Dermatologic Therapy, Vol. 28, 2015, 390–403
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ISSN 1396-0296

REVIEW ARTICLE

An evolution in switching therapy for psoriasis patients who fail to meet treatment goals

Francisco Kerdel*,† & Martin Zaiac†

**Department of Dermatology, Larkin Community Hospital, Miami, Florida and †The Department of Dermatology, Herbert Wertheim College of Medicine, Florida International University, Miami, Florida*

ABSTRACT: Switching psoriasis treatment is a common, accepted practice that is used to improve disease management and improve patient outcomes (e.g., when patients are experiencing suboptimal efficacy and/or tolerability with a given therapy). Historically, switching treatment was often performed to limit patients' cumulative exposure to conventional systemic agents (e.g., methotrexate, cyclosporine) with the goal of reducing end-organ toxicity. However, the practice of switching treatments has evolved in recent years with the availability of highly effective and tolerable biologic agents. In current practice, near-complete skin clearance with minimal side effects should be a realistic treatment goal for most patients with moderate-to-severe psoriasis, and consideration for switching therapies has shifted to become more focused on achieving maximum possible skin clearance, enhanced quality of life, and improved patient satisfaction. This review provides a discussion of recent guidance on switching psoriasis therapies, including initial considerations for when switching therapy may be advisable and challenges associated with switching therapy, along with an overview of published clinical studies evaluating outcomes associated with switching therapy. The goal of this review is to empower dermatologists to optimally manage their patients' psoriasis by providing the tools needed to develop rational strategies for switching treatments based on the pharmacologic characteristics of available treatments and each patient's clinical needs and treatment preferences.

KEYWORDS: psoriasis, switching, treatment goals, strategies, efficacy, disease management

Introduction

There is a wide range of options available for the treatment of moderate-to-severe chronic plaque psoriasis, including topical therapies, phototherapy, older small-molecule systemic agents (e.g., methotrexate, cyclosporine, acitretin, and fumaric acid in Europe), the newer oral phosphodiesterase-4-inhibitor apremilast, and the biologics etanercept, adalimumab, infliximab, and ustekinumab (1). Despite the availability of numerous therapies that can be highly effective and well tolerated, psoriasis is often undertreated such that patients do not achieve substantial skin clearance, symptom relief, or improvements in quality of life (2–4). This undertreatment is associated with widespread patient dissatisfaction (3) and is due, in part, to the reluctance among practitioners to initiate or alter systemic treatment regimens in patients with moderate-to-severe disease (2). In many cases, patients are left on ineffective or poorly tolerated regimens for long periods of time (2), which can

Address correspondence and reprint requests to: Francisco Kerdel, MD, Florida Academic Dermatology Centers, The University of Miami Hospital, 1400 NW 12th Ave., Suite 4, Miami, FL 33136, or email: dr.kerdel@fadcenter.com.
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result in sustained underlying inflammation and worsening of skin signs and symptoms, as well as comorbidities associated with psoriasis (e.g., psoriatic arthritis, metabolic syndrome, and cardiovascular disease) (5).

In an effort to improve patient care, several international groups have established objective parameters to help clinicians set psoriasis treatment goals and monitor patients' progress. Guidance based on the consensus of experts from 19 European countries defines treatment success as at least a 75% improvement in Psoriasis Area and Severity Index score (PASI 75) from the time of treatment initiation (2). Intermediate response is defined as PASI $\geq$50 and $<$75, with a Dermatology Life Quality Index (DLQI) score of 5 or lower. If at least an intermediate response is not achieved within about 2 months, treatment modification is recommended (2). Similar treatment goals have been issued by the British Association of Dermatologists (6), the National Institute for Health and Clinical Excellence (7), the European Medicines Agency (8), and in an Australian consensus statement (4). The United States Food and Drug Administration also considers these endpoints in the assessment of new agents for psoriasis treatment. Conversely, some guidelines (e.g., those of the National Psoriasis Foundation) advocate against using numerical cutoffs to measure response in clinical practice, and instead recommend using "the patient's own perception of the disease and its burdens" to assess treatment adequacy (9).

