 2017	135	234	0.58	[0.51; 0.64]
Murage, 2019a	79	98	0.81	[0.71; 0.88]
Total		650	0.63	[0.44; 0.80]
Heterogeneity: $\chi_2^2 = 33.15$ ($p < .001$), $I^2 = 94\%$				
Biological drug = ETN				
Dommasch, 2018	4454	6470	0.69	[0.68; 0.70]
Doshi, 2016	301	1025	0.29	[0.27; 0.32]
Feldman, 2019	385	1153	0.33	[0.31; 0.36]
Hsu, 2016	30	39	0.77	[0.61; 0.89]
Malatestinic, 2017	340	1171	0.29	[0.26; 0.32]
Murage, 2019a	273	677	0.40	[0.37; 0.44]
Thorneloe, 2017	52	70	0.74	[0.62; 0.84]
Wu, 2020	435	771	0.56	[0.53; 0.60]
Total		11,376	0.50	[0.36; 0.65]
Heterogeneity: $\chi_7^2 = 1444.93$ ($p < .001$), $I^2 = 100\%$				
Biological drug = IXE				
Blauvelt, 2020a	290	646	0.45	[0.41; 0.49]
Blauvelt, 2020b	299	645	0.46	[0.42; 0.50]
Total		1291	0.46	[0.43; 0.48]
Heterogeneity: $\chi_1^2 = 0.28$ ($p = .60$), $I^2 = 0\%$				
Biological drug = SEC				
Blauvelt, 2020b	463	1152	0.40	[0.37; 0.43]
Feldman, 2019	128	275	0.47	[0.41; 0.53]
Wu, 2020	414	609	0.68	[0.64; 0.72]
Total		2036	0.52	[0.35; 0.68]
Heterogeneity: $\chi_2^2 = 128.11$ ($p < .001$), $I^2 = 98\%$				
Biological drug = UST				
Dommasch, 2018	1735	2338	0.74	[0.72; 0.76]
Doshi, 2016	121	280	0.43	[0.37; 0.49]
Feldman, 2019	273	910	0.30	[0.27; 0.33]
Hsu, 2016	95	95	1.00	[0.96; 1.00]
Murage, 2019a	200	373	0.54	[0.48; 0.59]
Thorneloe, 2017	149	160	0.93	[0.88; 0.97]
Wu, 2020	1655	2023	0.82	[0.80; 0.83]
Total		6179	0.72	[0.48; 0.91]
Heterogeneity: $\chi_6^2 = 1087.17$ ($p < .001$), $I^2 = 99\%$				
Biological drug = NotSpecified				
Armstrong, 2018	254	478	0.53	[0.49; 0.58]
Chan, 2013	29	29	1.00	[0.88; 1.00]
Degli Esposti, 2014	139	378	0.37	[0.32; 0.42]
Li, 2014	1373	3249	0.42	[0.41; 0.44]
Zschocke, 2017	143	246	0.58	[0.52; 0.64]
Total		4380	0.61	[0.33; 0.85]
Heterogeneity: $\chi_4^2 = 114.71$ ($p < .001$), $I^2 = 97\%$				
Test for subgroup differences: $\chi_6^2 = 13.03$ ($p = .04$)				

Figure 3. Forest plot of proportions, and their 95% confidence intervals, of adherent patients stratified according to biological drugs.

Figure 4. Percentage of adherent patients according to biological drugs. Confidence intervals (95%) are reported within the vertical bars.

There were differences stratifying by study design, with the cross-sectional design (85%; 55–100) showing a higher adherence compared to the retrospective cohort design (54%; 43–66) (*p*-value from subgroup test = 0.06) (Table 2 and Figure S2); however, only 3 studies had a cross-sectional design in contrast with 13 retrospective cohort studies. There were no differences stratifying by biological-naïve patients and not-specified patients (*p*-value = 0.24) (Table 2 and Figure S3) or stratifying by risk of bias (*p*-value = 0.40) (Figure S4).

