Psoriasis is a chronic, inflammatory, lifelong disease with a high prevalence (afflicting approximately 1–5% of the population worldwide) and is associated with significant morbidity. The introduction of biologic therapies has improved the management of this disease. Multiple biologic medicines that block cytokine signaling, including tumor necrosis factor (TNF) antagonists (adalimumab, etanercept, and infliximab) and inhibitors of interleukin (IL)-17 (brodalumab, ixekizumab, and secukinumab), IL-23 (guselkumab), or IL-12/23 (ustekinumab), are approved for the treatment of psoriasis. Despite the clinical benefits associated with use of biologics in psoriasis, many patients are not treated with biologic therapy, and access to treatment may be limited for various reasons, such as high treatment costs.

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INTRODUCTION

Psoriasis is a chronic, inflammatory disease that affects between 1% and 5% of the population worldwide [1]. Psoriasis is associated with significant morbidity and imparts a negative impact on health-related quality of life similar to the impact of depression, diabetes mellitus, and congestive heart failure [1, 2]. Indeed, patients with psoriasis often experience social stigmatization, pain, discomfort, physical disability, psychological distress, and financial hardship [3]. Psoriasis is also associated with an increased prevalence of comorbid diseases and risk factors, such as obesity, metabolic syndrome, cardiovascular disease, psoriatic arthritis (PsA), and autoimmune disease [4]. Furthermore, severe psoriasis is associated with an increased risk of mortality, most commonly due to cardiovascular death [5].

Psoriasis is a lifelong disease, and long-term treatment is necessary to manage the debilitating and serious consequences of this condition. Biologic therapies have changed the way psoriasis is managed, offering systemic treatments that target key mechanisms of disease pathogenesis. Biologics approved for the treatment of psoriasis include tumor necrosis factor (TNF) antagonists (adalimumab, etanercept, and infliximab), interleukin (IL)-17 antagonists (brodalumab, ixekizumab, and secukinumab), and inhibitors of IL-23 (guselkumab) or IL-12/23 (ustekinumab) [6–19].

Patents for many biologics are expiring [20], thus granting others besides the patentees the ability to make or sell the off-patented products. This has led to the development and approval of biosimilars. A biosimilar is a biologic product that is highly similar to an approved biologic (i.e., originator or reference) product, “notwithstanding minor differences in clinically inactive components,” and has no clinically meaningful differences in safety, purity, and potency from the reference product [21]. This review provides dermatologists and those who treat and/or manage psoriasis with a working knowledge of the scientific principles for biosimilar development. It also examines real-world experience with biosimilars that may enable physicians to make informed decisions for treatment of patients with psoriasis.

Compliance with Ethics Guidelines

This article does not involve any new studies of human or animal subjects performed by any of the authors.

CHALLENGES WITH BIOLOGIC THERAPY FOR PSORIASIS: THE ROLE OF BIOSIMILARS

Despite the benefits associated with clinical use of biologics in patients with psoriasis or PsA [18, 22–32], not all patients with these diseases receive biologic therapy [33–37]. In a 2011 National Psoriasis Foundation survey of patients with psoriasis or PsA in the USA, fewer than 30% reported receiving biologic therapies [33]. Similarly, in the 2012 Multinational Assessment of Psoriasis and Psoriatic Arthritis survey of patients, dermatologists, and rheumatologists in North America and Europe, 5–25.9% of patients with moderate-to-severe psoriasis or PsA reported receiving biologic therapies [34–36]. Physician-reported estimates of prescribing biologic therapies were higher (dermatologists, 19.6–46.9%; rheumatologists, 33.4–52.7%), but also indicated underutilization [36, 37].

Concerns regarding safety and/or tolerability and lack or loss of effectiveness were the most common reasons that patients discontinued treatment or why physicians did not initiate or continue patients’ treatment with biologic therapies [33–37]. However, patients, dermatologists, and rheumatologists also reported inadequate insurance coverage and/or cost as a contributing factor [33–37]. The extent or absence of insurance coverage impacts treatment costs, and such factors can create financial barriers that limit or contribute to inequalities in access to biologic therapies. This is particularly true in regions such as Latin America where biologics used to treat moderate-to-severe psoriasis are reimbursed in some (e.g.,
Argentina, Colombia, Mexico, Venezuela) but not other (e.g., Brazil, Chile) countries [38, 39].

The percentage of patients with moderate-to-severe psoriasis worldwide who could benefit from biological therapy may increase if financial constraints were improved. Patents for adalimumab, etanercept, and infliximab have expired or will soon expire in Europe and in the USA [20]. As a result, anti-TNF biosimilars are available or in development. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved biosimilars of adalimumab [Amjevita/Solymbic and Imraldi (EMA); Amjevita (FDA) and Cyltezo (EMA and FDA)], etanercept [Benepali (EMA) and Erelzi (EMA and FDA)], and infliximab [Remsima/Inflectra and Flixabi (EMA); Inflectra, Ixifi, and Renflexis (FDA)] (Table 1) [40–59]. Additional biosimilars are under review by these regulatory agencies, and more are in research and development (Table 2) [60–63]. As a treatment option for patients with psoriasis, biosimilars may provide savings and efficiencies to healthcare systems and increase patient access to therapy, improving the problem of underutilization of biologic therapy [64–66].

