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SYSTEMATIC REVIEW

Efficacy and Safety Outcomes for Originator TNF Inhibitors and Biosimilars in Rheumatoid Arthritis and Psoriasis Trials: A Systematic Literature Review

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Abstract

Objective Regulatory approval of biosimilar versions of originator biotherapeutics requires that new biological products be highly similar to originator products, with no clinically meaningful differences in safety, purity, and potency. In some trials of biosimilars of tumor necrosis factor inhibitors for the treatment of rheumatoid arthritis (RA) and plaque psoriasis (PsO), pre-specified margins for efficacy and safety have been met, but differences in treatment responses between pivotal originator trials and biosimilar trials have been noted. The objective of this systematic review was to examine these differences.

Methods Searches were conducted to identify comparative randomized clinical trials of approved or proposed biosimilars of adalimumab, etanercept, and infliximab.

Results Of 83 publications identified, 16 publications were included for analysis (RA: originators, $n = 5$; biosimilars, $n = 6$; PsO: originators, $n = 2$; biosimilars, $n = 3$). American College of Rheumatology 20% response rates were higher among patients with RA receiving originator biologics and biosimilars in biosimilar trials than among patients receiving the originator biologics in pivotal trials. In etanercept studies in PsO, a difference was observed in Psoriasis Area and Severity Index 75% response rates between biosimilar and pivotal trials. Insufficient efficacy data were available from adalimumab and infliximab biosimilar studies in PsO to determine any differences in treatment responses between pivotal and biosimilar studies.

Conclusions Observed differences in treatment response rates between pivotal originator trials and trials of originator biologics and their respective biosimilars may be attributable to fundamental differences in study design and/or baseline patient characteristics, which require further analysis.

Key Points

Biosimilarity between originator and biosimilar tumor necrosis factor inhibitors for the treatment of rheumatoid arthritis and plaque psoriasis has been demonstrated, but differences in treatment responses and safety outcomes between pivotal originator trials and recent biosimilar trials have been noted.

This systematic literature review comparing pivotal originator biologic trials with head-to-head trials of originator biologics and biosimilars indicates an overall similarity in baseline characteristics between the two types of studies, yet identifies some differences in responses to treatment.

The reasons for the noted differences in both efficacy and safety between the pivotal trials of originators and their respective biosimilars are currently only speculative.

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1 Introduction

Regulatory approval of biosimilar versions of originator biotherapeutics requires that new biological products be highly similar to originator products, with no clinically meaningful differences in safety, purity, and potency [1, 2]. Head-to-head comparison with the originator product is required at all stages of the biosimilar development pathway. Analytical studies establish high similarity, followed by pre-clinical and clinical studies to demonstrate the same level of efficacy and safety already established for the originator product. A phase I and a phase III clinical study can be sufficient to achieve regulatory approval for biosimilars [3]. Pre-specified margins for equivalence in efficacy supporting biosimilarity have been met in comparative trials of biosimilars of tumor necrosis factor inhibitors (TNFis) in rheumatoid arthritis (RA) [4–9] and plaque psoriasis (PsO) [10–12], but differences in treatment responses and safety outcomes between pivotal originator trials [13–19] and recent biosimilar trials [4–12] have also been noted. The objective of this systematic review was to examine differences in efficacy and safety between pivotal originator biologic trials and biosimilar trials in RA and PsO.

2 Methods

A systematic literature review (SLR) was conducted to obtain comprehensive, up-to-date data on the efficacy and safety of biosimilars of adalimumab, etanercept, and infliximab in the treatment of adults with RA and PsO. This SLR included randomized clinical trials where patients were treated with the originator biologics adalimumab, etanercept, and infliximab, and their biosimilars ABP 501 (Amjevita), SB5, M923, MSB 11022, GP2017, CHS-1420, CT-P17, SB4 (Benepali), GP2015 (Erelzi), CHS-0214, CT-P05, CT-P13 (Remsima or Inflectra), SB2 (Flixabi), and GP1111. Pivotal studies were head-to-head comparisons between originator and placebo. Study outcomes were efficacy (American College of Rheumatology [ACR] 20/50/70% response rates, Disease Activity Score in 28 joints [DAS28], Psoriasis Area Severity Index [PASI] 50/75/90% response rates) and safety (adverse events [AEs], serious AEs [SAEs], and anti-drug antibodies [ADAbs]).