3.3.2. Persistence

The meta-analysis conducted on 46 studies including 156,801 patients showed a persistence proportion of 63% (57–68, Figure 5), with considerable heterogeneity (I^2 = 100%). Less than half of the studies (19 out of 46) reported the reasons for drug discontinuation or switching. The most common reasons were loss of efficacy and adverse events (nine studies) followed by ineffectiveness (three studies). Qualitative descriptions of the reasons are shown in Table S3.
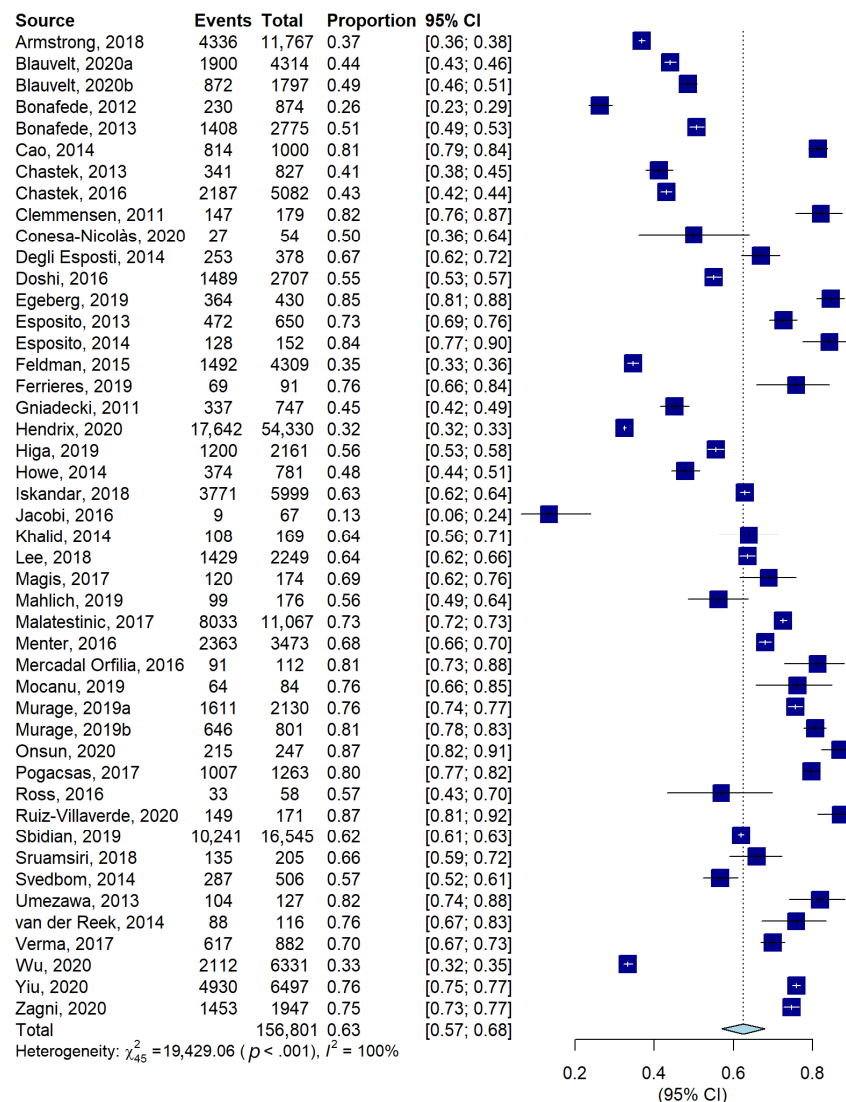
Source	Events	Total	Proportion	95% CI
Armstrong, 2018	4336	11,767	0.37	[0.36; 0.38]
Blauvelt, 2020a	1900	4314	0.44	[0.43; 0.46]
Blauvelt, 2020b	872	1797	0.49	[0.46; 0.51]
Bonafede, 2012	230	874	0.26	[0.23; 0.29]
Bonafede, 2013	1408	2775	0.51	[0.49; 0.53]
Cao, 2014	814	1000	0.81	[0.79; 0.84]
Chastek, 2013	341	827	0.41	[0.38; 0.45]
Chastek, 2016	2187	5082	0.43	[0.42; 0.44]
Clemmensen, 2011	147	179	0.82	[0.76; 0.87]
Conesa-Nicolàs, 2020	27	54	0.50	[0.36; 0.64]
Degli Esposti, 2014	253	378	0.67	[0.62; 0.72]
Doshi, 2016	1489	2707	0.55	[0.53; 0.57]
Egeberg, 2019	364	430	0.85	[0.81; 0.88]
Esposito, 2013	472	650	0.73	[0.69; 0.76]
Esposito, 2014	128	152	0.84	[0.77; 0.90]
Feldman, 2015	1492	4309	0.35	[0.33; 0.36]
Ferrieres, 2019	69	91	0.76	[0.66; 0.84]
Gniadecki, 2011	337	747	0.45	[0.42; 0.49]
Hendrix, 2020	17,642	54,330	0.32	[0.32; 0.33]
Higa, 2019	1200	2161	0.56	[0.53; 0.58]
Howe, 2014	374	781	0.48	[0.44; 0.51]
Iskandar, 2018	3771	5999	0.63	[0.62; 0.64]
Jacobi, 2016	9	67	0.13	[0.06; 0.24]
Khalid, 2014	108	169	0.64	[0.56; 0.71]
Lee, 2018	1429	2249	0.64	[0.62; 0.66]
Magis, 2017	120	174	0.69	[0.62; 0.76]
Mahlich, 2019	99	176	0.56	[0.49; 0.64]
Malatestinic, 2017	8033	11,067	0.73	[0.72; 0.73]
Menter, 2016	2363	3473	0.68	[0.66; 0.70]
Mercadal Orfilia, 2016	91	112	0.81	[0.73; 0.88]
Mocanu, 2019	64	84	0.76	[0.66; 0.85]
Murage, 2019a	1611	2130	0.76	[0.74; 0.77]
Murage, 2019b	646	801	0.81	[0.78; 0.83]
Onsun, 2020	215	247	0.87	[0.82; 0.91]
Pogacsas, 2017	1007	1263	0.80	[0.77; 0.82]
Ross, 2016	33	58	0.57	[0.43; 0.70]
Ruiz-Villaverde, 2020	149	171	0.87	[0.81; 0.92]
Sbidian, 2019	10,241	16,545	0.62	[0.61; 0.63]
Sruamsiri, 2018	135	205	0.66	[0.59; 0.72]
Svedbom, 2014	287	506	0.57	[0.52; 0.61]
Umezawa, 2013	104	127	0.82	[0.74; 0.88]
van der Reek, 2014	88	116	0.76	[0.67; 0.83]
Verma, 2017	617	882	0.70	[0.67; 0.73]
Wu, 2020	2112	6331	0.33	[0.32; 0.35]
Yiu, 2020	4930	6497	0.76	[0.75; 0.77]
Zagni, 2020	1453	1947	0.75	[0.73; 0.77]
Total		156,801	0.63	[0.57; 0.68]

