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Systematic Review

Switching between Originators and Biosimilars in Dermatology: A Systematic Review of Real-World Clinical Studies

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Abstract: Background. Although biosimilars have been increasingly used over recent years, some concerns about a potential loss of efficacy and altered safety profile when switching from an originator to a biosimilar still exist. Interchangeability can be a challenge for dermatologists too. An extensive systematic review of published switching studies among originators and biosimilars was carried out in order to provide evidence regarding the effects derived from the switch in terms of efficacy and safety outcomes in real-life contexts. Results. Thirty-seven articles were included in this systematic review (14 studies related to adalimumab, 10 to etanercept, 12 to infliximab, and 1 each to adalimumab, etanercept, and infliximab). Studies were mainly carried out among European countries. Most of them were observational studies or register-based studies. The majority of studies enrolled patients diagnosed with psoriasis or psoriatic arthritis who underwent a single switch from the originator to the biosimilar. Overall, the studies' results demonstrated that switching between adalimumab, etanercept, and infliximab originators and biosimilars is safe and effective in a real-life setting of patients with dermatological conditions. Only a few studies highlighted an increase in the risk of loss of efficacy as well as an increased rate of AEs, both of which were identified as the main causes of biosimilar discontinuation, probably associated with the well-known phenomenon of the nocebo effect. Conclusion. Switching from a biologic originator to its biosimilar is safe and effective. Only a few studies have evaluated the switch among biosimilars; thus, no firm conclusion can be drawn for this type of switch in terms of the efficacy and safety outcomes. Based on our results, we believe that biosimilars can be considered interchangeable with their reference products and that no additional switch studies are necessary to support switching among originators and biosimilars in clinical practice. However, the continuous monitoring of all biologics (both originators and biosimilars) in routine clinical practice is strongly needed given their peculiar safety profile.

Keywords: biosimilar; originator; real-world studies; switch; systematic review

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1. Introduction

Across the European Union (EU) countries, biosimilars started to receive the marketing authorization in 2006. Since that date and up to January 2023, 86 biosimilar medicines received the marketing approval by the European Commission (EC). At the beginning, biosimilars were mainly represented by copies of small therapeutic proteins, such as hormones (somatropin) and growth factors (filgrastim and epoetin). Instead, in recent years in the European market, there has been a gradual increase in the access to more complex biosimilars (monoclonal antibodies—mAbs—and fusion proteins) used for the treatment of rheumatic, dermatological, gastroenterological, and hematological disorders (including neoplastic diseases) [1]. Biosimilars currently approved for the treatment of

dermatologic disorders (psoriasis, psoriatic arthritis—PsA, hidradenitis suppurativa—HS, and pemphigus vulgaris) include those bearing etanercept, adalimumab, infliximab, and rituximab [2]. Apart from etanercept, which is a fusion protein that blocks the tumor necrosis factor alpha (TNF-α), the other biosimilars are mAbs. In particular, infliximab is a chimeric mAb that blocks TNF-α, rituximab is a chimeric mAb acting against CD-20, while adalimumab is a human mAb that blocks TNF-α [3,4]. TNFα is a pro-inflammatory cytokine that promotes inflammation, through the increase of inflammatory cells entry into lesional skin, the stimulation of keratinocyte production, and the activation of dermal macrophages and dendritic cells [5]. This inflammatory pathway explains the complex alterations in epidermal growth of patients affected by psoriasis who have high levels of TNF-α in both blood and lesional skin [6].

In EU countries, the development of biosimilars for regulatory purposes follows a well-defined step-wise approach, the so-called comparability exercise, which assess and compare the Quality, Nonclinical and Clinical aspects of new biosimilars with their respective reference products [7–9]. This process consists of three main phases. The first phase aims to demonstrate the comparability between the biosimilar and the reference product in terms of quality, through the analysis of potential differences in the structure, physicochemical properties, impurities, and variability from batch to batch. In this phase, the manufacturing process, features related to protein binding, signal transduction, and functional activity are assessed as well. It is not expected that the biosimilar and the reference product will be identical in terms of all quality attributes, but if differences are detected, the marketing authorization holder should demonstrate that they have no impact on the clinical performance of the biosimilar [10]. The second phase of the comparability exercise aims to evaluate pharmacokinetics, pharmacodynamics, and toxicological aspects of the new biosimilar. These studies include the conduction of immunogenicity tests. Lastly, the clinical comparability is assessed in the last phase when phase I and III clinical studies are performed [8,9]. Thus, according to the European regulatory framework on biosimilars, the conduction of switching studies demonstrating the interchangeability before the marketing authorization of biosimilars is not required. As recently reported in a joint statement released by the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) in September 2022, based on the experience gained in the clinical practice over the past years on biosimilars and their reference products, they should be considered as interchangeable considering that they are comparable in terms of efficacy, safety, and immunogenicity [11]. Even though biosimilars have been increasingly used over recent years, patients and certain clinicians are still concerned about a potential loss of efficacy and altered safety profile when switching to a biosimilar [12]. Concerns are mainly related to the non-medical switch that could be performed for situations not related to the drug's efficacy, safety, or other medical reasons. Interchangeability is a major challenge for dermatologists too, who are dealing with the choice to switch from an originator to a biosimilar in patients with an established treatment.

Here, an extensive systematic review of published switching studies was carried out in order to provide evidence regarding the effects derived from the switch between originators and biosimilars in terms of the efficacy and safety outcomes.

2. Results

A systematic search yielded 89 citations. Following an initial screening of the title and abstract, 50 records were chosen, and a more thorough examination yielded 34 citations [13–46]. In addition, both authors (MMN and CS) agreed regarding the inclusion of 3 additional publications based on the screening of the articles' references [47–49]. Overall, 37 articles were included in this systematic review (14 studies related to adalimumab, 10 to etanercept, 12 to infliximab, and 1 each to adalimumab, etanercept and infliximab) (Figure 1). No switching studies among rituximab products in dermatology were found.

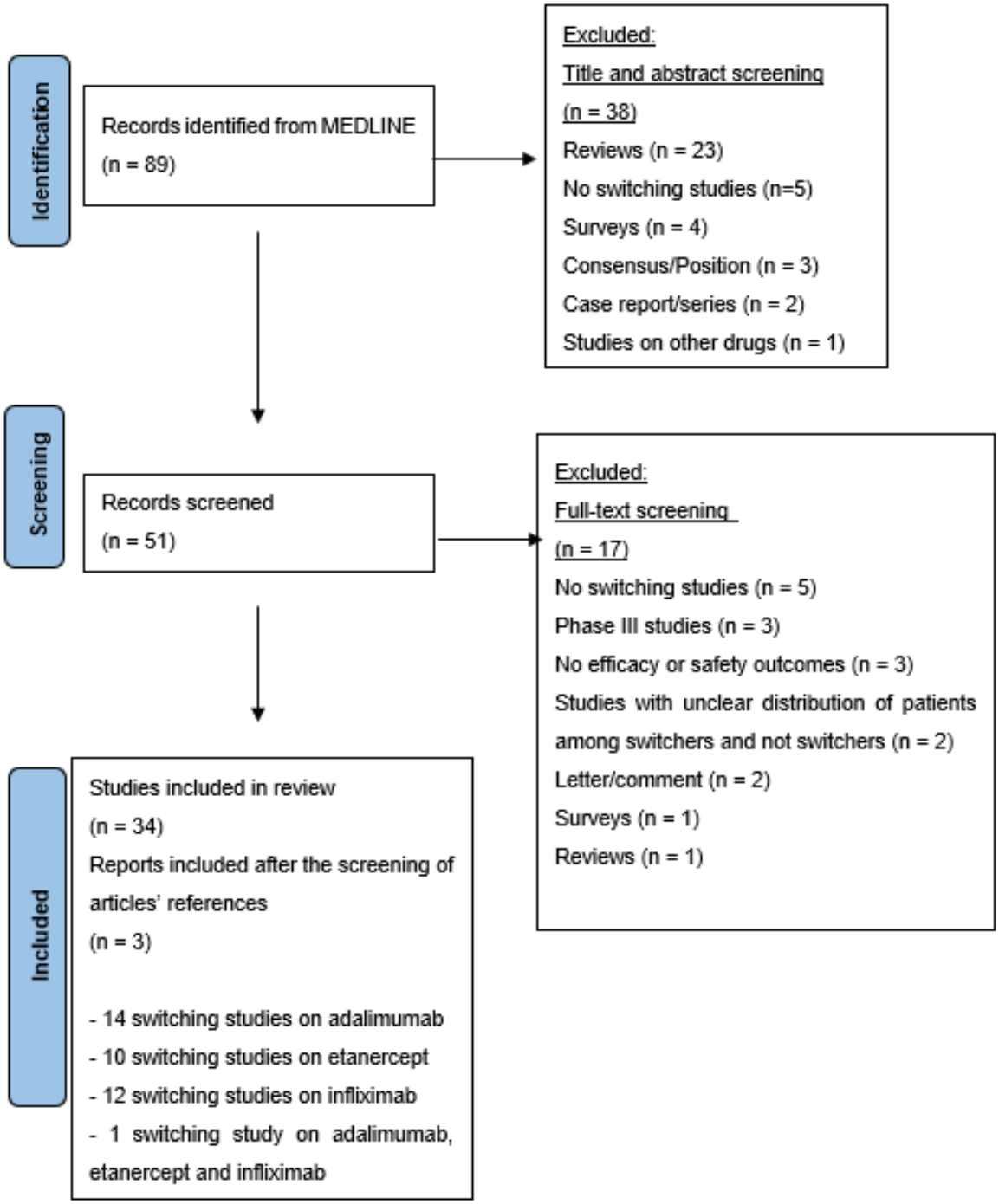

Figure 1. Flow chart illustrating literature search outcomes.

The main characteristics of switching studies included in this review are reported in Table 1. In Table 2, an overview of the outcomes and results of the included studies has been reported.

2.1. Adalimumab Switching Studies

Fourteen studies [13–25,49] evaluated the effects in terms of the efficacy and safety derived from the switch among adalimumab products. All studies were carried out in Europe (10/14 in Italy). Taken together, the included studies enrolled 3791 patients, of whom 1504 suffered from dermatologic disorders [PsA and HS (5 studies each) and psoriasis (4 studies)]. The follow-up duration of included studies ranged from 12 weeks to 1 year.

Table 1. Overview of switching studies included in the systematic review.