REGULATORY FRAMEWORK FOR BIOSIMILAR DEVELOPMENT AND APPROVAL: A GLOBAL PERSPECTIVE

Biologic medicines include a range of products that are isolated from natural sources or manufactured using living systems. Biologics are typically 100- to 1000-fold larger than chemically synthesized drugs and have molecular structures that are not as easily characterized [67]. Many biologics are proteins developed through recombinant DNA technology. This multistep process is technically challenging, and knowledge about the development of a biologic is proprietary and confidential to the manufacturer [68]. Consequently, a biosimilar developer must use reverse-engineering manufacture to independently establish a new production process capable of delivering a drug that is highly similar to the originator [68, 69].

Variability in or changes to any step of the manufacturing process for a biologic or differences between the manufacturing processes for an originator and biosimilar can substantially impact the physicochemical and functional properties of a biologic product (Fig. 1) [68, 69]. For this reason, and because of the size and complexity of biologics, it is not possible to create an exact copy of an originator drug. Therefore, developers must demonstrate biosimilarity between the proposed biosimilar and the licensed product [21, 70–72], which means “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product” [21]. This is in contrast to regulatory approval of small-molecule generics, which only requires a demonstration of pharmaceutical equivalence and bioequivalence.

The process of biosimilar development and approval is well regulated in many countries, with guidelines developed by the EMA, FDA, Health Canada, and World Health Organization (WHO), among others [21, 70–74]. Regulatory agencies recommend using a stepwise approach to generate data that support a demonstration of biosimilarity [21, 70–72]. As a first step, guidelines recommend extensive analytical (structural and functional) assessments, beginning with a detailed analysis of the primary amino acid sequence and secondary and tertiary structure for the potential biosimilar and the originator [21, 71–74].

Additional relevant characterization studies are usually conducted to confirm similarity between the potential biosimilar and originator and may include higher-order structural analyses of dimers or other complexes, post-translational modifications, and other potential variations (e.g., deamidation and oxidation) that could impact the biologic activity of the protein [21, 72, 74]. For example, immunoglobulin (Ig) class G (IgG) therapeutic proteins are typically glycosylated, and the degree of glycosylation at the Fc (crystallizable fragment) domain affects
their interaction with target cells and subsequent effector functions [67, 75, 76]. IgGs lacking terminal galactose demonstrate reduced binding to complement protein C1q, resulting in reduced complement-dependent cytotoxicity [76]. By contrast, IgGs lacking the core fucose residue demonstrate enhanced binding to the Fc receptor FcγRIIIa and, therefore, show increased antibody-dependent cellular cytotoxicity [76]. The presence of high mannose or sialeylated glycans can also affect IgG binding and, as a consequence, increase or decrease antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [77]. In addition, high-mannose glycans can influence protein half-life by increasing serum clearance of IgG [75]. Furthermore, deamidation, oxidation, and other chemical modifications that promote degradation could lead to the formation of protein aggregates that exhibit little or no drug activity and increase the potential for immunogenicity [78].

Next, in vitro studies of biologic activity, and any other relevant characteristics, are conducted to confirm that the biosimilar acts on the same target or physiologic process and with similar potency as the originator [21, 71–74]. The potential impact of (even subtle) differences in structure or function between the biosimilar and originator on efficacy and safety may not be clear on the basis of analytical data alone and, therefore, must be further evaluated in nonclinical and clinical studies. Nonclinical

Table 1 Anti-TNF biosimilars approved in Europe and the USA for the treatment of patients with moderate-to-severe plaque psoriasis

| Reference product, brand name (INN) | Biosimilar | Brand name (INN); year of authorizationa | Indication(s) testedb | PASI (%), biosimilar product | PASI (%), reference product |
|-------------------------------------|------------|----------------------------------------|----------------------|----------------------------|---------------------------|
| Humira (adalimumab)                | ABP 501    | Amgevita/Solyctic (adalimumab); 2017 [52] | Moderate-to-severe plaque psoriasis; moderate-to-severe RA [58, 59] | Week 16 | 82.7 |
|                                     |            | Amjevita (adalimumab-atto); 2016 [49]   |                      | Week 16 | 47.4 |
| BI 695501                           |            | Cyltezo (adalimumab); 2017 [52]         | Moderate-to-severe active RA [53] | NA | NA |
| SB5                                |            | Imraldi (adalimumab); 2017 [52]         | Moderate-to-severe RA [57] | NA | NA |
| Enbrel (etanercept)                 | SB4        | Benepali (etanercept); 2016 [52]        | RA [41]              | NA | NA |
| GP2015                              |            | Erelzi (etanercept); 2017 [52]          | Moderate-to-severe plaque psoriasis [42] | Week 12 | 75.7 |
|                                     |            | Erelzi (etanercept-szz); 2016 [43]      |                      | Week 12 | 75.7 |
| Remicade (infliximab)               | SB2        | Flixabi (infliximab); 2016 [52]         | Moderate-to-severe RA [40] | NA | NA |
|                                     |            | Renflexis (infliximab-adba); 2017 [50]  |                      | NA | NA |
| CT-P13                              |            | Inflectra/Remsima (infliximab); 2013 [52] | AS; RA [44, 45, 47, 48, 54] | NA | NA |
|                                     |            | Inflectra (infliximab-dyyb); 2016 [46]  |                      | NA | NA |
| PF-06438179/GP1111                  | –c         | Izifi (infliximab-qbtx); 2017 [56]      | RA [55]              | NA | NA |