Heterogeneity: χ^2_{45} = 19,429.06 (p < .001), I^2 = 100%

Figure 5. Forest plot of proportions, and their 95% confidence intervals, of persistent patients.

Regarding the stratification according to the type of biological drug, the highest persistence (Table 3, Figures 6 and 7) was found for UST (77%, 70–84), followed by SECU (72%, 58–84), IXE (70%, 52–85), INF (64%, 60–68), ADA (57%, 50–63), and ETN (53%, 42–65).

The heterogeneity between groups was statistically significant (*p*-value < 0.01). ADA, ETN, and UST represent the three biological drugs most considered in the included studies, as the use of each of them was evaluated in a considerable number of studies compared to the others: 22 studies for the first drug [29,31,36,39,48,50–52,55,61,64–67,69,70,74,75], 19 for the second [29–31,36,39,48,50–52,55,56,66,67,70,74,75], and 17 for the third [23,31,39,48,50, 51,60,61,64,67,69,70,72,75].

Table 3. Pooled proportions of persistent patients stratified according to study design, type of biological drug, and type of patient.

	No. of Studies	No. of Patients	Persistence, %, [CI 95%]	I²	Q	*p*-Value for Heterogeneity within Strata	*p*-Value for Heterogeneity between Strata
Overall	46	156,801	63 [57; 68]	100.0%	19,429.06	0	
Study design							
Retrospective cohort	42	146,657	62 [56; 68]	100.0%	16,496.95	0	0.07
Prospective cohort	4	10,144	71 [63; 77]	96.1%	76.69	<0.001	
Biological drug							
ADA	22	21,176	57 [50; 63]	99.0%	2428.85	0	
ETN	19	12,914	53 [42; 65]	99.0%	2770.05	0	
INF	14	1465	64 [60; 68]	56.0%	29.85	0.0049	
UST	17	11,869	77 [70; 84]	98.0%	1045.48	<0.001	<0.001
IXE	4	2155	70 [52; 85]	98.0%	176.12	<0.001	
SECU	9	3053	72 [58; 84]	99.0%	585.42	<0.001	
Not specified	12	90,014	55 [44; 66]	100.0%	9286.07	0	
Type of patient							
Biological naïve	21	66,821	56 [49; 64]	100.0%	5408.54	0	
Biological experienced	4	43,097	50 [35; 65]	100.0%	1638.78	<0.001	0.05
Not specified	25	46,583	67 [60; 74]	100.0%	5961.35	0	