Reference (First Author, Year [Number of Reference])	Drug/Biosimilar	Study Design	Country	Dermatologic Disorder	Total Number of Patients	Number of Patients with a Dermatologic Disorder (Number of Switchers and Type of Switch)	Study/Follow-Up Duration	Disease Duration among Switchers (Median and IQR or Mean ± SD, Years)
Becciolini A, 2022 [13]	Adalimumab/ABP501	Retrospective observational study (BIRRA)	Italy	PsA	1046	316 (48 O-to-B)	9805.6 patient-months (12.9 months for switchers)	12.6 (5.8–19.1)
Benucci M, 2022 [35]	Etanercept/SB4	Prospective study	Italy	PsA	124	47 (28 O-to-B)	12 months	8.36 (±3.38)
Bonifati C, 2019 [32]	Etanercept/SB4	Prospective study	Italy	PsA	87	87 (87 O-to-B)	12 months	n.a.
Boone NW, 2018 [41]	Infliximab/n.a.	Pragmatic trial	The Netherlands	PsA	125	5 (5 O-to-B)	12 months	n.a.
Bruni C, 2020 [14]	Adalimumab/SB5	Retro-prospective observational study	Italy	PsA	82	28 (28 O-to-B)	6 months	n.a.
Bruni C, 2021 [15]	Adalimumab/SB5	Retrospective study	Italy	PsA	172	59 (59 O-to-B)	18 months	n.a.
Bruni C, 2020 [31]	Etanercept/SB4	Retrospective study	Italy	PsA	220	81 (81 O-to-B)	24 months	n.a.
Burlando M, 2022 [21]	Adalimumab/n.a.	Retrospective study	Italy	HS	326	326 (66 O-to-B and 28 B-to-O)	13 months (1670 months of observation for switchers)	10 (5, 19)
Dapavo P, 2016 [39]	Infliximab/n.a.	Prospective study	Italy	Pso	35	35 (30 O-to-B)	23 weeks	n.a.
Di Cesare A, 2020 [49]	Adalimumab/SB5	Prospective, observational cohort study	Italy	Pso and PsA	23	20 (20 O-to-B)	12 weeks	18.3 ± 11.11 (2–35)
Ditto MC, 2020 [29]	Etanercept/SB4	Prospective study	Italy	PsA	87	26 (* O-to-B)	12 months	n.a.
Felis-Giemza A, 2019 [30]	Etanercept/SB4	Prospective study	Poland	PsA	162	13 (13 O-to-B)	6 months	n.a.
Gallo G, 2021 [16]	Adalimumab/n.a.	Prospective study	Italy	Pso	73	73 (73 O-to-B)	6 months	n.a.
Gisondi P, 2020 [47]	Infliximab/CT-P13 and SB2	Prospective, observational cohort study	Italy	Pso	96	96 (96 O-to-B and B-to-B)	6 months	n.a.
Giunta A, 2021 [17]	Adalimumab/ABP501	Retrospective study	Italy	Pso and PsA	94	46 psoriasis (21 O-to-B) and 48 PsA (25 O-to-B)	24 weeks	n.a.
Glintborg B, 2017 [42]	Infliximab/CT-P13	Registry-based study (DANBIO)	Denmark	PsA	802	120 (92 O-to-B)	1 year	n.a.
Glintborg B, 2019 [33]	Etanercept/SB4	Registry-based study (DANBIO)	Denmark	PsA	2061	407 (351 O-to-B)	1 year	n.a.

Table 1. *Cont.*

Reference (First Author, Year [Number of Reference])	Drug/Biosimilar	Study Design	Country	Dermatologic Disorder	Total Number of Patients	Number of Patients with a Dermatologic Disorder (Number of Switchers and Type of Switch)	Study/Follow-Up Duration	Disease Duration among Switchers (Median and IQR or Mean ± SD, Years)
Goll GL, 2019 [38]	Infliximab/CT-P13	Extension of the NOR-SWITCH	Norway	Pso and PsA	380	20 PsA (11 O-to-B) and 31 psoriasis (15 O-to-B)	78 weeks	17.3 (10.4)
Jørgensen KK, 2017 [37]	Infliximab/CT-P13	Randomized, non-inferiority, double-blind, phase 4 trial (NOR-SWITCH)	Norway	Pso and PsA	482	30 PsA (16 O-to-B) and 35 psoriasis (17 O-to-B)	52 weeks	17·5 (10·5)
Kilts U, 2022 [26]	Etanercept/SB4 and GP2015	Retrospective chart review study	Germany	PsA	100	19 (19 O-to-B-to-B)	1 year	9.7 (8.9)
Kirsten N, 2022 [22]	Adalimumab/ABP501	Registry-based study (German HSBest registry)	Germany	HS	94	94 (94 O-to-B)	14 weeks	n.a.
Lauret A, 2020 [48]	Infliximab/CT-P13 and SB2	Prospective, observational cohort study	France	PsA	309	26 (22 O-to-B and 4 B-to-B)	3 years	7 ± 6
Loft N, 2021 [18]	Adalimumab/GP2017 and SB5	Registry-based study (DERMBIO)	Denmark	Pso and PsA	470 **	133 PsA (O-to-B) and 215 PsO (O-to-B)	1 year	30.6 (12.6)
Montero-Vilchez T, 2022 [23]	Adalimumab/n.a.	Retrospective observational study	Spain	HS	17	17 (17 O-to-B)	Evaluation every 12 weeks after switching	n.a.
Morita A, 2022 [45]	Infliximab/CT-P13	Prospective study	Japan	Pso and PsA	165	165 (*** O-to-B)	32 weeks	18.5 ± 11.4
Nabi H, 2021 [20]	Adalimumab/GP2017 and SB5	Registry-based study (DANBIO)	Denmark	PsA	1318	321 (321 O-to-B)	1 year	13 (9–17) (GP2017) and 14 (9–20) (SB5)
Nabi H, 2022 [36]	Infliximab/CT-P13 and GP1111	Registry-based study (DANBIO)	Denmark	PsA	1605	314 (70 B-to-B)	1 year	16 (12–25)
Pescitelli L, 2019 [28]	Etanercept/SB4	Prospective study	Italy	Pso and PsA	44	32 (32 O-to-B)	24 weeks	27.34 + 12.13 (PsO) and 12.61 + 4.31 (PsA)
Piaserico S, 2021 [27]	Etanercept/SB4 and GP2015	Prospective, observational cohort study	Italy	Pso	76	75 (75 O-to-B-to-B)	12 months	n.a.
Provenzano G, 2021 [46]	adalimumab, etanercept and infliximab/n.a.	Prospective study	Italy	PsA	145	45 (14 O-to-B adalimumab) (28 O-to-B etanercept) (3 O-to-B infliximab)	17.5 months (range 12–23)	n.a.

Table 1. *Cont.*

Reference (First Author, Year [Number of Reference])	Drug/Biosimilar	Study Design	Country	Dermatologic Disorder	Total Number of Patients	Number of Patients with a Dermatologic Disorder (Number of Switchers and Type of Switch)	Study/Follow-Up Duration	Disease Duration among Switchers (Median and IQR or Mean ± SD, Years)
Ricceri F, 2020 [19]	Adalimumab/SB5	Retrospective study	Italy	HS	11	11 (7 O-to-B)	36 weeks	15.6 ± 11.8
Roccuzzo G, 2022 [24]	Adalimumab/n.a.	Retrospective study	Italy	HS	37	37 (37 O-to-B)	12 months	n.a.
Scherlinger M, 2018 [40]	Infliximab/CT-P13	Prospective cohort study	France	PsA	89	12 (O-to-B)	median follow-up of 33 weeks	16.0 (9.9)
Scrivo R, 2022 [25]	Adalimumab/ABP501 and SB5	Prospective, observational cohort study	Italy	PsA	150	65 (40 O-to-B and 25 B-to-B)	4 months	n.a.
Tweehuysen L, 2018 [43]	Infliximab/CT-P13	Prospective, observational cohort study	The Netherlands	PsA	192	50 (50 O-to-B)	6 months	13 (8–18)
Tweehuysen L, 2018 [34]	Etanercept/SB4	Prospective, observational cohort study (BIO-SPAN)	The Netherlands	PsA	635	128 (128 O-to-B)	6 months	9 (4–16)
Valido A, 2019 [44]	Infliximab/CT-P13	Prospective, observational cohort study	Portugal	PsA	60	8 (8 O-to-B)	12 months	16 (10–22)

PsA: psoriatic arthritis; Pso: psoriasis; HS: hidradenitis suppurativa; O-to-B: switch from Originator to Biosimilar; B-to-B: switch from Biosimilar to Biosimilar; O-to-B-to-B: two switches from switch from Originator to Biosimilar and subsequently to another Biosimilar; n.a.: not available. * the number of switchers is not reported. ** 348 patients were included in the adalimumab biosimilar cohort, 378 were instead included in the adalimumab originator cohort. Since 256 patients were included in both cohorts, the total number of patients is 470. *** the distribution of switchers by PsO and PsA is not reported.

Table 2. Outcome and main results of switching studies included in the systematic review.

Drugs	First Author, Ref. n.	Main Outcomes	Main Results
ADA	Becciolini, [13]	Retention rate in naive patients and in switchers	The BIRRA study enrolled 1046 patients treated with adalimumab (193 patients switched from the originator to the biosimilar ABP 501). Among all switchers, 9 interrupted the treatment due to primary inefficacy, 8 due to secondary inefficacy, and 3 due to AEs. In the overall cohort of patients (RA, PsA, and axSpA), switchers were more persistent than patients receiving the originator and naïve patients receiving the biosimilar (88.0%, 81.5%, and 84.0%, respectively; $p > 0.05$)
	Bruni, [14]	Efficacy (ESR, RCP, VAS pain, patient fatigue VAS, HAQ, DAS28(ESR), DAS28(CRP), DAPSA) and safety (AEs)	Among PsA patients, at 6 months, no differences were found in efficacy markers compared to baseline. Most frequent AEs were infection and joint disease relapses, while no serious AE was recorded