This SLR was conducted using a standardized, thorough, and transparent approach following Cochrane dual-reviewer methodology [20]. The SLR protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol (PRISMA-P) guidelines [21]. All processes and methodologies used to conduct this SLR are described fully in the Electronic Supplementary Material (ESM).

3 Results

3.1 Search and Screening

The initial list of 351 publications was screened on December 7, 2016. After removing duplicates, 265 titles and abstracts were screened for relevance; 146 references underwent full-text screening and 83 references were quality assessed and retained for full data extraction (Fig. 1). Most references were of excellent or good quality (Supplementary Tables 1 and 2, see ESM). Of the 83 publications, 34 and 16 reported on originator trials in RA and PsO, respectively, and 29 and 6 on biosimilar trials in those conditions. Two publications contained data for both RA and PsO. Biologic pivotal trials were identified through screening of systematic reviews.

Of the 83 selected publications, only those that reported on studies in disease-modifying anti-rheumatic drug (DMARD)-experienced patients who were treated with the same biologic dosages and assessed at the same time points were selected for final analysis (N = 16: RA originators, n = 5; RA biosimilars, n = 6; PsO originators, n = 2; PsO biosimilars, n = 3). Studies of adalimumab and infliximab biosimilars in PsO did not report sufficient efficacy data and were not included. For RA, two pivotal originator studies were identified for adalimumab [13, 14], and one each for etanercept [15] and infliximab [16, 17]. One pivotal originator PsO study was identified for etanercept [18] and one for adalimumab [19]. All pivotal studies demonstrated efficacy of active treatment versus placebo (statistically significantly higher ACR and PASI response rates for RA and PsO studies, respectively [13–19]).

3.2 Baseline Characteristics

Compared with the pivotal originator studies [13–19], biosimilar studies had larger sample sizes, included patients with a shorter disease duration, and were conducted in a wider range of countries [4–12] (Supplementary Table 3, see ESM). Beyond that, baseline patient characteristics were similar across the studies, with the following exceptions: in the RA study of SB4 (etanercept biosimilar) [6], mean patient age was higher and mean disease duration was shorter compared with the pivotal etanercept study [15]; in the RA study of SB2 (infliximab biosimilar) [8], mean disease duration was shorter and mean values for tender joint count (TJC) and swollen joint count (SJC) were lower than in the pivotal infliximab originator study [16, 17]. In most studies, there was not enough information to assess baseline differences in DAS28, TJC, or SJC.