Different persistence proportions (*p*-value from heterogeneity test = 0.05) were observed among 21 studies on biological-naïve patients (56%, 49–64), 4 studies on biological-experienced patients (50%, 35–65), and 25 studies where it was not specified (67%, 60–74) (Table 3 and Figure S5). There were also statistical differences in study design stratification (*p*-value from subgroup test = 0.07) (Table 3 and Figure S6). However, only 4 studies had a cross-sectional design in contrast with 42 retrospective cohort studies. There were no statistical differences in the risk of bias stratification (*p*-value = 0.78) (Figure S7).
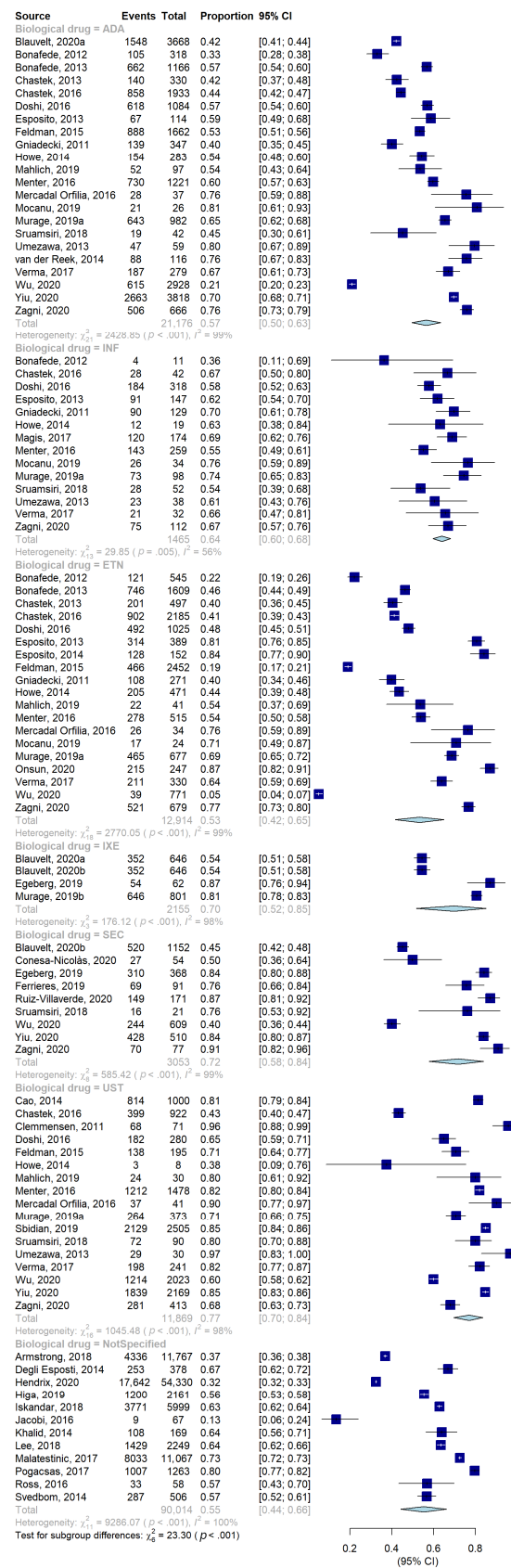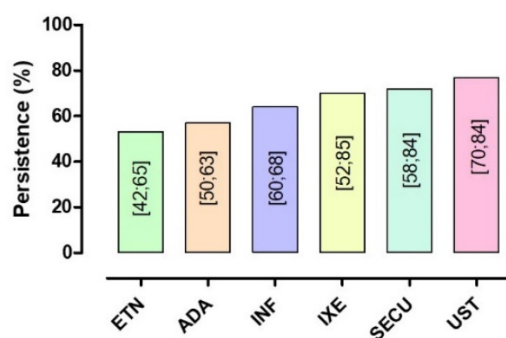
Source	Events	Total	Proportion	95% CI
Biological drug = ADA				
Blauvelt, 2020a	1548	3668	0.42	[0.41; 0.44]
Bonafede, 2012	105	318	0.33	[0.28; 0.38]
Bonafede, 2013	662	1166	0.57	[0.54; 0.60]
Chastek, 2013	140	330	0.42	[0.37; 0.48]
Chastek, 2016	858	1933	0.44	[0.42; 0.47]
Doshi, 2016	618	1084	0.57	[0.54; 0.60]
Esposito, 2013	67	114	0.59	[0.49; 0.68]
Feldman, 2015	888	1662	0.53	[0.51; 0.56]
Gniadecki, 2011	139	347	0.40	[0.35; 0.45]
Howe, 2014	154	283	0.54	[0.48; 0.60]
Mahlich, 2019	52	97	0.54	[0.43; 0.64]
Menter, 2016	730	1221	0.60	[0.57; 0.63]
Mercadal Orfilia, 2016	28	37	0.76	[0.59; 0.88]
Mocanu, 2019	21	26	0.81	[0.61; 0.93]
Murage, 2019a	643	982	0.65	[0.62; 0.68]
Sruamsiri, 2018	19	42	0.45	[0.30; 0.61]
Umezawa, 2013	47	59	0.80	[0.67; 0.89]
van der Reek, 2014	88	116	0.76	[0.67; 0.83]
Verma, 2017	187	279	0.67	[0.61; 0.73]
Wu, 2020	615	2928	0.21	[0.20; 0.23]
Yiu, 2020	2663	3818	0.70	[0.68; 0.71]
Zagni, 2020	506	666	0.76	[0.73; 0.79]
Total		21,176	0.57	[0.50; 0.63]
Heterogeneity: $\chi^2_{21} = 2428.85$ ($p < .001$), $I^2 = 99\%$				
Biological drug = INF				
Bonafede, 2012	4	11	0.36	[0.11; 0.69]
Chastek, 2016	28	42	0.67	[0.50; 0.80]