Table 2. *Cont.*

Drugs	First Author, Ref. n.	Main Outcomes	Main Results
	Bruni, [15]	Efficacy (persistence on treatment with adalimumab biosimilar and predictors of drug interruption) and safety (AEs and prevalence)	The treatment persistence was considered satisfactory and the predictive factors of treatment discontinuation were found to be concomitant NSAIDs (HR 2.876, 95% CI 1.229–6.727, $p = 0.015$) or CCS (HR 3.209, 95% CI 1.193–8.635, $p = 0.021$) as baseline treatment. In total, 65 patients experienced at least one AE (1 serious), while 46 patients reported a loss of efficacy, resulting in 42 articular, 7 cutaneous, 5 gastrointestinal, and 3 ocular disease flares
	Burlando, [21]	Treatment ineffectiveness	The incidence of ineffectiveness was 4.9 per 100 person-months (95% CI 3.6–6.3) for originators vs. 10.7 per 100 person-months (95% CI 8.3–13.5) for biosimilars. A greater loss of effectiveness was observed in the biosimilar group compared to the originator group (IRR = 2.2; 95% CI 1.5–3.2, $p < 0.001$)
	Gallo, [16]	Efficacy (PASI and VAS) and safety (AEs)	No significant differences were observed in the PASI and VAS scores between the switch moment to the biosimilar and at the 3-month and 6-month follow-ups. VAS at 3 months from the switch was significantly higher compared to the switch moment only in the subgroup of patients with BMI > 25 ($p = 0.04$). Seven patients (9.6%) experienced mild expected AEs (recurrent candida cheilitis, asthmatic-like symptoms, asthenia, gastrointestinal symptoms, and pain at the injection site)
	Di Cesare, [49]	Efficacy (PASI) and safety (AEs)	No changes in the PASI score were observed in 90% of patients who were switched from originators. In 20 patients, the loss of efficacy on cutaneous symptoms was reported. Six patients reported injection site reactions
	Giunta, [17]	Efficacy (PASI, pain-VAS, ESR, CRP, DAS28-ESR) and safety (AEs)	In the cohort of switchers, the mean PASI was 0.45, 0.39, and 0.45 at week 16 before the switch, at the switch, and 24 weeks after the switch, respectively (no statistically significant differences). Similarly, no differences were observed in PsA patients in the mean DAS-28 ESR. No safety concerns were reported in the cohort of switchers. One patient switched back to the adalimumab originator at week 8 for primary inefficacy
	Kirsten, [22]	Efficacy (IHS4 and HiSCR) and safety (AEs)	A total of 33% of patients (n = 31) experienced AEs or loss of response (defined as an increase in the HIS4 score of at least 50%) within 12 to 14 weeks after switching to the biosimilar. All AEs were mild and limited to injection site reactions, fatigue, and pruritus. Significant differences between t1 (switch) and t2 (12–14 weeks after the switch) were identified for the IHS4 score ($p < 0.001$) in both patient groups (with and without loss of efficacy)
	Loft, [18]	The 1-year drug retention and risk of treatment discontinuation from all causes, AEs, lack and loss of effectiveness (PASI and Dermatology Life Quality Index) in the switchers cohort compared with the adalimumab originator cohort before the switch	No significant results (crude HRs) were found between switchers and non-switchers in terms of drug discontinuation for all causes, insufficient effect, or AEs. Twenty-nine patients in the switcher cohort (9.1%) and eighteen patients in the adalimumab originator cohort (5%) experienced AEs ($p = 0.04$)
	Montero-Vilchez, [23]	Efficacy (HiSCR) and safety outcomes	After the switch, 4 patients had severe pain at the injection site, 4 patients experienced loss of the HiSCR response, 1 patient had pain and loss of response simultaneously, and 1 patient reported dizziness and nausea. Of these 10 patients, 8 switched back to the originator
	Nabi, [20]	One-year treatment withdrawal, disease remission at 6 months, reasons for withdrawal, changes in disease activity at 6 months, and frequency of back-switch	No significant changes in disease activity were found 6 months before and after the switch. At 1 year, treatment withdrawal occurred in 8.5% of patients treated with GP2017 and 12.9% of patients receiving SB5. The main reasons of treatment discontinuation were the loss of efficacy and AEs. Patients who withdrew biosimilars were more commonly women, had higher disease activity, and had received fewer prior biologic therapies
	Ricceri, [19]	Efficacy (IHS4, HS-PGA, HiSCR, DLQI) and safety (AEs)	No patient had to interrupt the treatment. After 36 weeks, the rates of clinical remission were similar to those before the switch. No statistically significant differences were found in the incidence of AEs before and after the switch

Table 2. *Cont.*

Drugs	First Author, Ref. n.	Main Outcomes	Main Results
	Roccuzzo, [24]	Efficacy (IHS4, HiSCR) and safety (AEs)	No significant differences were found between adalimumab originators and biosimilars in terms of the clinical response following nonmedical switch. At the 1-year follow up, 16 patients (43.2%) discontinued the treatment (8 due to treatment inefficacy, 5 due to severe injection site pain, and 3 for unspecified reasons)
	Scrivo R, [25]	Efficacy (ESR, RCP, VAS pain, patient fatigue VAS, HAQ, DAS28(ESR), DAS28(CRP), DAPSA) and safety (AEs)	A total of 110 patients (40 with PsA) switched from the adalimumab originator to the SB5 biosimilar and 40 patients (25 with PsA) switched from the ABP501 biosimilar to the SB5 biosimilar. No differences were observed in disease activity scores for rheumatic diseases, even though PsA patients belonging to the first group experienced worsening pain [detected through the VAS ($p = 0.02$) and the HAQ ($p = 0.03$)]
ETA	Benucci M, [35]	Efficacy (ESR, CRP, IL-6, TNF, serum calprotectin MRP, DAS28, ASDAS, DAPSA, HAQ) and safety (drug levels, ADA, and AEs)	Out of 79 patients undergoing non-medical switching, 53 successfully completed the 12-months of follow-up of the study, while 26 patients interrupted SB4 treatment prematurely (19 cases of loss of efficacy of the drug and 7 cases of AEs, which included psoriasis, hypertension, cancer, and lower respiratory tract infection). Among naïve patients, 33 after 1 year were responders while 12 were non-responders (of these patients, 10 reported a loss of efficacy and 2 experienced AEs)
	Bonifati C, [32]	Efficacy (cDAPSA after 1 year and 6 months; 1-year and 6-month drug retention; reasons for SB4 discontinuation) and safety (AEs)	After 12 months from switching, 12.4% of patients failed to maintain a cDAPSA score ≤ 13. Three patients dropped out of the study during SB4 therapy after experiencing a flare of skin disease. After 6 months, 95.4% of patients still maintained a cDAPSA ≤ 13 score (difference not significant when compared to the baseline). After 6 months, 96.5% of patients were still taking SB4. Eleven patients failed to maintain a state of low disease activity at the end of the study. Loss of efficacy in the above subjects was determined on subjective evaluations given by patients
	Bruni C, [31]	Efficacy (treatment persistence and reasons for drug discontinuation) and safety (AEs)	Fifty patients (19 with PsA) experienced at least one AE (including local injection site reactions and non-severe systemic AEs). At 6 months, SB4 treatment was stopped for safety issues in 2/212 patients (1 with RA and 1 with PsA). At the 12-month of follow-up, 15 patients (8 with PsA) interrupted SB4 treatment due to the loss of efficacy or other safety concerns. The probability of persistence on treatment at 6, 12, and 18 months was 99.1%, 88.6%, and 64.6%, respectively
	Ditto MC, [29]	Efficacy (DAS28, DAPSA) and safety (AEs)	No significant differences in disease scores after the switch were found. Eleven patients (5 with PsA) stopped the treatment after the switch due to lack of efficacy, subjective features, and AEs
	Felis-Giemza A, [30]	Efficacy (PsARC) and treatment discontinuation due to loss of efficacy or AEs	The study enrolled 168 patients, of which 162 underwent a switch from an etanercept originator to the biosimilars. The remaining 6 patients were biologic-naïve. In almost 85% of switchers, the biosimilar was well tolerated. Twenty-four patients switched back to the originator due to AEs or loss of efficacy. Nine patients reported the subjective loss of efficacy and worsening of general health condition. Thirteen patients reported AEs, most often headache, skin lesions, itchy rash, and exacerbation of skin psoriasis or flare of pustular psoriasis
	Glintborg B, [33]	Efficacy (DAS28) and retention rate	No clinically relevant differences were found in disease activity and flare rates 3 months before and after the switch. During the follow-up (median 401 days), 18% of switchers and 33% of non-switchers withdrew the treatment, mainly due to the loss of efficacy. Among switchers, no major safety signals emerged. Switchers were less likely to withdraw from treatment than non-switchers (adjusted HR reported no statistically significant differences)
	Kilts U, [26]	Efficacy (DAS28) and the physical function by using the 'Funktionsfragebogen Hannover' (FFbH) score, which strongly correlates with the HAQ	A total of 100 patients switched twice from the etanercept originator to SB4 and then to GP2015 (109 PsA). The retention rate 6 months after the second switch was 89%. Six patients discontinued due to inefficacy. Overall, 8 patients experienced 14 AEs, including pancreatic cancer, laboratory abnormalities, infectious complications, flulike symptoms, pneumonia, gingivitis, and suspicion of bone tuberculosis. No injection site reactions were documented

Table 2. *Cont.*

Drugs	First Author, Ref. n.	Main Outcomes	Main Results
	Pescitelli L, [28]	Efficacy (PASI and DAS 28) and safety (AEs)	Enrolled patients were divided in two cohorts: the first included patients who were switched from the originator to SB4 and the second that included naïve patients who started the treatment with SB4. In the first cohort, at 24 weeks, the clinical remission was confirmed in 92% of patients with psoriasis and 64% of patients with psoriatic arthritis. No statistically significant differences in terms of DAS 28 before and after the switch have been identified, while the PASI score improved significantly ($p < 0.001$). In the same cohort, 4 patients experienced injection site-reaction to SB4
	Piaserico S, [27]	Efficacy (PASI) and safety (AEs)	The median PASI was 10.5 at baseline, 2 after the first switch, and 0.5–1 after the second switch (12-month follow-up). Three patients showed a loss of response to SB4 and were switched to another biologic, while two patients developed a flare-up while they were receiving GP2015. One patient was switched back to SB4, with a PASI decrease to 1 in 3 months, while the other patient reported a relapse of psoriasis and arthritis 2 months after switching; he was prescribed secukinumab with control of the disease
	Tweehuysen L, [34]	Treatment discontinuation, reasons for SB4 or ETN discontinuation, and differences in disease activity measurements over 6 months. Efficacy (CRP, DAS28-CRP) and safety (AEs)	For the BIO-SPAN study, two cohorts of patients were established: the transition cohort that included patients who consented to switch to SB4 and the historical cohort that included patients being treated with originators. At 6 months, the crude treatment persistence rate for SB4 and etanercept originator was 90% and 92%, respectively. During the same period, compared to the historical cohort, patients belonging to the transition cohort had a statistically significantly higher relative risk of treatment discontinuation (adjusted HR 1.57, 95% CI 1.05–2.36) and showed smaller decreases in the CRP level and DAS28-CRP over 6 months
INF	Boone NW, 2018 [41]	Efficacy (DAS28-ESR) and safety (AEs)	The study enrolled 125 patients. After 9 months, 5 patients with PsA were effectively being treated with infliximab biosimilar after a median number of three, four, and four infusions, respectively. No neutralizing antibody against infliximab was observed in different indications
	Dapavo P, 2016 [39]	Efficacy (PASI and VAS) and safety (AEs)	Thirty patients switched from infliximab originator (median treatment duration of 237 weeks) to the biosimilar. No changes in the PASI and VAS scores have been identified before and after the switch. In term of safety profile, 1 patient experienced herpes zoster and no other adverse events were observed
	Gisondi P, 2020 [47]	Efficacy (PASI) and safety (AEs)	A total of 96 patients underwent a non-medical switch. No significant difference was found in the PASI score before and after the switch. Ten patients withdrew the treatment due to the loss of efficacy or acute infusion reactions
	Glintborg B, 2017 [42]	Efficacy (DAS28 or ΔDAS28, HAQ, CRP) and safety (AEs)	A total of 802 patients who had previously treated with infliximab originator for >6 years were enrolled. Three months after the switch, no differences in disease activity (evaluated for 94 out of 120 PsA patients) were found. In the entire cohort of enrolled patients, 132 withdrew the treatment with CT-P13 due to lack of efficacy (n = 71), AEs (n = 37), remission or cancer (n = 5 each one), death (n = 2), more than one reason (n = 3), other reasons, including pregnancy and surgery (n = 8), and unknown (n = 1)
	Goll GL, 2019 [38]	Efficacy (ΔDAS28, DAS28, ΔPASI, PASI, ESR, CRP, overall remission status based on the main composite measures, and study drug discontinuation) and safety (drug-level, ADA, and AEs)	Of the 438 patients who completed the NOR-SWITCH, 380 continued into this 26-week extension study (20 with PsA and 31 with PsO). Patients were divided in two groups: the switch group (those who received the originator in the main trial and switched to CT-P13 during the extension study) and the maintenance group (those who have been treated always with CT-P13). At the end of the study (week 78), 61.1% of patients in the maintenance group and 67.6% of patients in the switch group were in clinical remission. A similar number of patients in both groups reported at least one AE. The most frequent AEs were infections. Lastly, although the drug concentrations were similar in both the groups during follow-up, ADA was observed in 5 patients in the maintenance group and in 4 patients in the switch group
	Jørgensen KK, 2017 [37]	Efficacy (DAS28, PASI, time to disease worsening, study drug discontinuation, overall remission status based on the main composite measures, changes in ESR and CRP, and DLQI) and safety (AEs, drug level, and ADA)	Out of 481 enrolled patients, 240 switched to CT-P13. The results highlighted that CT-P13 is not inferior to infliximab originator; disease worsening occurred in 26% of patients in the infliximab originator group and in 30% of patients in the CT-P13 group (adjusted risk difference −4.4%, 95% CI—12.7–3.9%). AEs occurred in 70% of patients in the infliximab originator group vs. 68% of patients in the CT-P13 group (mainly infections in both groups). Drug discontinuation occurred in 4% of patients in the infliximab originator group vs. 3% of patients in the CT-P13 group. Drug levels were similar in the two groups during follow-up while ADA was observed in 11% of patients in the infliximab originator group and 13% of patients in the CT-P13 group