While psoriasis treatment guidelines provide target goals for skin clearance and quality of life improvements, these benchmarks are not always used, in part, because physicians and patients are often hesitant to discontinue therapies that are at least partially effective or because these parameters are not frequently assessed in daily practice (9,10). However, survey results showing that lack of treatment effectiveness is the most important factor in determining satisfaction in patients with psoriasis (11) highlight the need to adjust treatment regimens until efficacy is maximized. Moreover, it has been suggested that PASI 75 and DLQI $\leq$5 treatment goals should be considered the minimal acceptable degree of improvement (principle of the lowest hurdle), and that more ambitious goals are realistic for many patients (12). For dissatisfied patients or those who simply express a preference to achieve maximal skin clearance, more aggressive treatment goals, such as PASI 90, Physician Global Assessment (PGA) of 0 or 1, or DLQI of 0 or 1, may be appropriate, particularly given current trends emphasizing patient satisfaction and happiness as key components in reimbursement practices (13). Results from clinical trials of biologics indicate that such ambitious treatment goals are attainable by a substantial proportion of patients with moderate-to-severe psoriasis (14–17). In fact, evidence suggests that even PASI 100 (i.e., complete clearance of psoriasis) may be achievable for many patients with moderate-to-severe psoriasis using biologics in development (brodalumab and ixekizumab) or recently approved (secukinumab) that inhibit interleukin (IL)-17 (15–17). These measures of disease clearance are not used in most private clinical practices, thus there are no standardized definitions for treatment success or failure and physicians must subjectively determine the response of patients to treatment.

To improve psoriasis outcomes, it is important not only to define treatment goals, but also to implement strategies to promptly alter treatment regimens if goals are not met within about 2–3 months or by the end of the induction phase of treatment for biologics (2,12,18). As with other chronic diseases, the importance of maximizing improvements early in the course of psoriasis has been noted because cumulative effects of the disease can negatively impact a patient's overall life course (12). Early control of the psoriasis inflammatory cascade may also reduce the risk for comorbidities such as cardiovascular disease, obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver disease, certain cancers, depression, and inflammatory bowel disease, as well as improve long-term outcomes (5,19).

Switching therapies on treatment failure (defined here as the inability to reach prespecified goals) is a viable option that can improve outcomes for many patients (20,21). This review provides an overview of recent guidance and clinical data on switching psoriasis therapies, as well as key factors to consider when developing rational strategies for switching treatments based on individual patient characteristics.

The importance of treatment goals

As discussed above, there are different thresholds that can be used to measure the success of psoriasis treatments (e.g., PASI 75/90/100, DLQI, PGA, and body surface area affected). However, these measures of disease severity are not routinely used in clinical practice. Treatment goals are usually

subjectively assessed in this setting by a 10-point patient-assessed or physician-assessed visual analog scale or a modified PGA/Investigator's Global Assessment (22) scale (0 = no disease, 1 = minimal disease, 2 = mild disease, 3 = moderate disease, and 4 = severe disease) and progress is discussed with the patient. Patients and physicians often have very different expectations of the extent of disease control that will be achieved with treatment; therefore, communication between patients and practitioners is essential to set agreed-on treatment goals (12,23). Treatment goals should be tailored based on disease severity and the degree of improvement that is possible. However, individual treatment goals can vary considerably, even between patients with similar disease severity. Treatment goals should be clearly discussed with the patient when initiating care in order to align patient and physician expectations. In addition to skin signs and symptoms, important factors to consider when setting treatment goals are the impact that psoriasis has on the patient's quality of life and the impact of comorbidities on the patient's overall health (12).

Treatment goals based on patient input should be established early in the course of the disease because patient involvement in decision-making can make patients feel more empowered and increase their compliance with treatment, thereby improving clinical outcomes (23). Clinical response to treatment should be assessed regularly and patient feedback should be collected frequently to ensure that patients both understand and are satisfied with the management of all aspects of their disease.

If clinical responses are insufficient to achieve psoriasis treatment goals, treatment should be modified promptly (12). Recent evidence suggests that patients who are less likely to attain their psoriasis treatment goals include individuals who are in generally poor health, those with psoriasis affecting a large percent of their body surface area, and those who report acute worsening of psoriasis signs and symptoms (1,12,18). Aggressive intervention that yields a rapid response must be emphasized for these types of patients to prevent further deterioration in their condition (1). Other clinical features indicative of poor prognosis include psoriasis that progresses over time, flaring or progressing psoriatic arthritis, and worsening of markers for inflammation, such as C-reactive protein, tumor necrosis factor alpha (TNFα), IL-6, IL-8, and IL-17 (24). Patient dissatisfaction is also an indicator that treatment should be modified or switched; this can include dissatisfaction with therapeutic efficacy, tolerability, and/or medication administration (e.g., frequency of dosing, difficulty traveling with medication, etc.) (23).