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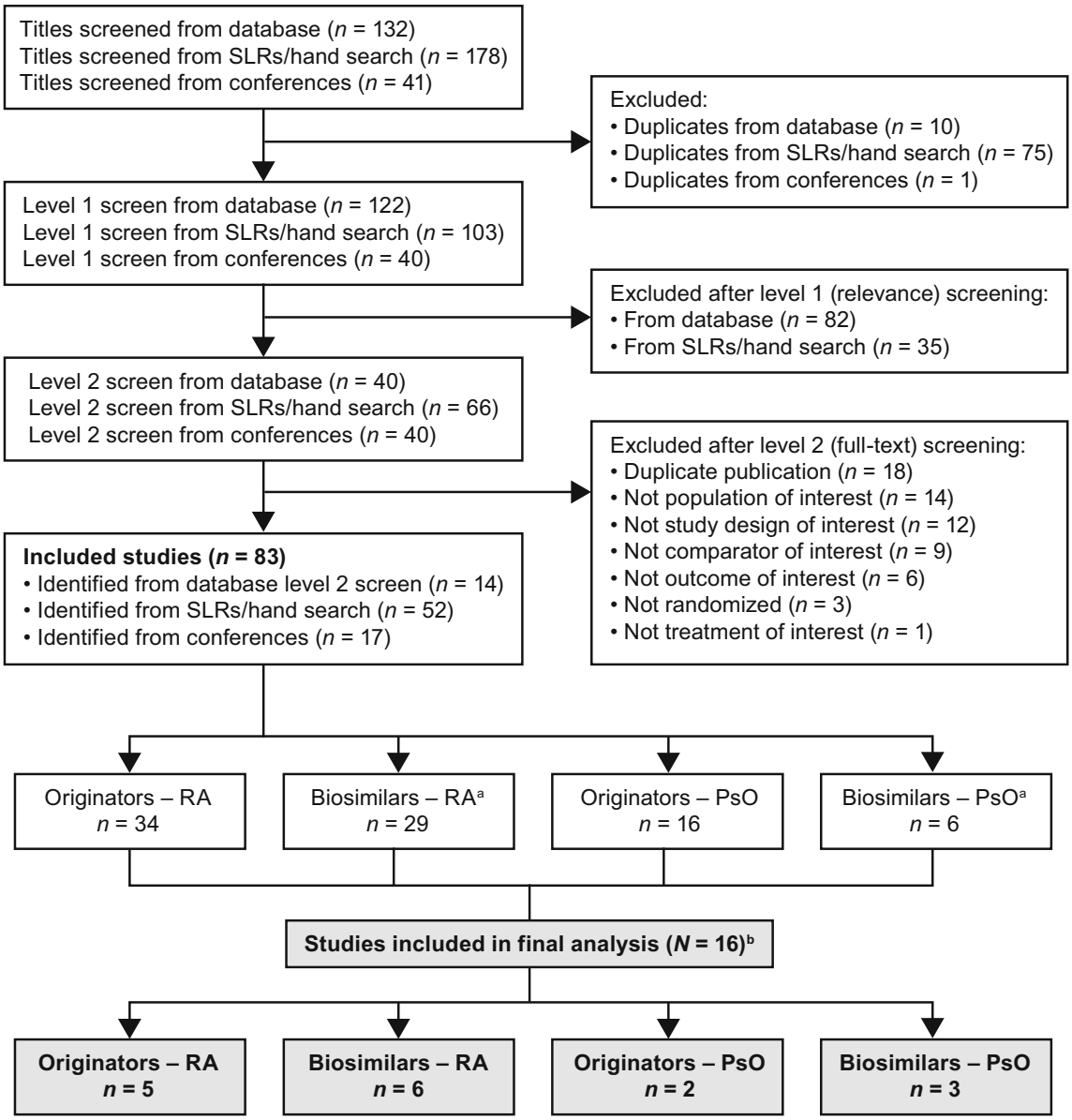

Fig. 1 Flow of papers screened and retained in the SLR. *DMARD* disease-modifying anti-rheumatic drug, *PsO* plaque psoriasis, *RA* rheumatoid arthritis, *SLR* systematic literature review. [a]Two abstracts contained data for both RA and PsO. [b]Only those publications that reported on studies in DMARD-experienced patients who were treated with the same biologic dosages and assessed at the same time points were selected for final analysis

3.3 Efficacy Outcomes

In the biosimilar studies, ACR20 response rates for both the originator and the biosimilar were numerically higher than those in the pivotal originator studies for all treatments. The same trend was observed for ACR50 and ACR70 in the etanercept biosimilar studies, and for ACR70 in the infliximab studies (Table 1), but there were exceptions. The two pivotal studies of adalimumab had very different ACR50 response rates (39% [13] and 55% [14]). The ABP 501 biosimilar study [4] had adalimumab/biosimilar ACR50 response rates similar to the Weinblatt pivotal study [14], but the SB5 biosimilar study [5] had adalimumab/biosimilar ACR50 response rates that more closely resembled the Keystone pivotal study [13] (Table 1). The pivotal study ACR70 response rates were more similar to each other than was seen for ACR50 [13, 14], and the ACR70 response rates for the adalimumab/biosimilar studies closely resembled these (ranging from 19 to 26%, Table 1). The ACR50 response rate for infliximab in the SB2 [8] and CT-P13 [9] biosimilar studies was lower than that seen in the pivotal originator study [16, 17], but the response rates for the biosimilars were higher (Table 1).