Table 2. *Cont.*

Drugs	First Author, Ref. n.	Main Outcomes	Main Results
	Lauret A, 2020 [48]	Immunogenicity, development of ADA, and retention rate	Patients were divided in two cohorts: cohort-1 whose patients were switched to CT-P13 (n = 265) and then to SB2 (n = 140); cohort 2 that included biologic-naive patients initiated with CT-P13 before being switched to SB2 (44 patients, of whom 29 switched to SB2). Over the 3-year observation period, the development of ADA was detected in 20 patients of cohort 1 (8.5%) vs. 11 patients of cohort 2 (25%). The risk of treatment discontinuation was significantly higher in patients with positive ADA in both cohorts
	Morita A, 2022 [45]	Efficacy (PASI, DLQI, DAS28-CRP) and safety (AEs)	Overall, the treatment with CT-P13 was associated with an excellent efficacy profile, confirmed both in patients naïve to biologics, those who switched from the originator, and patients switched from other biologics. A total of 44 AEs and 8 serious AEs were reported during the 1-year follow-up period (the most common AE was an infusion reaction that occurred in 11 patients). Only one case of pneumonia was reported. The incidence of infusion reaction was significantly lower in patients who switched than in naïve patients (OR = 0.43, 95% CI 0.08–2.42, $p = 0.012$) and significantly higher in patients who switched from other biologics than in naïve patients (OR = 19.7, 95% CI 1.33–291, $p = 0.009$). Comorbidities were associated with infusion reactions (OR = 41.6, 95% CI 1.87–923, $p = 0.018$)
	Nabi H, 2022 [36]	1-year GP1111 treatment retention, treatment withdrawal, changes in disease activity 4 months before and after the switch	At 1 year, 83% (95% CI: 81–85%) of the originator-naïve and 92% (95% CI: 90–95%) of switchers maintained GP1111 treatment. The main reasons for withdrawal were lack of efficacy (60% of naïve patients vs. 29% of switchers) and AEs (16% vs. 23%). The risk of GP1111 withdrawal was lower among switchers with PsA compared with naïve patients with PsA (HR = 0.23, 95% CI: 0.07 to 0.75). No statistically significant differences in disease activity were found 4 months before and after the switch
	Scherlinger M, 2018 [40]	Retention rate of CT-P13 among switchers, acceptance of the switch, reasons for switch failure, and predictive factors of switch failure	A total of 89 patients (12 with PsA) switched to CT-P13. After a median of 33 weeks, 64 (72%) patients were still treated with CT-P13. Nine patients experienced AEs (4 cases of non-serious infections, 2 cases of infusion reactions, 2 cases of post-infusion mild headaches, and 1 case of mild serum-sickness-like disease)
	Tweehuysen L, 2018 [43]	Change in disease activity at month 6 (DAS28-CRP, CRP level, and ESR), infliximab trough levels, ADA levels, and safety (AEs)	A total of 222 patients were enrolled, of whom 192 were switched to CT-P13. At 6 months, 47 patients (24%) discontinued CT-P13 due to a perceived lack of effect, AEs, or a combination of both. The majority of reported AEs (25/32) were categorized as subjective health complaints. The intent-to-treat analysis reported no differences in the mean DAS28-CRP in RA and PsA patients from baseline to month 6 (difference of 0.0 [95% CI −0.1, 0.2]). No differences in infliximab levels were found from the baseline (2.0 lg/mL) and month 6 (1.9 lg/mL) ($p = 0.45$). ADA were detected in 10% of patients at baseline and 7% of patients at month 6. A total of 141 patients (73%) experienced at least one AE. Serious AEs occurred in 9 patients and included 6 planned surgeries, 1 cardiovascular event, 1 pulmonary event, and 1 malignancy
	Valido A, 2019 [44]	Efficacy (DAS28, ESR, CRP, PtGA, and PhGA) and safety (infliximab levels, ADA, and AEs)	Sixty patients (8 with PsA) switched to CT-P13 for non-medical reasons. For PsA patients, DAS28 changed from 2.2 at baseline to 0.96 at 12 months (variation 1.4). After switching, 5 patients stopped the treatment with CT-P13, of whom 3 patients due to disease worsening. Forty-two switchers had blood samples collected before and after the switch. No significant differences in ADA and infliximab level before and after the switch were detected
ADA, ETA, INF	Provenzano, [46]	Retention rate	Out of 145 patients who were switched to biosimilars, 123 were stable on clinical remission or had low disease activity while on therapy with biosimilars. Twenty-two patients, of whom 5 with PsA, discontinued the treatment with biosimilars. In particular, 7 patients discontinued the biosimilar because of disease reactivation (3 months after the switch), while 15 patients discontinued the biosimilar (8 ETA, 4 ADA, and 3 INF, 8 months after the switch) because of disease reactivation, patient death, or long-standing remission. The majority of these patients were switched to another biologic drug

ADA: anti-drug antibody; AE: adverse event; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondylarthritis; ESR: erythrocyte sedimentation rate; CDAI: Clinical Disease Activity Index; CI: Confidence Interval; CPR: C-reactive proteins levels; DAPSA: Disease Activity in Psoriatic Arthritis; DAS28(CRP): Disease Activity Score in 28 joints using CRP level; DAS28(ESR): Disease Activity Score in 28 joints using ESR level; DLQI. Additionally, Dermatology Life Quality Index; HAQ: patient global health; HiSCR: Hidradenitis Suppurativa Clinical Response; HS: Hidradenitis Suppurativa; HS-PGA: Hidradenitis Suppurativa Physician's Global Assessment; HR: hazard ratio; IHS4: International Hidradenitis Suppurativa Severity Score System, IL-6: interleukin 6; PsA: psoriatic arthritis; JIA: juvenile idiopathic arthritis; MDA: Minimal Disease Activity; MRP: Myeloid-Related Protein; PhGA: Physician global assessment; PP: plaque psoriasis; PsARC: Psoriatic Arthritis Response Criteria; PtGA: Patient Global assessment; RA: Rheumatoid arthritis; SDAI: Simplified Disease Activity Index; TNF: Tumor necrosis factor; VAS: Visual Analogue Scale.

Overall, the majority of studies evaluating the switch among adalimumab products indicated a similarity in their efficacy and safety profiles. For instance, in the observational retrospective study BIRRA (BIologics Retention Rate Assessment) [13], which enrolled 1046 patients treated with adalimumab (193 patients switched from the originator to the biosimilar), authors found that switchers were more persistent than patients receiving the originator and naïve patients receiving the biosimilar. Similarly, Bruni C et al. [14] reported no difference in the control of disease activity, everyday life disability, and safety after switching from the adalimumab originator to SB5 in patients with PsA. Another recent study carried out by the same researchers [15] on a population of 172 patients (59 with PsA) showed that patients who had switched from the adalimumab originator to SB5 maintained a satisfactory level of persistence in treatment. Among patients who switched back to the originator, there were 3 patients with PsA who achieved disease control once switched back. Di Cesare A et al. [49], who described the effects of adalimumab switch among 20 patients with psoriasis, reported no changes in the psoriasis area severity index (PASI) score in 90% of patients who were switched from the originator. In 2 patients, the loss of efficacy on cutaneous symptoms led to biosimilar discontinuation and shift to anti-IL-12/23 (one case) and to adjuvant methotrexate (one case). No significant differences in PASI and the Visual Analogue Scale (VAS) scores before and after the switch were reported by Gallo G et al. who enrolled 73 patients with psoriasis who had received the adalimumab originator for a median time of 34 months [16]. Other studies that enrolled patients with psoriasis [17,18] and HS [19] reported similar conclusions. Finally, using the DANBIO registry, Nabi H et al. [20] evaluated the effects of a switch from the adalimumab originator to biosimilars among 321 with PsA (148 to GP2017 and 173 to SB5). Patients who switched to GP2017 had higher disease activity and had received more number of biologic treatments previously compared to those who switched to SB5. No significant changes in disease activity were found 6 months before and after the switch. At 1 year, treatment withdrawal occurred in 8.5% of patients treated with GP2017 and 12.9% of patients receiving SB5. The main reasons of treatment discontinuation were loss of efficacy and the occurrence of AEs.

Some of the included studies reported a higher discontinuation rate among biosimilar users mainly due to AEs or loss of efficacy. For instance, the results of the retrospective study carried out by Burlando M et al. [21] on 326 HS patients reported a greater loss of effectiveness among patients allocated in the biosimilar group vs. those in the originator group (IRR = 2.2; 95% CI 1.5–3.2, $p < 0.001$). The registry-based study carried out by Kirsten N et al. [22] among 94 HS patients highlighted that 33% of them experienced AEs or loss of efficacy after switching, and that significant differences at the time of switch and 12–14 weeks after the switch were identified for the IHS4 score ($p < 0.001$) in both groups of patients (with and without loss of efficacy). Similarly, Montero-Vilchez T et al. [23] reported that, out of 17 HS patients who switched from the adalimumab originator to the biosimilar for no medical reasons, 10 patients reported severe pain at the injection site and loss of HiSCR response. Finally, Roccuzzo G et al. [24] reported high discontinuation rates among biosimilar users due to severe pain at the injection site. Only Scrivo et al. [25] evaluated the effects of the switch among adalimumab biosimilars. They carried out a prospective cohort study among 150 patients, of whom 110 (40 with PsA) switched from the adalimumab originator to the SB5 biosimilar and 40 (25 with PsA) switched from the ABP501 biosimilar to the SB5 biosimilar. In both groups of patients at month 4, no differences in disease activity scores for rheumatic diseases were reported, even though PsA patients belonging to the first group experienced a worsening as detected through the VAS ($p = 0.02$) and the Health Assessment Questionnaire (HAQ) ($p = 0.03$).