Considerations for switching therapy

Despite the fact that treatment optimization is important to maximize improvement in psoriasis and that current guidelines provide information on altering treatment regimens when patients fail to achieve desired treatment goals, decision-making criteria for switching therapy are not well defined, and there are limited data on how to transition from one treatment to another in routine clinical practice (18). Part of the reason why this guidance is only now becoming available (18) is that the practice of switching has only recently evolved. In the past, the rationale for switching treatments was often related to safety concerns and involved rotating between conventional systemic agents (e.g., methotrexate, cyclosporine, and retinoids) with different target-organ toxicities in order to reduce cumulative exposure (25).

For example, an international consensus report recommended that cyclosporine should only be used intermittently for 3–6 months, and the package insert cautions against continuous treatment longer than 1 year (18,26). The risk-benefit profile of cyclosporine must be carefully considered, particularly in older patients, as long-term use can significantly increase risks of renal toxicity, hypertension, and skin cancer. Skin cancer risk is especially high in patients previously treated with psoralen plus ultraviolet A (PUVA); therefore, switching from PUVA to cyclosporine is generally not recommended (12). When discontinuing cyclosporine treatment, it is important to note that abrupt cessation can cause psoriasis flares (12).

Long-term (e.g., >10 years) methotrexate therapy can be effective for many patients with moderate-to-severe psoriasis (18); however, only an estimated 50–60% of patients who tolerate oral methotrexate doses of 15–20 mg/week will achieve marked improvement, leaving 40–50% of patients without an effective therapy (27). In addition, side effects of methotrexate are common, and regular safety monitoring is required (18). Up to 30% of patients discontinue methotrexate treatment due to adverse events including gastrointestinal intolerability, hepatotoxicity, bone marrow suppression, acute pneumonitis, and pulmonary fibrosis (27). Risk factors that

can result in hepatotoxicity are coexisting hepatitis B or C, alcohol consumption, obesity, and type 2 diabetes mellitus. To reduce the potential for liver toxicity, the American Academy of Dermatology Guidelines suggest switching to a different therapy (or performing liver biopsy) once patients reach a cumulative methotrexate exposure of 3.5–4.0 g (27). Patients should be carefully screened for comorbidities before initiating treatment and methotrexate should be avoided in high-risk patients (28).

The recent availability of biologic agents that may be safer and more effective than conventional systemic has focused considerations for switching on safety, achieving greater skin clearance, and patient satisfaction. The high specificity and efficacy of biologics generally greatly outweighs the low risk of experiencing adverse events with these agents (29), as little-to-no cumulative toxicity has been observed in studies of biologics, and biologics are associated with less systemic toxicity than conventional agents (30,31).

Findings from real-world observational studies indicate that patients with moderate-to-severe psoriasis who are switched from conventional systemic agents to biologics typically do very well, experiencing improvements in PASI score and measures of overall and dermatology-specific quality of life (21). However, while biologics are generally very effective, 27% of patients treated with TNFα inhibitors were found to discontinue treatment after 29 months due to lack of initial efficacy (primary failure), loss of efficacy over time (secondary failure), or intolerance (32). Therefore, strategies are needed to maintain efficacy with acceptable tolerability. Switching from one biologic to another is now commonplace, although guidance on switching practices is limited (20). Alternatively, dose adjustments can be made with some biologics (i.e., adalimumab, etanercept, and ustekinumab) (18), or biologics can be combined with conventional systemic or topical therapies to improve or maintain efficacy (12,18,29). When different types of treatments are combined, efficacy goals can often be met using lower doses of each drug, potentially resulting in less treatment-associated toxicity (18).

The practice of switching to achieve goals

Limited guidance is available on how and when to switch therapies to achieve optimal clinical outcomes in real-world clinical practice. Perhaps the best guidance to date has been provided by the Transitioning Therapies program, which developed a consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis based on systematic literature reviews and the expert opinions of 107 dermatologists from 33 countries (18). Key recommendations from this report on the practice of switching therapy are summarized in Table 1.