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Table 1 Comparison of ACR response rates in pivotal versus biosimilar studies in patients with RA

	ACR20	ACR50	ACR70
Response at 24 weeks: ADA vs biosimilars			
ADA from pivotal study 1 [13]	63	39	21
ADA from pivotal study 2 [14]	67	55	27
ADA from ABP 501 study [4]	72	52	23
ABP 501 [4]	75	49	26
ADA from SB5 study [5]	72	40	20
SB5 [5]	73	38	19
Response at 24 weeks: ETN vs biosimilars			
ETN from pivotal study [15]	71	39	15
ETN from SB4 study [6]	80	42	23
SB4 [6]	78	47	26
ETN from CHS-0214 study [7]	91	64	38
CHS-0214 [7]	91	68	38
Response at 30 weeks: INF vs biosimilars			
INF from pivotal study [16, 17]	50	27	8
INF from SB2 study [8]	59	16	17
SB2 [8]	56	31	16
INF from CT-P13 study [9]	59	17	16
CT-P13 [9]	61	35	34

ACR American College of Rheumatology, *ADA* adalimumab, *ETN* etanercept, *INF* infliximab, *RA* rheumatoid arthritis

In the only PsO study assessed, the PASI75 response rates at 12 weeks for etanercept (72%) and GP2015 (70%) in the biosimilar study [10] were greater than the corresponding rate for etanercept in the pivotal originator study (49%) [18].

3.4 Safety Outcomes

There were no comparable safety outcomes for pivotal originator and biosimilar studies of adalimumab in RA. In the two head-to-head studies of etanercept versus the biosimilars SB4 [6] and CHS-0214 [7], the occurrence of ADAbs following treatment with etanercept was higher than the occurrence of ADAbs in the pivotal etanercept study [15]; the opposite was the case with ADAb occurrence for either biosimilar (Supplementary Table 4a, see ESM). The occurrence of injection site reactions (ISRs) was lower for etanercept and SB4 in the biosimilar study [6] than for etanercept in the pivotal study [15], which was also observed for etanercept and CHS-0214 [7, 15]. In the head-to-head study of infliximab versus SB2 [8], the occurrence of SAEs was similar between both the infliximab and SB2 arms in the biosimilar study [8] and the infliximab arm in the pivotal originator infliximab study [16, 17]. The percentage of patients with a skin rash was lower in the SB2 [8] and CT-P13 [9] biosimilar studies than in the pivotal originator infliximab study [16, 17] (Supplementary Table 4b, see ESM).

There were no comparable safety outcomes for pivotal originator and biosimilar studies of infliximab in PsO. In the only PsO study of adalimumab versus the biosimilar ABP 501 [12], the percentage of patients with SAEs was higher for both adalimumab (5.1%) and ABP 501 (4.6%) than for adalimumab (1.8%) in the pivotal originator study [19]. The occurrence of ISRs with adalimumab in the biosimilar study was higher than that observed in the pivotal originator study of adalimumab (5.2 versus 3.2%) but lower with ABP 501 (1.7%) (Supplementary Table 4c, see ESM). In the only PsO study of etanercept versus the biosimilar GP2015, ISRs were reported in fewer etanercept-treated (14.2%) and GP2015-treated patients (4.9%) in the biosimilar study [10] compared with etanercept-treated patients (18.0%) in the pivotal originator study [18] (Supplementary Table 4d, see ESM).

4 Discussion

This SLR of pivotal originator biologic trials versus head-to-head trials of originator biologics and biosimilars indicates, as expected, an overall similarity in baseline characteristics between the two types of studies, yet identifies some differences in responses to treatment.

This SLR did not establish any major differences in the baseline characteristics of the patients in the pivotal originator versus biosimilar trials other than disease duration, which was lower for the RA biosimilar trials than the pivotal trials (where reported). However, it should be noted that this analysis was based on publicly available information only (additional clinical information is available in the European public assessment reports and FDA reports) and that there may have been between-trial differences that could not be identified. For example, biosimilar trials tended to recruit patients from a wider range of countries than pivotal originator trials [22], which may have resulted in study population differences that were not captured using standard baseline parameters (such as genetic variations affecting drug metabolism or cultural attitudes to medication) but might affect study results. Additionally, patient status in the two trial groups was arguably different because of the decades of additional research on both treatments and treatment strategies that patients in the biosimilar studies benefited from. Patients in the pivotal originator studies had access to lower-quality treatment and fewer treatment options before commencing biological therapy.