2.2. Etanercept Switching Studies

Ten studies [26–35] evaluated the effects in terms of efficacy and safety deriving from the switch among etanercept products. All studies were carried out in Europe (6/10 in Italy). Taken together, the included studies enrolled 3596 patients, of which 915 suffered from dermatologic disorders [PsA (8 studies) and psoriasis (2 studies)]. The duration of the

included studies ranged from 24 weeks to 24 months. Out of 10 studies, 2 [26,27] evaluated the efficacy and safety of cross-switching from etanercept originator to the biosimilar SB4 and subsequently to the biosimilar GP2015. In particular, Kiltz U et al. [26] carried out a retrospective chart review of 100 patients (19 with PsA) who underwent a cross-switching from the etanercept originator to SB4 and subsequently to GP2015. The mean time of treatment with the originator ETN prior to the first switch was 3.3 years. According to the DAS-28 score, at the first-switch visit, PsA patients had a moderate-to-high disease activity. After the second switch, the retention rate at 6 months was 89%. Six patients discontinued due to inefficacy; of them, 4 patients were switched back to the etanercept originator reaching their former state of low disease activity during follow-up, while 2 patients received another biologic. Piaserico S et al. [27] carried out a multi-center, prospective, observational cohort study among 76 patients with moderate-to-severe psoriasis. At the beginning of the study, the median PASI was 10.5, while it decreased to 2 after the first switch and to 0.5–1 after the second switch (follow-up at 12 months after the second switch). Based on the overall results, authors concluded that switching between two etanercept biosimilars (from SB4 to GP2015) is safe and effective. A similar conclusion was made by Pescitelli L et al. [28] who evaluated the effects of switching among 44 patients with psoriasis, of whom 32 underwent a switch to SB4. Over a follow-up period of 24 weeks, clinical remission was confirmed in 92% of patients with psoriasis and 64% of patients with psoriatic arthritis.

Ditto MC et al. [29] carried out a prospective study among 87 patients who accepted the switch from the originator (median duration of treatment 7 years) to the biosimilar. The biosimilar was discontinued in 11/85 patients (5 with PsA) mainly due to loss of efficacy, subjective reasons or the occurrence of AEs. Switching from the originator to the biosimilar was associated with the occurrence AEs or loss of efficacy in the study of Felis-Giemza A et al. too [30]. Indeed, the authors reported 24 switch-back to the originator. The loss of efficacy was confirmed in 9 patients using clinical scores, while 9 patients reported subjective loss of efficacy. In the retrospective study of Bruni C et al. [31], out of 200 enrolled patients (81 PsA; originator treatment duration 7 ± 4 years), 30 experienced SB4 withdrawals due to the occurrence of AEs (n = 11) or loss of efficacy (n = 19).

The effects of switching were evaluated by Bonifati C et al. [32] one year after the switch from the reference etanercept to SB4 among 87 patients with PsA. Almost 90% of patients maintained a clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) ≤ 13, suggesting that SB4 is effective in maintaining a state of low disease activity in the majority of patients switched from the originator. Using the DANBIO registry, Glintborg B et al. [33] evaluated the effects of switch from etanercept originator to SB4 among 407 with PsA, reporting similar disease activity 3 months before and after the switch. During the follow-up, 120 patients switched back to the etanercept originator mainly due to subjective reasons. Overall, the results of switcher studies highlighted a crude persistence on treatment at 1 year of 82% vs. 88% in an ETN historic cohort and 70% in the non-switched population. Tweehuysen L et al. [34] carried out a prospective study among 635 patients who switched from the originator to SB4 (128 with PsA). At 6 months, the crude treatment persistence rate for SB4 and etanercept originator was 90% and 92%, respectively. Lastly, Benucci M et al. [35] evaluated the effects of non-medical switching also in terms of immunogenicity through the detection of etanercept and levels of anti-drug antibodies (ADA). The activity disease status (through the DAPSA for PsA patients) and TNF-α levels were evaluated as well. Out of 79 patients who switched to SB4, 26 patients (33%) withdrew the treatment due to loss of efficacy (n = 19) or AEs (n = 7). The results of this study highlighted a difference at 6 and 12 months between switchers and naïve in terms of the HAQ and CRP, which decreased at 6 months in the naïve cohort, while HAQ decreased later (between 6 and 12 months) in the switcher cohort. In addition, among non-responder switcher patients, there was a progressive reduction in the circulating drug level at 6 and 12 months. Lastly, TNF-α levels were higher among switcher responders than in non-responders at 6 and 12 months. These data seem to be not a proof of SB4's immunogenicity, since no anti-SB4 antibodies

have been detected neither in the naïve group nor in the switcher group and, as reported by the authors, etanercept is in general associated with a low risk of immunogenicity in switching studies.

2.3. Infliximab Switching Studies

Twelve studies [36–45,47,48] evaluated the effects in terms of the efficacy and safety derived from the switch among infliximab products. Eleven studies were carried out in Europe, while one study was conducted in Japan. Overall, the included studies enrolled 3125 patients, of which 639 suffered from dermatologic disorders [PsA (9 studies) and psoriasis (5 studies)]. The duration of included studies ranged from 23 weeks to 78 weeks. Apart from Nabi H et al. [36], who evaluated the effects of switching among infliximab biosimilars, all included studies analyzed the effects associated with the switch from the originator to one of infliximab biosimilars. Specifically, using data from the DANBIO registry, Nabi H et al. [36] carried out a cohort study among 434 patients (70 with PsA) with the aim to evaluate the retention rates one year after the switch between infliximab biosimilars CT-P13 and GP1111 and factors associated with GP1111 withdrawal. Retention rates at 1 year were 83% and 92% for the originator-naïve and originator-experienced, respectively. GP1111 retention rates were higher in originator-experienced patients compared to originator-naïve patients with PsA [HR = 0.2 (95% CI: 0.1 to 0.8)]. No significant changes in disease activity were found before and after the switch.

The NOR-SWITCH [37] study was a randomized, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up evaluating the effects of the switch to the infliximab biosimilar among 241 patients (30 with PsA and 35 with psoriasis) on stable treatment with the infliximab originator (at least 6 months of treatment). Disease worsening occurred in 53 patients in the infliximab originator group and in 61 patients in the CT-P13 group (adjusted treatment difference −4.4%, 95% CI −12.7 to 3.9). The frequency of AEs was similar between the groups. Goll GL et al. [38] carried out the extension study of the NOR-SWITCH study among 380 patients (20 with PsA and 31 with psoriasis), demonstrating no differences in disease worsening between groups (patients switched at main study baseline and those switched at extension study baseline). Gisondi et al. assessed the efficacy and safety of switching from the infliximab originator to SB2 in 96 patients with chronic plaque psoriasis, highlighting that the severity of psoriasis remained stable also after the switch as confirmed using the PASI at 6 months. Out of 96 patients, 10 experienced losses of efficacy or acute infusion reactions, leading to treatment withdrawal [47]. Similarly, the results of the prospective study carried out by Dapavo P et al. [39] in 35 patients with psoriasis (of whom, 30 underwent a switch from the infliximab originator to the biosimilar, while 5 were biologic naïve and started the treatment with the biosimilar) revealed no differences in the PASI and VAS scores before and after the switch to the biosimilar.

Similar results were reported by Lauret et al. [48], who carried out a 3-year observational study in 140 PsA patients who underwent to a switch from the innovator infliximab to an infliximab biosimilar (CT-P13), followed by a switch to a second infliximab biosimilar (SB2). The study's results reported that the risk of treatment discontinuation was significantly higher in patients with positive ADA at the baseline visit or during follow-up compared to patients without ADA (Hazard Ratio 2.37, 95% CI 1.38–4.05, p = 0.002). Moreover, patients who discontinued infliximab (n = 60) were more likely to have positive ADA (p = 0.002). ADA were detected in 12 patients out of 26 who discontinued infliximab because of primary or secondary loss of efficacy and in 4 patients who discontinued due to infusion-related reaction.

Scherlinger M et al. [40] enrolled 89 patients, of whom 12 with PsA underwent a switch from an infliximab originator to a biosimilar. After a median follow-up of 33 weeks, 72% of patients were still treated with CT-P13. Almost half of the patients requesting to re-switch to the originator reported a negative perception of the new treatment without any worsening of their disease activity score, suggesting a possible reluctance of patients to switch. Boone NW et al. [41] carried out a pragmatic trial among 125 patients, of whom

5 with PsA were switched from the originator (mean treatment duration 2.9 ± 1.2 years). The authors reported a good response in switchers with PsA, and no neutralizing antibody against infliximab was observed. Positive results were reported by Glintborg B et al. [42] who used data from the DANBIO registry to evaluate the efficacy and safety of switching from the infliximab originator among 802 patients (120 with PsA with a prior infliximab treatment duration of 6.3 years). No difference was found in disease activities 3 months before and after the switch. Among patients with PsA, 16 (11 women) withdrew the treatment. Tweehuysen L et al. [43] carried out the BIO-SWITCH study, a multicenter prospective cohort study among 192 patients (50 with PsA). The results revealed that the DAS28-CRP remained stable at month 6 and that the levels of CRP, infliximab, and ADA did not change. AEs more commonly reported were arthralgia, fatigue, pruritus, and myalgia. Valido A et al. [44] evaluated the effects of a non-medical switch at 1 year among 60 patients (8 with PsA with a mean treatment duration with the infliximab originator of 9.6 years), demonstrating that disease activity remained stable over the observation period and similar to the values observed with the infliximab originator. For 42 patients (2 with PsA), blood samples were collected before and after the switch. The analysis of these samples revealed no major changes in the levels of ADA and infliximab before and after the switch.

Lastly, the only study performed outside European countries (the study location was Japan) was the one carried out by Morita A et al. [45]. The authors carried out a prospective post-marketing surveillance with the aim to evaluate the safety, efficacy, and drug survival after non-medical switching from the infliximab originator among 165 patients with psoriasis (105 switchers). At the follow-up of 1 year, AEs occurred in 29 patients (infusion reaction was the most frequently reported AE), of whom 2 had serious AEs (acute cholecystitis and interstitial pneumonia). Among switchers, 57% of patients had already reached PASI < 1 owing to pretreatment with infliximab and CT-P13 maintained this status.

Finally, only one study, the one carried out by Provenzano G et al. [46], evaluated the effects of non-medical switching in patients receiving adalimumab, etanercept, or infliximab. One hundred forty-five patients (45 diagnosed with PsA) who had been treated for at least 2 years with these drugs and who had achieved stable clinical remission or low disease activity for at least 6 months were switched to the corresponding biosimilars. After a median of 17.5 months, almost 85% were stable on clinical remission or had low disease activity while on therapy with biosimilars.

3. Materials and Methods

3.1. Literature Search

Two authors (MMN and CS) independently performed a literature search of all publications up to January 2023 on the Medline database using the following keywords: (rituximab OR etanercept OR adalimumab OR infliximab OR biosimilar) AND originator AND (switch OR switching OR transitioning) AND (dermatology OR psoriasis OR psoriatic arthritis OR Hidradenitis Suppurativa OR pemphigus vulgaris). In addition, linked references in all relevant articles were searched.

3.2. Study Selection

Publications were included if they were clinical studies carried out after the marketing approval of each biosimilar (both randomized clinical trials and observational studies that provide real-world evidence) and described the switch from originators to biosimilars or from one biosimilar to another in terms of the efficacy or safety (occurrence of adverse events—AEs) outcomes. Non-English publications, non-human research, phase I–III clinical studies, editorials, comments, and surveys were excluded. Phase I–III clinical studies were excluded because we aimed to provide an overview of the effects of switching in real-life conditions, thus reporting data from clinical studies carried out after the marketing approval of biosimilars. Screening was based on reading the titles and abstracts of the

publications and included all clinical studies that mentioned switching between originators and biosimilars.