AS ankylosing spondylitis, EMA European Medicines Agency, FDA US Food and Drug Administration, INN International Nonproprietary Name, NA not applicable, NR not reported, PASI Psoriasis Area and Severity Index, RA rheumatoid arthritis, TNF tumor necrosis factor

a Authorization by EMA or FDA
b Refers to comparative efficacy and safety trials of biosimilar to reference product(s)
c Marketing authorization application was submitted for review by EMA, May 2017 [62]
in vivo studies include assessment of toxicokinetics and/or toxicity [21, 72, 73]. The need for and extent of in vivo animal studies will depend on “the extent of known similarities or differences” between the proposed biosimilar and originator, as determined through analytical assessments [21]. However, regulatory agencies may be moving away from requiring in vivo nonclinical evaluation because extensive physicochemical and in vitro biological

| Reference product | Proposed biosimilar (Pharma) | Stage of development |
|-------------------|-----------------------------|----------------------|
| Adalimumab        | BCD-057 (Biocad)            | Clinical trials (phase III in moderate-to-severe plaque psoriasis)* |
|                   | CHS-1420 (Coherus BioSciences Inc) | Clinical trials (phase III in moderate-to-severe plaque psoriasis)* |
|                   | FKB327 (Fujifilm Kyowa Kirin Biologics Co, Ltd) | Clinical trials (phase III in active RA)*; submitted for review by EMA, May 2017 [61] |
|                   | GP2017 (Sandoz)             | Clinical trials (phase III in moderate-to-severe active RA and moderate-to-severe plaque psoriasis)*; submitted for review by EMA, May 2017 [62] |
|                   | LBAL (LG Life Sciences Ltd/Mochida Pharmaceutical Co, Ltd) | Clinical trials (phase III in active RA)* |
|                   | M923 (Momenta Pharmaceuticals Inc) | Clinical trials (phase III in moderate-to-severe plaque psoriasis)* |
|                   | MSB11022 (EMD Serono Research & Development Institute, Inc/Merck KGaA) | Clinical trials (phase III in moderate-to-severe plaque psoriasis, and moderate-to-severe active RA)*; submitted for review by EMA, December 2017 [63] |
|                   | Myl-1401A (Mylan)           | Clinical trials (phase III in moderate-to-severe chronic plaque psoriasis)* |
|                   | ONS-3010 (Oncobiologics Ltd) | Clinical trials (phase III in moderate-to-severe plaque psoriasis)* |
|                   | PF-06410293 (Pfizer Inc)    | Clinical trials (phase III in moderate-to-severe active RA)* |
| Etanercept        | CHS-0214 (Coherus BioSciences Inc/ Daichi Sankyo Co, Ltd/Shire) | Clinical trials (phase III in active RA and plaque psoriasis)* |
|                   | LBEC0101 (LG Life Sciences Ltd/ Mochida Pharmaceutical Co, Ltd) | Clinical trials (phase III in active RA)*; submitted for review by Japanese Medicines Regulatory Agency, Jan 2017 [60] |
| Infliximab        | ABP 710 (Amgen)             | Clinical trials (phase III in moderate-to-severe active RA)* |
|                   | BCD-055 (Biocad)            | Clinical trials (phase III in AS, and active RA)* |
|                   | NI-071 (Nichi-Iko Pharmaceutical Co, Ltd) | Clinical trials (phase III in active RA)* |

AS ankylosing spondylitis, Pharma pharmaceutical company, RA rheumatoid arthritis, TNF tumour necrosis factor

* Registered on ClinicalsTrials.gov, the International Clinical Trials Registry Platform, or the European Union Clinical Trials Register
characterization establishes the core of biosimilarity [79].

On the basis of the totality of the evidence from analytical and nonclinical studies, a tailored clinical trial program for the potential biosimilar is designed as a final comparative evaluation to confirm that the product has similar efficacy, safety, and immunogenicity to the originator. Requirements include comparative clinical pharmacokinetics and clinical studies [21, 71–73]. The most suitable design for biosimilarity studies is an equivalence trial because its primary objective is to show that differences between treatment groups are not clinically meaningful [80]. Furthermore, guidelines recommend using a population of patients, treatment setting, and clinical endpoints that are adequately sensitive to identify any potential differences versus the originator [21, 72, 73]. Finally, biosimilarity studies are not required to demonstrate the mechanism of action, dose-finding, or clinical benefit over the current standard treatment because these were established by clinical studies conducted for the originator [72, 81].

BIOSIMILARS IN DERMATOLOGY: KEY ISSUES AND CLINICAL EXPERIENCE

Postapproval Safety Monitoring

As for most biological products, data from preapproval clinical studies of a biosimilar are usually too limited to identify all potential adverse events (AEs) [72]. In addition, preapproval clinical testing is usually insufficient to detect rare but potentially serious safety risks.
because of the small or limited study populations in which the biosimilar is evaluated [21, 72, 73]. Therefore, the WHO and regulatory agencies such as the EMA and FDA recommend postapproval monitoring to evaluate the long-term safety of biosimilar products [21, 72, 73].

In general, the WHO and regulatory agencies recommend that pharmacovigilance plans consider any known or potential safety issues associated with use of the reference product and its class, correspond with plans used for the originator, and include ongoing assessment of immunogenicity [21, 72, 73]. However, regulatory agencies vary in their requirements for postapproval monitoring. For example, the EMA requires that pharmacovigilance and risk management plans are included as part of biosimilars regulatory submissions [73]. By contrast, the FDA has not yet defined a requirement for pharmacovigilance plans [21]. Rather, the agency encourages sponsors to discuss their pharmacovigilance plans with appropriate regulatory divisions as some aspects of postapproval safety monitoring are product-specific [21].