This systematic review showed that ACR20 and PASI75 response rates were higher in biosimilar studies compared

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with pivotal originator studies. This was also observed in a recently published study of the etanercept biosimilar GP2015, where ACR20 response at week 24 was 88.8% for GP2015 and 93.6% for etanercept [23] compared with 71% in the pivotal study [15]. Higher response rates in the biosimilar trials could be due, at least in part, to a longer disease duration in the pivotal originator trials. It is also possible that the absence of a placebo arm in the biosimilar studies resulted in higher expectations among patients and investigators as all participants knew they were receiving active treatment; it has been previously reported that using active comparators only is associated with increased effect sizes compared with placebo-controlled studies [24–28]. Indeed, ACR20/50/70 responses from open-label trials of originator etanercept [29–31] more closely resemble the results from the biosimilar trials reviewed here than the pivotal originator etanercept trial, suggesting that the open-label design can impact treatment efficacy. However, there are many variations in trial design, patient population, and study type between these etanercept studies and the biosimilar studies that must be taken into consideration when assessing the impact of open-label treatment on efficacy outcomes. Other differences in trial design could also contribute, each in part, to the differences seen between efficacy results in different trials. Finally, biological differences between products in the pivotal originator and biosimilar trials would also contribute to the differences in efficacy results seen in these studies.

Comparison of safety data was limited, as the available data were too scarce to allow a useful comparison between pivotal and biosimilar studies. Where safety outcomes could be compared, the rates of ADAbs, ISRs, and skin rashes were generally lower for both the originator and biosimilar treatments in the biosimilar trials of RA than in the pivotal originator trials (Supplementary Tables 4a, b, see ESM). These discrepancies are likely to be the result of many interplaying factors. For instance, the pivotal and biosimilar studies often used different laboratory testing methods; the pivotal studies used enzyme-linked immunosorbent assays to assess ADAbs, whereas the biosimilar studies used electrochemiluminescence immunoassays. Since the pivotal studies were conducted, improvements have been made in clinical techniques (such as detection methods for etanercept ADAbs) and updates made to MedDRA coding. ADAb monitoring has become more rigorous; in the biosimilar trials, monitoring was carried out throughout the trial, whereas in the pivotal trials it was carried out on Day 1 and at study end only. Patients may be more comfortable with products after 10–20 years of commercial use, meaning that they might be less likely to report AEs.

The major limitation of this SLR was the small number of studies available for comparison. The numbers of patients in the pivotal originator studies were also small compared with the biosimilar studies.

5 Conclusion

Although the biosimilars of biologics for inflammatory diseases were shown to be comparable with the originator products throughout the regulatory approval process, there are numerical differences in both efficacy and safety outcomes between the pivotal trials of originators and confirmatory clinical trials of their respective biosimilars. The reasons for these differences are currently only speculative.

Author Contributions All authors contributed to the development of the systematic literature review that forms the basis of this manuscript, were involved in drafting the manuscript and revising it critically for important intellectual content, and approved the final version for publication. All authors are accountable for all aspects of the work. RJM is the guarantor for the overall content.

Compliance with Ethical Standards

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Conflict of interest Robert J. Moots has received research grants from AKL Pharmaceuticals, UCB Pharma, Novartis, and Pfizer; consulting fees from Chugai, Novartis, Pfizer, Roche, and Sandoz; support for travel to meetings where presenting research from Chugai, Novartis, Pfizer, Roche, and Sandoz; provision of writing assistance from Engage Scientific Solutions; and payment for lectures including service on speakers bureaus from Chugai, Pfizer, and Roche. Catherine Rolland is an employee of Envision Pharma Group and was a paid consultant to Pfizer in connection with the development of this manuscript. Eduardo Mysler has no conflicts to declare. Cinzia Curiale, Danielle Petersel, and Heather Jones are employees of and hold stock in Pfizer.

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