3.3. Data Extraction, Quality Assessment, and Analysis

Data on selected articles were imported into MS Excel. Data were collected from the full-text publications relevant to originator-to-biosimilar and biosimilar-to-biosimilar switch, including study design and duration, country, patient demographics, and efficacy and safety outcomes. All endpoints were reported in a descriptive manner; no meta-analysis was performed because of varying study designs, endpoints, and statistical methodologies used in the selected studies.

At the end of study selection and analysis, three authors (CP, AC, and AA) carried out a further analysis on the extracted data to check whether information were missed or not.

Due to variability in individual studies, a cross-study quality assessment was not feasible.

4. Discussion

In this systematic review, an overview of switching clinical studies among biologic originators and biosimilars used to treat dermatologic conditions and carried out in real-life settings has been provided. Studies included in this review enrolled patients who received infliximab, adalimumab, and etanercept, all TNF-α-blocking agents, mainly used to treat psoriasis and PsA (32 out of 37 studies). Only a limited number of studies enrolled patients diagnosed with HS (5 out of 37 studies). In our opinion, this difference in disease distribution in included studies could be explained by the different prevalence of psoriasis, PsA, and HS. Indeed, the prevalence of PsA is estimated to be 2–3% (among patients with psoriasis the prevalence of PsA varies from 6% to 42%), while the prevalence of HS seems to be much lower (0.40%) [50,51].

We found that the 36 out of 37 included studies were carried out in Europe and mainly in Italy (only 1 study was carried out in Japan). This can be related to the regulatory policies that were issued across EU countries in recent years in order to increase the prescription of biosimilars by physicians. For instance, across Italian regions, biosimilar prescribing and switching are recommended and there are prescribing quotas in some regions [52]. As reported by Ditto et al. [29], in a region of northern Italy (Piedmont), SB4/Benepali won the auction vs. Enbrel in 2017 with a significant price difference. Thus, in this Region, a commission including members of the Regional Pharmaceutical Service and rheumatologists was established in order to produce a regional guidance on prescribing drugs for naïve patients and in case of a switch. Similarly, policies to encourage the use and prescription of biosimilars were also approved in Denmark and in Germany [53].

Out of 37 included studies, only 1, the NOR-SWITCH trial [37], was designed as a randomized controlled trial. This was one of the first studies to be carried out with the specific aim to evaluate the effects deriving from switching among infliximab products. It was designed as an independent study sponsored by the Norwegian government that is characterized by few limitations, such as the choice to enroll patients with different diseases, the baseline characteristics in relation to disease activity (not all patients were in clinical remission at the time of enrollment), and the concomitant treatment with immunosuppressants that was higher in the biosimilar group (this may have led to better results with the biosimilar) [54]. Therefore, although the NOR-SWITCH study concluded that switching from the infliximab originator to the biosimilar is non-inferior to continued treatment, its results should be interpreted with caution due to its limitations. In order to provide the highest level of evidence, a switching study should have the following characteristics: study design randomized and controlled; at least one switch from the originator to the biosimilar; assessment of the effects of the switch on the immunogenicity profile; a sufficient washout period between switches; a sufficient study power to assess efficacy and safety; and a sufficient follow-up period [55]. Based on these recommendations, the majority of studies included in this systematic review do not fulfill the criteria to provide high level of

evidence on switching among biologic products. Apart from the limitations of the NOR-SWITCH study, many other weaknesses have been identified in the other included studies. Indeed, many of them have an unclear methodology, such as for example the studies by Ditto et al. [29] and Felis-Giemza et al. [30] that seem to be trials even though nothing is reported in the methodology regarding patient randomization and distribution among groups.

Overall, the results of the included studies demonstrated a good efficacy and safety profile for all biologics after the switch and no unexpected AEs were reported in any of the included studies. Where evaluated, no differences in AEs or immunogenicity before and after switching were reported, even though Lauret et al. [48] found that the risk of treatment discontinuation with the infliximab biosimilar was higher in patients with positive ADA and that patients who discontinued infliximab were more likely to have positive ADA. According to literature data, ADA tend to appear within the first 6 months of therapy with adalimumab and infliximab [56–58]. The development of ADA, mainly observed with murine and chimeric mAbs, represents the main sign of immunogenicity, which consists of a tendency to trigger an unwanted immune response against self-antigens [59]. Immunogenicity may have important consequences both in terms of efficacy and safety (reduction of therapeutic efficacy, alterations in drug exposure and plasma concentrations, and hypersensitivity reactions), which could explain the association between positive ADA and treatment discontinuation found in the study by Lauret et al. [48].

When a switch, especially multiple switches, is performed for non-medical reasons (as it happened in many of clinical studies included in this review), it can be frequently related to the so-called nocebo effect. This is a combination of psychological and physiological phenomena associated with actual or perceived harm that occur as a consequence of patients' negative expectancies (and not because of the pharmacologic actions of treatment) [60] and that can negatively affect the benefit/risk ratio of the drug [61]. Indeed, as reported by Felis-Giemza [30], the subjective loss of efficacy is defined as a disease' worsening perceptible only by the patient without objective measurements. Many risk factors for the occurrence of nocebo effects have been identified, including those related to the physician (expression of uncertainty, extensive reference to potential biosimilar-induced AEs), patient characteristics (female gender, personal belief, mental disorders), drug-related factors (route of administration, negative publicity), features of the healthcare setting (interaction with the staff and other patients), and factors related to the disease process (status, duration, and therapeutic history) [62]. For instance, a systematic review of original articles addressing physicians' perceptions on biosimilars' uptake reported different knowledge and attitudes towards biosimilars. Indeed, even though physicians had positive attitudes towards biosimilars, prescribing was limited. Thus, authors suggested that education programs are needed to support the uptake of biosimilars [63]. As observed in the BIO-SWITCH study [43], a Dutch registry of patients with long-term stable disease who switched from the infliximab originator to the biosimilar following a government mandate (thus, a non-medical switch), the discontinuation rate at month 6 was 24% and 78% of AEs were subjective events (mood disturbances, fatigue). Additionally, among those who discontinued the infliximab biosimilar due to a perceived lack of efficacy, scores on objective measures of disease (swollen joint count and C-reactive protein) from baseline were stable. Recently, Petit J et al. [64] evaluated an intervention aimed to reduce the nocebo effect associated with switching between the infliximab products. The study included 45 patients with inflammatory rheumatic disease and healthcare professionals who were trained on the switch. Authors evaluated the retention rate at 34 weeks and the discontinuation rates due to a possible nocebo effect (with a comparison with a historical cohort of patients). Results revealed that the retention rate after 34 weeks was 91.2%. At 12 months, the retention rate with SB2 was 84.5% vs. 88.4% for the historical cohort ($p = 0.52$). The biosimilar discontinuation due to a possible nocebo effect was 6.6% after 12 months. The results of this study suggest that a tailored training of healthcare professionals and communication to patients might reduce the risk of nocebo effects in non-medical switches.

5. Strengths and Limitations

This systematic review has several limitations. First of all, the search was made using a single database. In addition, the majority of the included studies were observational, which are themselves characterized by well-known limitations, such as the lack of appropriate controls or the absence of long-term effects of switching. Indeed, many studies were characterized by a relatively short follow-up ($\leq$6 months in 10 studies out of 36) and a limited sample size. In addition, only a few studies analyzed the effects of cross-switching or switch among biosimilars. Thus, conclusions about this type of switch should be made with caution. Lastly, the study was limited by a high heterogeneity, both clinical and statistical, across studies that could be explained by different populations, heterogeneous clinical samples, and diagnostic criteria. Finally, another limitation lies in the disease activity indices used in the included studies, such as the HAQ, PASI, CRP, DAS28 and DAS28-CRP, DAPSA, Psoriatic Arthritis Response Criteria (PsARC), and Minimal Disease Activity (MDA). Indeed, even though these tools have a good validity, there are still contrasting data in the classification of patients according to the disease activity levels [65]. In addition, in some cases, the loss of efficacy was inferred on the basis of the patients' subjective evaluations.

On the other hand, our study has many strengths. First of all, the literature search was done by two authors already experienced in performing this type of study. Secondly, we decided to include only clinical studies carried out after the marketing approval of each biosimilar. Indeed, even though randomized controlled trials represent the gold standard for determining the efficacy and safety of healthcare interventions, their intrinsic bars limit the results' generalizability [66]. Real-world studies, that include those based on the collection of primary or secondary data from healthcare registries, add new knowledge since they allow to investigate a more diverse group of patients than those included in clinical trials, such as patients with comorbid conditions, those taking multiple medications, geriatric patients, and other vulnerable populations normally excluded by clinical trials. Third, we provided an updated analysis to January 2023 about the effects deriving from switching for three biologic drugs that are among the most used worldwide [67,68].

6. Conclusions

Data from the literature provided in this systematic review suggest that switching between adalimumab, etanercept, and infliximab originators and biosimilars is safe and effective in a real-life setting of patients suffering from dermatological conditions. Only few studies have highlighted an increase in the risk of loss of efficacy or increased rate of AEs, both of which have been identified as main causes of biosimilar discontinuation. In our opinion, this observation could be related to the nocebo effect, which is a common phenomenon especially among patients receiving biologic therapies (given their administration route—intravenous—and the negative perceptions that persist among certain physicians and that, in turn, are able to influence patients' perceptions). Lastly, only few studies evaluated the switch among biosimilars; therefore, no conclusion can be drawn for this type of switch in terms of the efficacy and safety outcomes. Based on our results and given the clinical experience gained with biosimilars during last 15 years, in line with what was already stated by other authors [69] and with the latest joint statement released by the EMA and HMA, we believe that biosimilars approved by the EC according to the EMA's stringent regulatory requirements can be considered interchangeable with their reference products and that no additional switch studies are necessary to support switching among originators and biosimilars in clinical practice. Of course, the continuous monitoring of originators and biosimilars in real-life contexts is still necessary considering that biologic drugs, especially mAbs, have peculiar safety profiles. Thus, ongoing pharmacovigilance monitoring [70,71] is essential to detect uncommon AEs and unanticipated changes in efficacy or safety profiles that may arise as a result of modifications in the manufacturing process. Running ad hoc pharmacovigilance studies may improve the public trust in biosimilars, increasing their adoption that ultimately delivers savings and value-added services to support patient care.