### Extrapolation

Biosimilar guidelines permit extrapolation of data, allowing the approval of a biosimilar for use in an indication that was not directly studied in a comparative clinical trial with the biosimilar, but for which the originator biologic is approved [21, 70–73]. For example, biosimilars of infliximab [CT-P13 (Inflectra/Remsima), PF-06438179/GP1111 (Ixifi) and SB2 (Flixabi; Renflexis)] were studied in patients with rheumatoid arthritis (RA) and/or ankylosing spondylitis (AS) in the initial development programs [40, 44, 45, 47, 48, 54, 55], but through extrapolation have been approved by the EMA or FDA for all licensed indications of the originator, excluding those protected by data exclusivity [56, 82–86]. The comparative clinical study to assess efficacy and safety of the etanercept biosimilar GP2015 (Erelzi) was conducted in patients with chronic plaque psoriasis [42]. With the application of extrapolation, the EMA and FDA approved GP2015 for all licensed indications of the originator [43, 87]. After being evaluated in a comparative clinical study in patients with RA [41], another etanercept biosimilar, SB4 (Benepali), also was granted marketing authorization by the EMA for the full range of indications of the originator [88, 89].

Similarly, two comparative clinical studies were conducted for the adalimumab biosimilar ABP 501 (Amgevita/Solybmic; Amjevita): one in patients with moderate-to-severe psoriasis and one in patients with moderate-to-severe RA [58, 59]. Both were submitted for regulatory review, and through extrapolation, ABP 501 was approved by the EMA for all licensed indications of the originator and by the FDA for the treatment of RA, juvenile idiopathic arthritis, PsA, AS, psoriasis, adult Crohn’s disease (CD), and ulcerative colitis (UC) [49, 90, 91]. Finally, the adalimumab biosimilars SB5 (Imraldi) and BI 695501 (Cyltezo) were studied in patients with moderate-to-severe RA [53, 57], but through extrapolation SB5 was approved by the EMA for all and BI 695501 was approved by the EMA and FDA for multiple indications of the originator product [51, 92, 93].

Extrapolation reduces the need for clinical studies with the biosimilar in all licensed indications of the originator product [94]. However, there must be sufficient scientific justification for extrapolation that addresses the molecular mechanism(s) of action (e.g., target receptors, binding, dose–response and pattern of molecular signalling upon target binding, and location and expression of the target/receptors) in each indication for which approval is sought; the pharmacokinetics, biodistribution, and immunogenicity of the product in different patient populations; and differences in expected toxicities in each indication and patient population [21, 71–73]. Furthermore, to be considered for extrapolation, biosimilarity to the originator product must be demonstrated using a clinical model that is sensitive to detect potential differences between the originator and the potential biosimilar [21, 71–73]. Safety and immunogenicity of the biosimilar should be sufficiently characterized, and no unique or additional safety issues should be expected for the non-studied indications [72].

Different indications have been seen as the most sensitive clinical model for
extrapolation [95]. For example, in the case of infliximab, psoriasis may be more sensitive than RA to detecting potential differences between an originator and the potential biosimilar because of its greater discriminatory ability in terms of response [e.g., placebo-adjusted difference in response is 74–82% for Psoriasis Area and Severity Index (PASI) 75 vs. 8–25% for American College of Rheumatology 20] [95]. In addition, use of concomitant methotrexate for treatment of RA could confound conclusions about potential differences in immunogenicity [95]. While these considerations are important, regulatory decisions about extrapolation are based on the totality of the evidence, including structural, physicochemical, functional, non-clinical, and clinical data, all of which must support similarity of the biosimilar to the originator [21, 72, 73].

As described, all infliximab and some adalimumab and etanercept biosimilars were approved for psoriasis on the basis of extrapolation of clinical data from studies conducted in patients with rheumatic disease. The lack of clinical data for psoriasis and other extrapolated indications could impact the use of biosimilars in clinical practice. In a survey of US speciality physicians, including dermatologists, gastroenterologists, hematologist-oncologists, medical oncologists, nephrologists, and rheumatologists, only 12.3% of respondents cited they were comfortable with the concept of extrapolation and would use a biosimilar for all approved indications [96]. However, education of physicians about biosimilars could increase their acceptance of indication extrapolation. A cross-sectional survey of dermatologists worldwide reported that physicians who were “fairly to very familiar” with biosimilars were also more comfortable in prescribing biosimilars for psoriasis if studied in a non-psoriasis indication versus physicians who were “very unfamiliar” with biosimilars [97].

**Transitioning or Switching**

With the availability of biosimilars, clinicians may need to consider switching between an originator product and a biosimilar. Clinical decisions about switching should take into account the possible effects of changing therapy on drug efficacy and patient safety [98]. Accordingly, physicians may rely on data from biosimilar studies in which patients transition from one treatment to another (e.g., from A to B, but not vice versa), switch once from each treatment to the other (e.g., single-switch from A to B and from B to A), or switch treatments multiple times (e.g., from A to B to A and from B to A to B) [98].