Doshi, 2016	184	318	0.58	[0.52; 0.63]
Esposito, 2013	91	147	0.62	[0.54; 0.70]
Gniadecki, 2011	90	129	0.70	[0.61; 0.78]
Howe, 2014	12	19	0.63	[0.38; 0.84]
Magis, 2017	120	174	0.69	[0.62; 0.76]
Menter, 2016	143	259	0.55	[0.49; 0.61]
Mocanu, 2019	26	34	0.76	[0.59; 0.89]
Murage, 2019a	73	98	0.74	[0.65; 0.83]
Sruamsiri, 2018	28	52	0.54	[0.39; 0.68]
Umezawa, 2013	23	38	0.61	[0.43; 0.76]
Verma, 2017	21	32	0.66	[0.47; 0.81]
Zagni, 2020	75	112	0.67	[0.57; 0.76]
Total		1465	0.64	[0.60; 0.68]
Heterogeneity: $\chi^2_{13} = 29.85$ ($p = .005$), $I^2 = 56\%$				
Biological drug = ETN				
Bonafede, 2012	121	545	0.22	[0.19; 0.26]
Bonafede, 2013	746	1609	0.46	[0.44; 0.49]
Chastek, 2013	201	497	0.40	[0.36; 0.45]
Chastek, 2016	902	2185	0.41	[0.39; 0.43]
Doshi, 2016	492	1025	0.48	[0.45; 0.51]
Esposito, 2013	314	389	0.81	[0.76; 0.85]
Esposito, 2014	128	152	0.84	[0.77; 0.90]
Feldman, 2015	466	2452	0.19	[0.17; 0.21]
Gniadecki, 2011	108	271	0.40	[0.34; 0.46]
Howe, 2014	205	471	0.44	[0.39; 0.48]
Mahlich, 2019	22	41	0.54	[0.37; 0.69]
Menter, 2016	278	515	0.54	[0.50; 0.58]
Mercadal Orfilia, 2016	26	34	0.76	[0.59; 0.89]
Mocanu, 2019	17	24	0.71	[0.49; 0.87]
Murage, 2019a	465	677	0.69	[0.65; 0.72]
Onsun, 2020	215	247	0.87	[0.82; 0.91]
Verma, 2017	211	330	0.64	[0.59; 0.69]
Wu, 2020	39	771	0.05	[0.04; 0.07]
Zagni, 2020	521	679	0.77	[0.73; 0.80]
Total		12,914	0.53	[0.42; 0.65]
Heterogeneity: $\chi^2_{18} = 2770.05$ ($p < .001$), $I^2 = 99\%$				
Biological drug = IXE				
Blauvelt, 2020a	352	646	0.54	[0.51; 0.58]
Blauvelt, 2020b	352	646	0.54	[0.51; 0.58]
Egeberg, 2019	54	62	0.87	[0.76; 0.94]
Murage, 2019b	646	801	0.81	[0.78; 0.83]
Total		2155	0.70	[0.52; 0.85]
Heterogeneity: $\chi^2_3 = 176.12$ ($p < .001$), $I^2 = 98\%$				
Biological drug = SEC				
Blauvelt, 2020b	520	1152	0.45	[0.42; 0.48]
Conesa-Nicolàs, 2020	27	54	0.50	[0.36; 0.64]