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References

1. Available online: https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview (accessed on 20 January 2023).
2. Lebwohl, M. Biosimilars in Dermatology. *JAMA Dermatol.* **2021**, *157*, 641–642. [CrossRef]
3. Scavone, C.; Sportiello, L.; Sullo, M.G.; Ferrajolo, C.; Ruggiero, R.; Sessa, M.; Berrino, P.M.; di Mauro, G.; Berrino, L.; Rossi, F.; et al. Safety Profile of Anticancer and Immune-Modulating Biotech Drugs Used in a Real World Setting in Campania Region (Italy): BIO-Cam Observational Study. *Front. Pharmacol.* **2017**, *8*, 607. [CrossRef] [PubMed]
4. Scavone, C.; Sessa, M.; Clementi, E.; Corrao, G.; Leone, R.; Mugelli, A.; Rossi, F.; Spina, E.; Capuano, A. Real World Data on the Utilization Pattern and Safety Profile of Infliximab Originator Versus Biosimilars in Italy: A Multiregional Study. *BioDrugs* **2018**, *32*, 607–617. [CrossRef] [PubMed]
5. Gottlieb, A.B.; Chamian, F.; Masud, S.; Cardinale, I.; Abello, M.V.; Lowes, M.A.; Chen, F.; Magliocco, M.; Krueger, J.G. TNF inhibition rapidly down-regulates multiple proinflammatory pathways in psoriasis plaques. *J. Immunol.* **2005**, *75*, 2721–2729. [CrossRef]
6. Zaba, L.C.; Cardinale, I.; Gilleaudeau, P.; Sullivan-Whalen, M.; Suárez-Fariñas, M.; Fuentes-Duculan, J.; Novitskaya, I.; Khatcherian, A.; Bluth, M.J.; Lowes, M.A.; et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J. Exp. Med.* **2007**, *204*, 3183–3194. [CrossRef] [PubMed]
7. Available online: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed on 20 January 2023).
8. Scavone, C.; Rafaniello, C.; Berrino, L.; Rossi, F.; Capuano, A. Strengths, weaknesses and future challenges of biosimilars' development. An opinion on how to improve the knowledge and use of biosimilars in clinical practice. *Pharm. Res.* **2017**, *126*, 138–142. [CrossRef]
9. Scavone, C.; Sportiello, L.; Berrino, L.; Rossi, F.; Capuano, A. Biosimilars in the European Union from comparability exercise to real world experience: What we achieved and what we still need to achieve. *Pharm. Res.* **2017**, *119*, 265–271. [CrossRef]
10. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf (accessed on 28 February 2023).
11. Available online: https://www.ema.europa.eu/en/news/biosimilar-medicines-can-be-interchanged (accessed on 20 January 2023).
12. Cohen, H.P.; Blauvelt, A.; Rifkin, R.M.; Danese, S.; Gokhale, S.B.; Woollett, G. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. *Drugs* **2018**, *78*, 463–478. [CrossRef]
13. Becciolini, A.; Parisi, S.; Caccavale, R.; Bravi, E.; Lumetti, F.; Andracco, R.; Volpe, A.; Gardelli, L.; Girelli, F.; Di Donato, E.; et al. Adalimumab and ABP 501 in the Treatment of a Large Cohort of Patients with Inflammatory Arthritis: A Real Life Retrospective Analysis. *J. Pers. Med.* **2022**, *12*, 335. [CrossRef]
14. Bruni, C.; Bitti, R.; Nacci, F.; Cometi, L.; Tofani, L.; Bartoli, F.; Fiori, G.; Matucci-Cerinic, M. Efficacy and safety of switching from reference adalimumab to SB5 in a real-life cohort of inflammatory rheumatic joint diseases. *Clin. Rheumatol.* **2021**, *40*, 85–91. [CrossRef]
15. Bruni, C.; Gentileschi, S.; Pacini, G.; Bardelli, M.; Tofani, L.; Bartoli, F.; Baldi, C.; Cometi, L.; Fiori, G.; Nacci, F.; et al. Switching from originator adalimumab to biosimilar SB5 in a rheumatology cohort: Persistence on treatment, predictors of drug interruption and safety analysis. *Ther. Adv. Musculoskelet. Dis.* **2021**, *13*, 1759720X211033679. [CrossRef] [PubMed]
16. Gallo, G.; Rostagno, E.; Siliquini, N.; Stroppiana, E.; Verrone, A.; Ortoncelli, M.; Quaglino, P.; Dapavo, P.; Ribero, S. Efficacy of switching from adalimumab originator to adalimumab biosimilar in moderate to severe psoriasis patients: A Real-life experience in a tertiary referral centre. *Australas. J. Dermatol.* **2021**, *62*, e431–e432. [CrossRef] [PubMed]
17. Giunta, A.; Zangrilli, A.; Bavetta, M.; Manfreda, V.; Pensa, C.; Bianchi, L. A single-centre, observational, retrospective, real-life study evaluating adalimumab biosimilar ABP 501 in the treatment of plaque-type psoriasis and psoriatic arthritis in originator-naïve patients and in patients undergoing non-medical switch from originator. *Curr. Med. Res. Opin.* **2021**, *37*, 1099–1102. [CrossRef] [PubMed]

18. Loft, N.; Egeberg, A.; Rasmussen, M.K.; Bryld, L.E.; Nissen, C.V.; Dam, T.N.; Ajgeiy, K.K.; Iversen, L.; Skov, L. Outcomes following a Mandatory Nonmedical Switch from Adalimumab Originator to Adalimumab Biosimilars in Patients with Psoriasis. *JAMA Dermatol.* **2021**, *157*, 676–683. [CrossRef] [PubMed]
19. Ricceri, F.; Rosi, E.; Di Cesare, A.; Pescitelli, L.; Fastame, M.T.; Prignano, F. Clinical experience with adalimumab biosimilar imraldi in hidradenitis suppurativa. *Derm. Ther.* **2020**, *33*, e14387. [CrossRef]
20. Nabi, H.; Georgiadis, S.; Loft, A.G.; Hendricks, O.; Jensen, D.V.; Andersen, M.; Chrysidis, S.; Colic, A.; Danebod, K.; Hussein, M.R.; et al. Comparative effectiveness of two adalimumab biosimilars in 1318 real-world patients with inflammatory rheumatic disease mandated to switch from originator adalimumab: Nationwide observational study emulating a randomised clinical trial. *Ann. Rheum. Dis.* **2021**, *80*, 1400–1409. [CrossRef]
21. Burlando, M.; Fabbrocini, G.; Marasca, C.; Dapavo, P.; Chiricozzi, A.; Malvaso, D.; Dini, V.; Campanati, A.; Offidani, A.; Dattola, A.; et al. Adalimumab Originator vs. Biosimilar in Hidradenitis Suppurativa: A Multicentric Retrospective Study. *Biomedicines* **2022**, *10*, 2522. [CrossRef] [PubMed]
22. Kirsten, N.; Ohm, F.; Gehrdau, K.; Girbig, G.; Stephan, B.; Ben-Anaya, N.; Pinter, A.; Bechara, F.G.; Presser, D.; Zouboulis, C.C.; et al. Switching from Adalimumab Originator to Biosimilar in Patients with Hidradenitis Suppurativa Results in Losses of Response-Data from the German HS Registry HSBest. *Life* **2022**, *12*, 1518. [CrossRef]
23. Montero-Vilchez, T.; Cuenca-Barrales, C.; Rodriguez-Tejero, A.; Martinez-Lopez, A.; Arias-Santiago, S.; Molina-Leyva, A. Switching from Adalimumab Originator to Biosimilar: Clinical Experience in Patients with Hidradenitis Suppurativa. *J. Clin. Med.* **2022**, *11*, 1007. [CrossRef]
24. Roccuzzo, G.; Rozzo, G.; Burzi, L.; Repetto, F.; Dapavo, P.; Ribero, S.; Quaglino, P. Switching from adalimumab originator to biosimilars in hidradenitis suppurativa: What's beyond cost-effectiveness? *Derm. Ther.* **2022**, *35*, e15803. [CrossRef]
25. Scrivo, R.; Castellani, C.; Mancuso, S.; Sciarra, G.; Giardina, F.; Bevignani, G.; Ceccarelli, F.; Spinelli, F.R.; Alessandri, C.; Di Franco, M.; et al. Effectiveness of non-medical switch from adalimumab bio-originator to SB5 biosimilar and from ABP501 adalimumab biosimilar to SB5 biosimilar in patients with chronic inflammatory arthropathies: A monocentric observational study. *Clin. Exp. Rheumatol.* **2022**. [CrossRef] [PubMed]
26. Kiltz, U.; Tsiami, S.; Baraliakos, X.; Andreica, I.; Kiefer, D.; Braun, J. Effectiveness and safety of a biosimilar-to-biosimilar switch of the TNF inhibitor etanercept in patients with chronic inflammatory rheumatic diseases. *Ther. Adv. Musculoskelet. Dis.* **2022**, *14*, 1759720X221119593. [CrossRef]
27. Piaserico, S.; Conti, A.; Messina, F.; Meneguzzo, A.; Odorici, G.; Bellinato, F.; Gisondi, P. Cross-Switch from Etanercept Originator to Biosimilar SB4 and to GP2015 in Patients with Chronic Plaque Psoriasis. *BioDrugs* **2021**, *35*, 469–471. [CrossRef]
28. Pescitelli, L.; Lazzeri, L.; Di Cesare, A.; Tripo, L.; Ricceri, F.; Prignano, F. Clinical experience with the etanercept biosimilar SB4 in psoriatic patients. *Int. J. Clin. Pharm.* **2019**, *41*, 9–12. [CrossRef] [PubMed]
29. Ditto, M.C.; Parisi, S.; Priora, M.; Sanna, S.; Peroni, C.L.; Laganà, A.; D'Avolio, A.; Fusaro, E. Efficacy and safety of a single switch from etanercept originator to etanercept biosimilar in a cohort of inflammatory arthritis. *Sci. Rep.* **2020**, *10*, 16178. [CrossRef] [PubMed]
30. Felis-Giemza, A.; Chmurzyńska, K.; Nałęcz-Janik, J.; Romanowska-Próchnicka, K.; Świerkocka, K.; Wudarski, M.; Olesińska, M. Observational study of inflammatory arthritis treatment by etanercept originator switched to an etanercept biosimilar. *Reumatologia.* **2019**, *57*, 257–263. [CrossRef] [PubMed]
31. Bruni, C.; Gentileschi, S.; Pacini, G.; Baldi, C.; Capassoni, M.; Tofani, L.; Bardelli, M.; Cometi, L.; Cantarini, L.; Nacci, F.; et al. The switch from etanercept originator to SB4: Data from a real-life experience on tolerability and persistence on treatment in joint inflammatory diseases. *Ther. Adv. Musculoskelet. Dis.* **2020**, *12*, 1759720X20964031. [CrossRef]
32. Bonifati, C.; De Felice, C.; Lora, V.; Morrone, A.; Graceffa, D. Effectiveness of etanercept biosimilar SB4 in maintaining low disease activity in patients with psoriatic arthritis switched from etanercept originator: An open-label one year study. *J. Dermatol. Treat.* **2020**, *31*, 687–691. [CrossRef]
33. Glintborg, B.; Loft, A.G.; Omerovic, E.; Hendricks, O.; Linauskas, A.; Espesen, J.; Danebod, K.; Jensen, D.V.; Nordin, H.; Dalgaard, E.B.; et al. To switch or not to switch: Results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. *Ann. Rheum. Dis.* **2019**, *78*, 192–200. [CrossRef]
34. Tweehuysen, L.; Huiskes, V.J.B.; van den Bemt, B.J.F.; Vriezekolk, J.E.; Teerenstra, S.; van den Hoogen, F.H.J.; van den Ende, C.H.; den Broeder, A.A. Open-Label, Non-Mandatory Transitioning from Originator Etanercept to Biosimilar SB4: Six-Month Results from a Controlled Cohort Study. *Arthritis Rheumatol.* **2018**, *70*, 1408–1418. [CrossRef]
35. Benucci, M.; Damiani, A.; Russo, E.; Li Gobbi, F.; Grossi, V.; Amedei, A.; Infantino, M.; Manfredi, M. Predicting Loss of Efficacy after Non-Medical Switching: Correlation between Circulating TNF-α Levels and SB4 in Etanercept to SB4 Switchers and Naïve Patients with Rheumatic Disease. *J. Pers. Med.* **2022**, *12*, 1174. [CrossRef] [PubMed]
36. Nabi, H.; Hendricks, O.; Jensen, D.V.; Loft, A.G.; Pedersen, J.K.; Just, S.A.; Danebod, K.; Munk, H.L.; Kristensen, S.; Manilo, N.; et al. Infliximab biosimilar-to-biosimilar switching in patients with inflammatory rheumatic disease: Clinical outcomes in real-world patients from the DANBIO registry. *RMD Open.* **2022**, *8*, e002560. [CrossRef]
37. Jørgensen, K.K.; Olsen, I.C.; Goll, G.L.; Lorentzen, M.; Bolstad, N.; Haavardsholm, E.A.; Lundin, K.E.A.; Mørk, C.; Jahnsen, J.; Kvien, T.K.; et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): A 52-week, randomised, double-blind, non-inferiority trial. *Lancet* **2017**, *389*, 2304–2316. [CrossRef]