**Infliximab**

Three randomized controlled trials (RCTs) have compared originator infliximab (Remicade®) and the infliximab biosimilar CT-P13 (Inflectra/Remsima) in patients with rheumatic disease: the PLANETRA trial in patients with RA, the PLANETAS trial in patients with AS, and a phase I/II trial in Japanese patients with RA (Takeuchi et al.) [44, 45, 47, 48, 54]. In each trial, patients who completed the 54-week double-blind treatment phase received CT-P13 in an open-label extension (OLE) study and, therefore, provided data on single transition from originator infliximab to CT-P13 (transition group) versus continued treatment with CT-P13 (maintenance group) [99–101].

All studies demonstrated similar efficacy between transition and maintenance groups after 48 (PLANETRA and PLANETAS) or 72 (Tanaka et al.) weeks [99–101]. Furthermore, in each trial the proportion of patients with anti-drug antibodies (ADAs) was similar between transition and maintenance groups, suggesting that there is no detrimental effect of transitioning on immunogenicity: PLANETRA: 44.8% (64/143) versus 40.3% (64/159); PLANETAS: 27.4% (23/84) versus 23.3% (21/90); Tanaka et al.: 17.4% (4/23) versus 15.6% (5/32) [99–101]. The incidence of treatment-emergent AEs (TEAEs) was comparable between transition and maintenance groups in the PLANETRA [53.8% (77/143) vs. 53.5% (85/159)] and Tanaka et al. [87.9% (29/33) vs. 89.5% (34/38) at week 105] studies, but numerically higher for transition versus maintenance groups in the PLANETAS study [71.4% (60/84) vs. 48.9% (44/90)] [99–101]. However, incidence of TEAEs in both groups of the PLANETAS study was within the
range reported in historical studies of originator infliximab, and the majority of TEAEs were mild to moderate in severity [99].

A limitation of these OLE studies is that they were not designed or powered to evaluate noninferiority or equivalence of transitioning from originator infliximab to CT-P13 versus continued treatment with CT-P13 [99–101]. However, their results are complemented by data from the NOR-SWITCH study that was designed to evaluate noninferiority of transitioning from originator infliximab to CT-P13 versus continued treatment with originator infliximab. In the NOR-SWITCH trial, adult patients with psoriasis, PsA, RA, spondyloarthritis, CD, and UC on stable infliximab treatment for at least 6 months were randomized in a blinded manner to either continued treatment with originator infliximab (maintenance group, \( n = 241 \)) or a transition to CT-P13 (transition group, \( n = 241 \)) [102]. The incidences of TEAEs (70% vs. 68%) and ADAs (7% vs. 8%) were similar between maintenance and transition groups, respectively [102]. Among all patients, 26.2% of those in the maintenance group and 29.6% in the transition group experienced disease worsening after 52 weeks [102]. The 95% confidence interval (CI; \(-12.7\% \) to \(3.9\%\)) of the adjusted treatment difference \(-4.4\%\) was within the prespecified non-inferiority margin (15%) and confirmed noninferiority in efficacy between groups [102]. However, sample sizes were small (psoriasis, \( n = 35 \); PsA, \( n = 30 \); RA, \( n = 77 \); spondyloarthritis, \( n = 91 \); CD, \( n = 155 \); and UC, \( n = 93 \)) and the study was not powered to demonstrate noninferiority within each indication [102]. In addition, the noninferiority margin of 15% might have been too wide to exclude all clinically important differences between treatments [102].

One RCT evaluated the safety and efficacy of switching (at week 30) from CT-P13 to originator infliximab (CT-P13 switch) and from originator infliximab to CT-P13 (INX switch; \( n = 55/group \)) versus continued treatment with CT-P13 (CT-P13 maintenance, \( n = 56 \)) or originator infliximab (INX maintenance, \( n = 54 \)) in patients with CD [103]. At week 54, Crohn’s Disease Activity Index-70 response rate (CT-P13 maintenance, 78.6%; CT-P13 switch, 70.9%; INX maintenance, 70.4%; and INX switch, 76.4%) and other measures of efficacy were comparable among the treatment groups [103]. Likewise, after week 30, incidence of adverse drug reactions (CT-P13 maintenance, 5.4%; CT-P13 switch, 7.3%; INX maintenance, 11.1%; and INX switch, 9.1%) and other safety outcomes were comparable across groups [103]. The study was not powered to compare groups after switching [103]; however, the data build on other evidence that support switching patients from originator infliximab to CT-P13.

Observational studies of real-world experience with CT-P13 also provide transition data. One of the largest transition cohorts comprised 802 patients in Denmark with RA, PsA, or axial spondyloarthritis treated with originator infliximab for a median of more than 6 years [104]. All patients transitioned to CT-P13 for economic (non-medical) reasons and were monitored prospectively in the nationwide DANBIO registry for 413 (339–442) days. Disease activity and flare rates were similar in the 3 months before and after transition to CT-P13 [104]. Furthermore, preliminary data in a subgroup of patients (\( n = 231 \)) demonstrated comparable rates of ADA-positivity before and after transitioning (56% vs. 51%) [105].

Real-world data on transitioning from originator infliximab to CT-P13 in patients with psoriasis are available from a small, single-center observational study [106]. The authors reported no changes of PASI and visual analog pain scale scores \( (p > 0.05) \) and no additional AEs in patients (\( n = 30 \)) who transitioned to CT-P13 [106]. However, clinical response data after transition were not reported, and follow-up was limited [median of 23 \( (range 13–33) \) weeks] [106]. One additional study of patients in Denmark with moderate-to-severe psoriasis treated with biologics and monitored prospectively in the DERMBIO registry reported no significant difference in risk of discontinuation between patients who transitioned from originator infliximab to CT-P13 (Remsima) and those who continued originator infliximab over a 2-year period [hazard ratio 1.64, 95% CI 0.69–3.89, \( p = 0.264 \)] [107].