Egeberg, 2019	310	368	0.84	[0.80; 0.88]
Ferrieres, 2019	69	91	0.76	[0.66; 0.84]
Ruiz-Villaverde, 2020	149	171	0.87	[0.81; 0.92]
Sruamsiri, 2018	16	21	0.76	[0.53; 0.92]
Wu, 2020	244	609	0.40	[0.36; 0.44]
Yiu, 2020	428	510	0.84	[0.80; 0.87]
Zagni, 2020	70	77	0.91	[0.82; 0.96]
Total		3053	0.72	[0.58; 0.84]
Heterogeneity: $\chi^2_8 = 585.42$ ($p < .001$), $I^2 = 99\%$				
Biological drug = UST				
Cao, 2014	814	1000	0.81	[0.79; 0.84]
Chastek, 2016	399	922	0.43	[0.40; 0.47]
Clemmensen, 2011	68	71	0.96	[0.88; 0.99]
Doshi, 2016	182	280	0.65	[0.59; 0.71]
Feldman, 2015	138	195	0.71	[0.64; 0.77]
Howe, 2014	3	8	0.38	[0.09; 0.76]
Mahlich, 2019	24	30	0.80	[0.61; 0.92]
Menter, 2016	1212	1478	0.82	[0.80; 0.84]
Mercadal Orfilia, 2016	37	41	0.90	[0.77; 0.97]
Murage, 2019a	264	373	0.71	[0.66; 0.75]
Sbidian, 2019	2129	2505	0.85	[0.84; 0.86]
Sruamsiri, 2018	72	90	0.80	[0.70; 0.88]
Umezawa, 2013	29	30	0.97	[0.83; 1.00]
Verma, 2017	198	241	0.82	[0.77; 0.87]
Wu, 2020	1214	2023	0.60	[0.58; 0.62]
Yiu, 2020	1839	2169	0.85	[0.83; 0.86]
Zagni, 2020	281	413	0.68	[0.63; 0.73]
Total		11,869	0.77	[0.70; 0.84]
Heterogeneity: $\chi^2_{16} = 1045.48$ ($p < .001$), $I^2 = 98\%$				
Biological drug = NotSpecified				
Armstrong, 2018	4336	11,767	0.37	[0.36; 0.38]
Degli Esposti, 2014	253	378	0.67	[0.62; 0.72]
Hendrix, 2020	17,642	54,330	0.32	[0.32; 0.33]
Higa, 2019	1200	2161	0.56	[0.53; 0.58]
Iskandar, 2018	3771	5999	0.63	[0.62; 0.64]
Jacobi, 2016	9	67	0.13	[0.06; 0.24]
Khalid, 2014	108	169	0.64	[0.56; 0.71]
Lee, 2018	1429	2249	0.64	[0.62; 0.66]
Malatestinic, 2017	8033	11,067	0.73	[0.72; 0.73]
Pogacsas, 2017	1007	1263	0.80	[0.77; 0.82]
Ross, 2016	33	58	0.57	[0.43; 0.70]
Svedbom, 2014	287	506	0.57	[0.52; 0.61]
Total		90,014	0.55	[0.44; 0.66]
Heterogeneity: $\chi^2_{11} = 9286.07$ ($p < .001$), $I^2 = 100\%$				
Test for subgroup differences: $\chi^2_6 = 23.30$ ($p < .001$)				