38. Goll, G.L.; Jørgensen, K.K.; Sexton, J.; Olsen, I.C.; Bolstad, N.; Haavardsholm, E.A.; Lundin, K.E.A.; Tveit, K.S.; Lorentzen, M.; Berset, I.P.; et al. Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: Open-label extension of the NOR-SWITCH trial. *J. Intern. Med.* **2019**, *285*, 653–669. [CrossRef] [PubMed]
39. Dapavo, P.; Vujic, I.; Fierro, M.T.; Quaglino, P.; Sanlorenzo, M. The infliximab biosimilar in the treatment of moderate to severe plaque psoriasis. *J. Am. Acad. Dermatol.* **2016**, *75*, 736–739. [CrossRef] [PubMed]
40. Scherlinger, M.; Germain, V.; Labadie, C.; Barnetche, T.; Truchetet, M.E.; Bannwarth, B.; Mehsen-Cetre, N.; Richez, C.; Schaeverbeke, T.; FHU ACRONIM. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. *Jt. Bone Spine* **2018**, *85*, 561–567. [CrossRef]
41. Boone, N.W.; Liu, L.; Romberg-Camps, M.J.; Duijsens, L.; Houwen, C.; van der Kuy, P.H.M.; Janknegt, R.; Peeters, R.; Landewé, R.B.M.; Winkens, B.; et al. The nocebo effect challenges the non-medical infliximab switch in practice. *Eur. J. Clin. Pharmacol.* **2018**, *74*, 655–661. [CrossRef]
42. Glintborg, B.; Sørensen, I.J.; Loft, A.G.; Lindegaard, H.; Linauskas, A.; Hendricks, O.; Hansen, I.M.J.; Jensen, D.V.; Manilo, N.; Espesen, J.; et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann. Rheum. Dis.* **2017**, *76*, 1426–1431. [CrossRef]
43. Tweehuysen, L.; van den Bemt, B.J.F.; van Ingen, I.L.; de Jong, A.J.L.; van der Laan, W.H.; van den Hoogen, F.H.J.; den Broeder, A.A. Subjective Complaints as the Main Reason for Biosimilar Discontinuation after Open-Label Transition from Reference Infliximab to Biosimilar Infliximab. *Arthritis Rheumatol.* **2018**, *70*, 60–68. [CrossRef]
44. Valido, A.; Silva-Dinis, J.; Saavedra, M.J.; Iria, I.; Gonçalves, J.; Lopes, J.P.; Fonseca, J.E. Efficacy, immunogenicity and cost analysis of a systematic switch from originator infliximab to biosimilar CT-P13 of all patients with inflammatory arthritis from a single center. *Acta Reum. Port.* **2019**, *44*, 303–311. (In English)
45. Morita, A.; Nishikawa, K.; Yamada, F.; Yamanaka, K.; Nakajima, H.; Ohtsuki, M. Safety, efficacy, and drug survival of the infliximab biosimilar CT-P13 in post-marketing surveillance of Japanese patients with psoriasis. *J. Dermatol.* **2022**, *49*, 957–969. [CrossRef]
46. Provenzano, G.; Arcuri, C.; Miceli, M.C. Open-label non-mandatory transitioning from originators to biosimilars in routine clinical care. *Clin. Rheumatol.* **2021**, *40*, 425–427. [CrossRef] [PubMed]
47. Gisondi, P.; Virga, C.; Piaserico, S.; Meneguzzo, A.; Odorici, G.; Conti, A.; Girolomoni, G. Switching from one infliximab biosimilar (CT-P13) to another infliximab biosimilar (SB2) in patients with chronic plaque psoriasis. *Br. J. Dermatol.* **2020**, *183*, 397–398. [CrossRef]
48. Lauret, A.; Moltó, A.; Abitbol, V.; Gutermann, L.; Conort, O.; Chast, F.; Goulvestre, C.; Le Jeunne, C.; Chaussade, S.; Roux, C.; et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. *Semin. Arthritis Rheum.* **2020**, *50*, 1449–1456. [CrossRef]
49. Di Cesare, A.; Tronconi, G.; Fastame, T.M.; Rosi, E.; Pescitelli, L.; Ricceri, F.; Prignano, F. SB5 adalimumab biosimilar in the treatment of psoriasis and psoriatic arthritis. *Derm. Ther.* **2020**, *33*, e13435. [CrossRef] [PubMed]
50. Gladman, D.D.; Antoni, C.; Mease, P.; Clegg, D.O.; Nash, P. Psoriatic arthritis: Epidemiology, clinical features, course, and outcome. *Ann. Rheum. Dis.* **2005**, *64* (Suppl. 2), ii14–ii17. [CrossRef]
51. Jfri, A.; Nassim, D.; O'Brien, E.; Gulliver, W.; Nikolakis, G.; Zouboulis, C.C. Prevalence of Hidradenitis Suppurativa: A Systematic Review and Meta-regression Analysis. *JAMA Dermatol.* **2021**, *157*, 924–931. [CrossRef]
52. Available online: https://www.aifa.gov.it/sites/default/files/pp_biosimilari_27.03.2018.pdf (accessed on 15 January 2023).
53. Vogler, S.; Schneider, P.; Zuba, M.; Busse, R.; Panteli, D. Policies to Encourage the Use of Biosimilars in European Countries and Their Potential Impact on Pharmaceutical Expenditure. *Front. Pharmacol.* **2021**, *12*, 625296. [CrossRef]
54. Gisbert, J.P.; Chaparro, M. Switching from an originator anti-TNF to a biosimilar in patients with inflammatory bowel disease: Can it be recommended? A systematic review. *Gastroenterol. Hepatol.* **2018**, *41*, 389–405. [CrossRef]
55. Moots, R.; Azevedo, V.; Coindreau, J.L.; Dörner, T.; Mahgoub, E.; Mysler, E.; Scheinberg, M.; Marshall, L. Switching between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician. *Curr. Rheumatol. Rep.* **2017**, *19*, 37. [CrossRef] [PubMed]
56. Krishna, M.; Nadler, S.G. Immunogenicity to Biotherapeutics—The Role of Anti-drug Immune Complexes. *Front. Immunol.* **2016**, *7*, 21. [CrossRef]
57. Mitrev, N.; Leong, R.W. Therapeutic drug monitoring of anti-tumor necrosis factor-α agents in inflammatory bowel disease. *Expert. Opin. Drug. Saf.* **2017**, *16*, 303–317. [CrossRef] [PubMed]
58. van Schouwenburg, P.A.; van de Stadt, L.A.; de Jong, R.N.; van Buren, E.E.; Kruithof, S.; de Groot, E.; Hart, M.; van Ham, S.M.; Rispens, T.; Aarden, L.; et al. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralization. *Ann. Rheum. Dis.* **2013**, *72*, 104–109. [CrossRef]
59. Bartelds, G.M.; Krieckaert, C.L.; Nurmohamed, M.T.; van Schouwenburg, P.A.; Lems, W.F.; Twisk, J.W.; Dijkmans, B.A.; Aarden, L.; Wolbink, G.J. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* **2011**, *305*, 1460–1468. [CrossRef]
60. Colloca, L.; Panaccione, R.; Murphy, T.K. The Clinical Implications of Nocebo Effects for Biosimilar Therapy. *Front. Pharmacol.* **2019**, *10*, 1372. [CrossRef] [PubMed]

61. Colloca, L.; Miller, F.G. The nocebo effect and its relevance for clinical practice. *Psychosom. Med.* **2011**, *73*, 598–603. [CrossRef] [PubMed]
62. Kravvariti, E.; Kitas, G.D.; Sfikakis, P.P. The role of the Nocebo effect in the use of biosimilars in routine rheumatology clinical practice. *Mediterr. J. Rheumatol.* **2019**, *30* (Suppl 1), 63–68. [CrossRef]
63. Sarnola, K.; Merikoski, M.; Jyrkkä, J.; Hämeen-Anttila, K. Physicians' perceptions of the uptake of biosimilars: A systematic review. *BMJ Open* **2020**, *10*, e034183. [CrossRef]
64. Petit, J.; Antignac, M.; Poilverd, R.M.; Baratto, R.; Darthout, S.; Desouches, S.; Louati, K.; Deparis, N.; Berenbaum, F.; Beauvais, C. Multidisciplinary team intervention to reduce the nocebo effect when switching from the originator infliximab to a biosimilar. *RMD Open* **2021**, *7*, e001396. [CrossRef]
65. Salaffi, F.; Ciapetti, A.; Carotti, M.; Gasparini, S.; Gutierrez, M. Disease activity in psoriatic arthritis: Comparison of the discriminative capacity and construct validity of six composite indices in a real world. *Biomed. Res. Int.* **2014**, *2014*, 528105. [CrossRef]
66. Rothwell, P.M. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* **2005**, *365*, 82–93. [CrossRef] [PubMed]
67. Available online: https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf (accessed on 15 January 2023).
68. Available online: https://www.verywellhealth.com/top-biologic-drugs-2663233#:~:text=Humira&text=The%20anti%2Dinflammatory%20drug%20Humira,drugs%20worldwide%2C%20regardless%20of%20class (accessed on 15 January 2023).
69. Kurki, P.; Barry, S.; Bourges, I.; Tsantili, P.; Wolf-Holz, E. Safety, immunogenicity and interchangeability of biosimilar monoclonal antibodies and fusion proteins: A regulatory perspective. *Drugs* **2021**, *81*, 1881–1896. [CrossRef]
70. Scavone, C.; Sportiello, L.; Rafaniello, C.; Mascolo, A.; Sessa, M.; Rossi, F.; Capuano, A. New era in treatment options of chronic hepatitis C: Focus on safety of new direct-acting antivirals (DAAs). *Expert. Opin. Drug. Saf.* **2016**, *15* (Suppl. 2), 85–100. [CrossRef] [PubMed]
71. Rafaniello, C.; Pozzi, M.; Pisano, S.; Ferrajolo, C.; Bertella, S.; Sportiello, L.; Carnovale, C.; Sullo, M.G.; Cattaneo, D.; Gentili, M.; et al. Second generation antipsychotics in 'real-life' paediatric patients. Adverse drug reactions and clinical outcomes of drug switch. *Expert. Opin. Drug. Saf.* **2016**, *15* (Suppl. 2), 1–8. [CrossRef] [PubMed]