Published data from other small (\( n = 31–56 \)) or single-center studies of transition from
originator infliximab to CT-P13 in patients with rheumatic disease are generally consistent, demonstrating no apparent negative impact of transitioning on efficacy or safety [108–112]. However, varying discontinuation rates (3–28.2%) have been reported across observational studies [104, 108–112]. In addition, some studies reported patients who discontinued CT-P13 and switched back to originator infliximab [108, 110, 111]. However, in at least some cases, these patients discontinued for subjective reasons without objective deterioration of disease [108, 110, 111].

Finally, one RCT evaluated the safety and efficacy of transitioning from originator infliximab to the infliximab biosimilar SB2 (Flixabi; Renflexis) [113]. In this study, patients with moderate-to-severe RA were randomized to receive originator infliximab or SB2 during a 46-week, double-blind treatment phase. Then, patients who received originator infliximab were re-randomized at week 54 to receive either SB2 (transition group, n = 94) or originator infliximab (maintenance group, n = 101) up to week 70. Disease activity was comparable between transition and maintenance groups, as was the incidence of TEAEs (36.2% vs. 35.6%) and ADA-positivity rates (45.7% vs. 50.5%).

**Etanercept**

One RCT has compared originator etanercept (Enbrel®) and the etanercept biosimilar SB4 (Benepali) in patients with RA [41]. In this trial, patients who completed a 52-week, double-blind treatment period were enrolled into an OLE study, during which they received SB4 for an additional 48 weeks and, therefore, provided data on single transition from etanercept to SB4 (transition group, n = 119) or originator etanercept (maintenance group, n = 126) [114]. Efficacy was comparable between transition and maintenance groups, as was the incidence of TEAEs (48.7% vs. 47.6%) and ADA-positivity rates (0.9% vs. 0.8%) [114]. Real-world data on transitioning from etanercept to SB4 are available from one observational study of patients in Denmark with moderate-to-severe psoriasis treated with biologics and monitored prospectively in the DERMBIO registry [107]. The authors reported no significant difference in risk of discontinuation between patients who transitioned from originator etanercept to SB4 and those who continued originator etanercept over a 6-month period (hazard ratio 0.46, 95% CI 0.11–1.98, p = 0.297) [107].

Another RCT (EGALITY) comparing originator etanercept to the etanercept biosimilar GP2015 (Erelzi) in patients with psoriasis incorporated a multiple-switch design to evaluate the safety and efficacy of alternating between treatments [42, 115]. In this study, patients were randomized to receive originator etanercept or GP2015 during a 12-week, double-blind treatment period [treatment period 1 (TP1)], after which patients were re-randomized either to continue the same treatment (continued etanercept and continued GP2015) or to undergo a sequence of three treatment switches (switch etanercept and switch GP2015) every 6 weeks until week 30 (TP2). Thereafter, patients were maintained on the last treatment received, up until week 52. An analysis of pooled continued and pooled switch groups demonstrated that repeated switching between the two treatments did not have any negative effect on drug efficacy [42, 115]. The incidence of TEAEs during TP2 was similar between pooled continued (34.9%) and pooled switch (36.7%) treatment groups [115]. Furthermore, no patients from either the pooled continued or pooled switch groups tested positive for ADAs during TP2 [115].

**Adalimumab**

Two RCTs have evaluated single transition from originator adalimumab (Humira®) to the adalimumab biosimilar ABP 501 (Amgevita/Solymbic; Amjevita), one each in patients with RA or psoriasis [116, 117]. In the RA study, patients who completed a 26-week, double-blind treatment period were enrolled into an OLE study, during which patients transitioned from originator adalimumab to ABP 501 (transition group) or continued treatment with ABP 501 (maintenance group) for an additional 68 weeks [114]. The authors reported similar safety and efficacy profiles between the transition and maintenance groups; however, clinical outcomes for individual groups were not presented [116].
In the psoriasis study, patients were randomized to receive originator adalimumab or ABP 501 during a 16-week, double-blind treatment phase, after which patients on originator adalimumab were re-randomized to either continued treatment with originator adalimumab (maintenance group) or a transition to ABP 501 (transition group) [117]. Safety and efficacy were not reported. However, incidence of ADAs in the transition group (72.7%) was noninferior to that in the maintenance group (74.7%); the upper bound of the 95% CI (−13.3% to 13.0%) for the treatment difference was within the noninferiority margin of 21.7% [117].

Transition data for the adalimumab biosimilars BI 695501 (Cyltezo) and SB5 (Imraldi) are available from RCTs conducted in patients with RA [118, 119]. In the study of BI 695501, patients receiving originator adalimumab during the initial 24-week treatment period were re-randomized to transition to BI 695501 (full analysis set, \( n = 147 \); safety analysis set, \( n = 146 \)) or continue on originator adalimumab (\( n = 148 \)) until week 48 [118]. Response rates and changes from baseline in disease activity were similar between transition and continuation groups up to week 48, as was the incidence of TEAEs from weeks 24 to 58 (42.5% vs. 34.5%) [118]. Likewise, immunogenicity was similar between groups up to week 48; ADA-positivity rates at weeks 24 and 48, respectively, were 44.5% and 36.2% for patients who transitioned to BI 695501 and 50.3% and 49.6% for patients who continued originator adalimumab [118]. In the study of SB5, patients on originator adalimumab during the initial 24-week treatment period were re-randomized to transition to SB5 (\( n = 125 \)) or continue on originator adalimumab (\( n = 129 \)) up to week 50 [119]. Efficacy was comparable between transition and continuation groups up to week 52, as was the incidence of TEAEs (37.6% vs. 33.1%) and ADA-positivity rates (16.8% vs. 18.3%) [119].