Figure 6. Forest plot of proportions, and their 95% confidence intervals, of persistent patients stratified according to biological drugs.

Figure 7. Percentage of persistent patients according to biological drugs. Confidence intervals (95%) are reported within vertical bars.

4. Discussion

We systematically reviewed data from 55 studies including 161,748 psoriatic patients and showed that 61% of patients were adherent to biologic therapy and 63% were persistent. Our findings are consistent with those reported in previous studies. In a systematic review on inflammatory bowel disease [76], 23–62% of patients were found adherent to biologics. Another systematic review on rheumatoid arthritis [77] reported a median adherence value of 63% for both ETN and ADA. Finally, two recent meta-analyses on psoriasis showed that 66% of patients were persistent at 1 year [78] and 53.2% at two years [79].

In the studies included in our systematic review, the main reported reasons for drug discontinuation, switching, or non-adherence were loss of efficacy and adverse events. However, many other aspects could affect the patient's behavior toward biological therapy. The female gender, recent disease onset, smoking, the presence of comorbidities, and a lack of efficacy of the previous treatments have been reported as predictors of non-persistence/non-adherence [42,71,80–82]. On the contrary, the presence of psoriatic arthritis has been generally associated with sustained drug survival of biological agents [69,81].

The variability in the included studies is reflected in the heterogeneity of our analysis. We found that biological-naïve patients were more persistent than biological-experienced patients. However, only four studies evaluated persistence in biological-experienced patients. Moreover, we observed a high percentage of adherent and persistent patients among cross-sectional and prospective cohort studies, respectively, compared to retrospective cohort ones. This is expected, even if only three studies evaluating adherence had a cross-sectional design and four studies evaluating persistence had a prospective cohort design. We did not investigate whether the inclusion of different definitions of the concepts of adherence and persistence influenced our results because few studies used the same definition. This represents a limitation of our study, as well as other meta-analyses aimed at pooling adherence and persistence. The proposal of a unified set of definitions might be useful to make the results of future studies more consistent and comparable [83].

At present, the data about adherence and persistence to individual biological drugs are quite scarce. This evaluation is essential to guide clinicians toward a more rational therapeutic choice, which is fundamental for both medical and economic purposes. In our study, the highest adherence was found for the human antibody UST (72%), followed by INF (63%), ADA (62%), SECU (52%), ETN (50%), and IXE (46%). Similar proportions were found for persistence as, in descending order, they were UST with 77%, SECU with 72%, IXE with 70%, INF with 64%, ADA with 57%, and ETN with 53%.

The variability in both adherence and persistence to specific biologics could derive, to a minimal extent, from the differences in the efficacy of treatments, which can reasonably affect patients' satisfaction and, consequently, adherence/persistence to therapy. Future studies are required to elucidate on comparative efficacy because few data derived from direct "head-to-head" comparisons, and short-term efficacy outcomes were mainly evaluated [84–87]. A role for body mass index (BMI) in the patient's attitude toward biological treatment has been recently proposed [88,89]. Indeed, the efficacy of TNF-α inhibitors and

UST is reduced in obese/overweight patients with psoriasis [90–92], with consequences for both adherence and persistence [93,94].

The difference between adherence and persistence to biological therapies can be certainly explained by discussing the origin, therapeutic class, administration route and timing, and toxicity profile of the biologics. Firstly, the immunogenic potential of chimeric antibodies (i.e., INF) might cause acute anaphylactic reactions following infusion, as well as hypersensitivity reactions (such as influenza-like syndrome, local skin reactions, and pyrexia) [95]. These phenomena can be counteracted with concomitant immunosuppressive therapy, with serious consequences on patient compliance and medication adherence/persistence [96]. On the contrary, pharmacological treatment with fully human antibodies (ADA, SECU, and UST) is less associated with anti-drug antibody production, although residual immunogenicity has been reported even for the most innovative biological drugs [97].

All biological drugs share the common risk of mild-to-moderate adverse events, including headache, cutaneous and upper respiratory tract infections, and injection site reactions, which can dramatically reduce quality of life [98]. Generally, these reactions do not require additional therapy, but they can be prevented by combining biological drugs with immunomodulators [99], with predictable detrimental effects on the patient's compliance. Notably, TNF-α inhibitors are generally associated with a higher risk of severe infections, and they can induce hypersensitivity reactions [100] and dermatological disorders [101]. Hence, the peculiar toxicity profile of TNF-α inhibitors might explain, at least in part, the sub-optimal medication adherence and persistence to ETN, ADA, and INF in psoriatic patients.

Among the TNF-α inhibitors, ETN is self-administered using pre-filled syringes or pens up to twice a week. Both self-administration and short intervals between administrations might reduce compliance [102]. ADA is administered subcutaneously every 2 weeks. Therefore, the interval between administrations is longer than that reported for ETN, partially justifying the better adherence and persistence proportions to ADA rather than ETN. Finally, INF is intravenously administered at weeks 0, 2, and 6 after initiation and then at an 8- to 12-week interval [103]. The outpatient administration of INF ensures periodic support is provided to psoriasis patients, as well as contributing to a more assiduous monitoring of therapy by clinicians. Importantly, patients with scheduled appointments do not forget to take drugs, and they do not make mistakes, which instead can occur in self-administered therapy.