**Summary and Considerations Regarding Transitioning or Switching**

Currently available studies of infliximab, etanercept, and adalimumab biosimilars are encouraging, and suggest that transitioning from an originator biologic to its biosimilar has no adverse effects on efficacy, safety, or immunogenicity. However, the level of evidence varies across products, with most published data for infliximab and most transition studies conducted in patients with rheumatic disease. No published studies of infliximab or adalimumab biosimilars and only one published study (EGALITY) of etanercept biosimilars investigated the safety and efficacy of alternating between an originator biologic and its biosimilar. Few studies were conducted in patients with psoriasis; however, switch data from EGALITY as well as transition data from one RCT of ABP 501 and one observational study of CT-P13 (Remsima) and SB4 are encouraging.

When considering a change in therapy, results obtained with one biosimilar should not be generalized to other biosimilars of the same biologic or to biosimilars of other biologic drugs [98]. For example, the effect of repeated switching between etanercept and GP2015 on immunogenicity should not be generalized to other etanercept biosimilars or to biosimilars of other anti-TNF biologics with higher immunogenic potential. Finally, not all studies were formally designed to evaluate non-inferiority or equivalence of transitioning, or switching between originator and biosimilar products. Accordingly, further studies with adequate power to evaluate statistical significance of differences between transition or switch and maintenance groups will be welcome and contribute clinically meaningful information about the safety and efficacy of transitioning, switching, or alternating between an originator biologic and its biosimilar drug.

**Interchangeability**

In the USA, an approved biosimilar may also be granted interchangeability status by the FDA [120]. To receive this regulatory designation, draft guidance issued by the FDA requires that an application for an interchangeable biosimilar product include sufficient evidence to show that the biosimilar product “can be expected to produce the same clinical result as the reference product in any given patient” [120].
Furthermore, for interchangeability designation, information in the application must be sufficient to show that “for a biological product [biosimilar] that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product [biosimilar] and the reference product is not greater than the risk of using the reference product without such alternation or switch” [120].

To support a demonstration of interchangeability, draft guidance requires data from a switching study(ies) that incorporates two or more alternating exposures (switch intervals) to the potential interchangeable product and the originator product [120]. VOLTAIRE-X is the first study in the USA to investigate interchangeability designation for an adalimumab biosimilar [121]. This study is recruiting patients with moderate-to-severe chronic plaque psoriasis and will compare the pharmacokinetics, efficacy, safety, and immunogenicity of repeated switching between originator adalimumab and the adalimumab biosimilar BI 695501 versus continued treatment with adalimumab [121]. The aforementioned EGALITY study also incorporated a multiple-switch design that is in agreement with draft interchangeability guidance; however, as noted above, the study was not powered to demonstrate equivalence of repeated switching between originator etanercept and the etanercept biosimilar GP2015 versus continued treatment with etanercept [42].

Interchangeable designation may allow for automatic substitution [120]; however, substitution policies are determined by individual state laws, not by the FDA. By contrast, European regulations do not define interchangeability, and such regulatory designation is not granted by the EMA [70, 122]. Rather, decisions about interchangeability and substitution are made by individual member states. Several national organizations and societies have issued papers or statements on interchangeability, substitution, and other considerations for the use of biosimilars in psoriasis with recommendations that support improving access to biologic therapies and ensuring patient safety (Table 3) [123–127].

NON-COMPAREABLE BIOTHERAPEUTIC PRODUCTS

Clinicians should also be aware of “non-comparable biotherapeutic products”, also known as “intended copies” [128]. Intended copies have not been approved following a regulatory pathway that is in alignment with requirements for establishing biosimilarity, as defined by leading regulatory authorities (e.g., EMA, FDA, and Health Canada) or the WHO [21, 70–72, 128]. As such, these products cannot be considered biosimilars [128]. Intended copies have not been identified in the USA or European Union [129], but were introduced in some countries without stringent regulatory frameworks or before the implementation of pathways for biosimilar approval [128]. Intended copies are marketed in several Latin American countries; however, some countries have issued regulation mandating re-evaluation of these products in accordance with current regulation for biosimilars [129, 130].