Concerning IL17A inhibitors, SECU is self-administered once a week for 4 weeks and then every 4 weeks [104], while IXE is self-administrated every 2 weeks for the first 12 weeks and then once a month [105].

The highest adherence and persistence proportions were found for the IL12/23 inhibitor UST (72% for adherence and 77% for persistence). UST is characterized by high efficacy in the treatment of moderate-to-severe forms of psoriasis [106] and a favorable safety profile [107]. Moreover, it is administered every 12 weeks, exclusively under the guidance of an experienced physician. Both the longest administration interval and the supervision of a healthcare provider might favorably impact adherence and persistence [108]. The subcutaneous administration of UST using pre-filled syringes or pens might also explain the wide difference in the adherence and persistence proportions from another biological drug administered in hospitals or clinics, namely, INF (63% vs. 64%, respectively). Indeed, the latter therapy requires a slow 2 h infusion followed by an additional monitoring period of 2 h; it is a demotivating protocol that might partially contribute to scarce medication adherence and persistence.

In accordance with our findings, a comparative meta-analysis showed that UST has the longest persistence at 5 years after initiation compared with TNF-α inhibitors (ETN, ADA, and INF) [79]. In a meta-analysis of real-world evidence, UST appeared as the biological drug less frequently discontinued due to loss of efficacy [78], thus confirming its clinical relevance in the pharmacological treatment of psoriasis. On the contrary, ETN showed

the worst persistence and the highest number of therapy interruptions for low efficacy, supporting the results of our meta-analysis.

Even if UST is one of the most expensive biological drugs, it is endowed with one of the most favorable cost-efficacy profiles among the biological drugs for psoriasis [109]. Indeed, both sustained adherence and persistence and a sporadic dose regimen reduce the direct costs of treatment in the long term [110], but great attention should be paid to obese patients requiring high dosage [111]. In addition, UST is associated with minor indirect costs for the healthcare system, as it reduces hospital visits for non-responders; treatment failure; and resultant drug switching, which is associated with a 7–17% increase in annual costs [112]. There are, however, some crucial aspects that must be considered before initiating biological therapy with UST. Of course, UST must be avoided in patients with hypersensitivity to this biological drug or any of the excipients [110]. Moreover, health insurance coverage does not apply in all cases in real clinical practice. This latter aspect is reported to be responsible for short-term intermittent treatment with UST [113], as uninsured patients cannot afford the economic burden of continuous treatment with this biologic drug. Hence, the expansion of insurance coverage might ameliorate both patients' satisfaction and adherence/persistence toward biological therapy. Finally, patient preferences should also be considered before starting therapy with UST, as involving patients in treatment decisions can influence both adherence to treatment and the outcomes of therapy [114].

5. Conclusions

The adherence and persistence to biological therapy in psoriasis patients are suboptimal; however, the initial therapeutic choice might be crucial to ensure better medication adherence/persistence. Psoriasis patients are more adherent and persistent to therapies with a favorable safety profile and that are characterized by less frequent administrations (i.e., UST). However, several aspects regarding comorbidities, insurance coverage, patient preferences, and costs must be considered before initiating therapy with UST. We suggest that constant real-life therapeutic discussions between health providers (dermatologists, general practitioners, pharmacists, and nurses) and their patients, as well as specific support programs, might promote the optimal levels of adherence and persistence to biological drugs for both clinical and economic purposes.

Our study has several strengths, including the high number of studies identified and the large sample size, which gives consistency to the results. Our study also has some limitations, such as having considered work from all over the world; therefore, it cannot be excluded that adherence and persistence to treatment may have a link with reimbursement policies that vary from country to country. In addition, the follow-up period was variable from study to study, although most papers were aligned in considering 12 months as the follow-up period. We are also aware that we had to exclude some studies because of the lack of usable data, even though they met all inclusion and exclusion criteria. The age and sex of the participants could influence adherence/persistence; however, in the studies included in our meta-analysis, patients were very similar in terms of age and sex. Finally, although we included all drugs approved before May 2021 (data of our literature search) to manage moderate-to-severe psoriasis, we did not include studies investigating new groups of drugs, for example, selective inhibitors of IL-23 in a recently published study [115], and this represents a limitation of our systematic review.

type of patient; Figure S6: Forest plot of proportions of prevalent patients with psoriasis to biological drugs stratified by study design; Figure S7: Forest plot of proportions of prevalent patients with psoriasis to biological drugs stratified by risk of bias.

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