ECONOMIC IMPACT OF BIOSIMILARS ON THE BURDEN OF PSORIASIS

Costs associated with psoriasis can place considerable economic burden on patients and healthcare systems. Recent estimates of the annual total and direct healthcare costs of moderate-to-severe psoriasis were $22,713 per patient and $13,731 (mean), respectively, in the USA (adjusted to 2012 US dollars) and €1617–13,343 and €1314–8966 per patient-year, respectively, across France, Germany, Italy, and Spain (adjusted to 2015 euros) [131, 132]. Furthermore, healthcare expenditure is substantially greater with biologic drugs versus conventional systemic therapies [39, 133]. In a 2014 meeting on economic crisis and healthcare, the Council of the European Union concluded “the prices of many new innovative medicines are very high in relation to the public health expenditure capacities of most Member
| Society | General considerations | Switching | Interchangeability | Substitution | Pharmacovigilance plan |
|---------|------------------------|-----------|--------------------|--------------|------------------------|
| AAD [123] | – | – | – | Yes, if biosimilar has unique INN; interchangeable designation; physician provides explicit permission for and patient is informed of substitution; pharmacist notifies prescriber and pharmacy and prescriber retain permanent record of substitution and document any AEs | – |
| CAPP [124] | Distinct INN eliminates confusion and accidental substitution, and facilitates accurate attribution of AEs Encourage developers to provide patient and physician support programs; payers to consider full costs to healthcare system vs. cost of medication | Yes, but not required | No | No automatic substitution | Yes |
| NPF [126] | – | – | – | Yes, if biosimilar has unique INN; interchangeable designation; follows same route of administration and dosage form as reference product; pharmacist notifies prescriber; prescriber has not blocked substitution; patient is informed of substitution and pharmacy and prescriber retain permanent record of substitution | – |
| PCD & SPDV [127] | Biosimilar development must be critically evaluated; evidence for bioequivalence, quality, efficacy, and safety should take priority over potential economic or financial benefit Choose biosimilars studied in patients with psoriasis as treatment instead of biosimilars studied in other indications Careful biosimilar identification and recording is critical for safety and traceability Physicians must retain full authority over selection of therapeutic agent | No | – | Yes, if recommended by prescribing physician and patient is informed of and consents to substitution; no automatic substitution | Yes |
| AEDV [125] | Biosimilar use should not imply reduction in therapeutic efficacy, patient safety, or prescriber’s choice of treatment Physician takes responsibility for prescribing biosimilar. Decision should be based on scientific evidence, not economic factors alone; assessed on a case-by-case basis and requires patient consent Include patients with psoriasis and PsA in biosimilar trials to obtain direct information about efficacy and safety vs. extrapolation of findings from other indications Patient and prescriber information about biosimilar product should be clear and precise to support treatment decisions | Yes, if decided by physician with patient consent | – | – | Yes |

AAD American Academy of Dermatology, AE adverse event, AEDV Spanish Academy of Dermatology and Venereology, CAPP Canadian Association of Psoriasis Patients, INN International Nonproprietary Name, NPF National Psoriasis Foundation, PCD Portuguese College of Dermatology, PsA psoriatic arthritis, SPDV Portuguese Society of Dermatology and Venerology, – not addressed
States, and that this pricing situation could destabilize health systems in Member States already weakened by the financial crisis” [134].

Biosimilars may provide a lower-cost alternative to biologic therapies. For example, an analysis of commercial databases providing data on biosimilar market share and price discounts (vs. originator biologics) in Europe estimated the average biosimilar price discount around 15% (range 0–32%) across Belgium, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the UK [135]. Likewise, a survey of biosimilar pricing and reimbursement in Central and Eastern European countries reported biosimilar price discounts ranging from 5% to 30% over the originator biologic across Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, and Slovakia [136].

As a lower-cost alternative to originator biologics, biosimilars have the potential to reduce economic burden among patients with psoriasis. For example, a budget impact analysis estimated that switching patients with RA in France, Germany, Italy, and the UK from originator infliximab to biosimilar infliximab (30% price discount) could generate a potential cost saving of €433,520,000 over a 5-year period [66]. Furthermore, cost savings from the use of a biosimilar could be reinvested to treat additional patients with the same agent or may allow for expanded access to other biologic therapies [64, 65], potentially improving overall health outcomes. For example, the potential annual cost savings generated from Remsima (30% price discount) could support Remsima treatment for an additional 7,561 patients in Belgium, Germany, Italy, the Netherlands, and the UK [65].

CONCLUSIONS

Although biologic therapies have greatly improved treatment of psoriasis, patient access to these therapies is often limited. Biosimilars have the potential to impact patient care by improving access to biologics and by reducing the economic burden on healthcare. As a lower-cost alternative to originator biologic products, biosimilars also may generate cost savings that can be reinvested into the development of innovative treatment options for patients with psoriasis.

In recent years, adalimumab, etanercept, and infliximab biosimilars have become available to patients with psoriasis (Table 1). Some anti-TNF biosimilars were studied in patients with psoriasis in the initial development programs and, consistent with the biosimilar concept, more were approved for treatment of psoriasis on the basis of extrapolation of clinical data from studies in patients with rheumatic disease. The currently available data for anti-TNF biosimilars are reassuring in terms of safety and efficacy and provide evidence to support transitioning patients from an originator product to a biosimilar. Further studies incorporating multiple-switch designs, such as VOLTAIRE-X [121], will contribute additional clinical data about the safety and efficacy of alternating between originator and biosimilar therapies.

An approved biosimilar is expected to have the same clinical efficacy and safety as the originator. Therefore, all patients who are eligible for treatment with anti-TNF agents are potential candidates for using a biosimilar. Differences exist between countries in biosimilar prescribing policies, and some regulations may favor the selection of biosimilars as first-line treatment or require the use of biosimilars over originator products unless a medical reason is specified [137]. Education of physicians about the scientific principles underlying biosimilar development and approval as well as key issues (e.g., interchangeability, switching, substitution, and intended copies) and clinical experience with biosimilar use may help them to make informed treatment decisions in clinical practice. With the availability of biosimilars, we can expect to see wider use of biologics in clinical practice, which may lead to better health outcomes for patients with psoriasis as well as potentially improved adherence to treatment.

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