Reliability of response

Reliability of response should be a key consideration when deciding which agent to switch to; preferred agents should have predictable, rapid efficacy that is highly reproducible and sustained (1,29,33). In comparative studies evaluating adalimumab, etanercept, infliximab, and ustekinumab for the treatment of moderate-to-severe psoriasis, evidence suggests that infliximab has the greatest efficacy (based on PASI improvement) and the fastest onset of action, followed by ustekinumab, adalimumab, and etanercept (34–36). It will be interesting to observe if newer therapies can offer a faster and more reliable response with improved efficacy because early findings suggest that these outcomes may be attainable through inhibition of IL-17 (15).

For patients who fail to respond to an anti-TNFα agent due to lack of efficacy, this may mean choosing a biologic with a different mechanism of action (e.g., ustekinumab). However, patients who have discontinued a previous anti-TNFα therapy due to intolerance may respond well to a different anti-TNFα agent (37). Switching to a different anti-TNFα agent may also be appropriate for patients with comorbid psoriatic arthritis because higher psoriatic arthritis response rates have been observed in clinical studies with adalimumab, etanercept, and infliximab than with ustekinumab (38).

Patient compliance (adherence)

Patient dissatisfaction with the efficacy of psoriasis treatments is associated with poor adherence (39). Thus, agents should be selected that give patients the best option for achieving their treatment goals. In a survey of patients receiving psoriasis treatment, the greatest level of adherence was observed with biologics, followed by oral systemic therapy, phototherapy, and then topical therapy (40). Additionally, patients receiving

Table 1. Recommendations for Switching Therapy to Treat Moderate-to-severe Psoriasis (18)

Switching from conventional systemic therapy to biologic therapy
General considerations
When switching for safety reasons, a washout period is recommended until the safety parameter is normalized or stabilized
When switching due to lack of efficacy, direct transition, or an overlap period can be considered
Use approved induction doses when starting biologic therapy
Switching from acitretin
Can be performed without a washout period
Women of childbearing age should continue with contraception for 2 years, as recommended for the use of acitretin
Switching from cyclosporine
Can be performed without a washout period
A short overlap period with biologic therapy (e.g., 2–8 weeks) can be considered to reduce the risk of rebound in partial responders; taper the dose of cyclosporine as soon as possible
Switching from methotrexate
Can be performed without a washout period
Methotrexate can be overlapped or used concomitantly with approved biologics
Switching from one biologic to another
General considerations
After considering dosage adjustments, switching should be performed if patients have an inadequate response (i.e., not achieving at least PASI 50) at the end of the induction phase (primary nonresponders) or if efficacy is lost over time (secondary nonresponders)
When switching for safety reasons, a washout period is recommended until the safety parameter is normalized or stabilized
When switching due to lack of efficacy, no washout period is necessary; switch to the new biologic at the time of the next scheduled dose of the original therapy
Start the new biologic with the approved induction dosing, followed by maintenance dosing
Switching from adalimumab
Administer the first treatment with etanercept, infliximab, or ustekinumab after a treatment transitioning from adalimumab at the time point of the next scheduled dose (typically 2 weeks)
Switching from etanercept
Administer the first treatment with adalimumab, infliximab, or ustekinumab after a treatment transitioning from etanercept at the time point of the next scheduled dose (typically 1 week)
Switching from infliximab
Initiation of the first treatment with adalimumab, etanercept, or ustekinumab after a treatment transitioning from infliximab can be considered as early as 2–4 weeks after the last infliximab dose, particularly in cases of treatment failure
Switching from ustekinumab
Initiation of the first treatment with adalimumab, etanercept, or infliximab after a treatment transitioning from ustekinumab should be performed at 8–12 weeks but can be considered as early as 2–4 weeks after the initial biologic dose in cases of treatment failure

PASI, Psoriasis Area and Severity Index.

systemic therapy have reported greater treatment satisfaction than individuals on topical therapies (11). The mode of administration for a therapy can also affect adherence. For example, many patients discontinue topical therapies due to the messiness of applying creams or lotions, which is not a concern with systemic therapies. Patients with rheumatoid arthritis receiving biologics were reported to prefer less frequent dosing and a lower frequency of dosing may lead to increased adherence in patients with chronic conditions (41,42). Convenience is also associated with adherence to psoriasis treatment (11) and the option for self-injection at home may be desirable for many patients, although some patients will be apprehensive about performing self-injections. Challenges in obtaining prescriptions can cause poor adherence and the costs of medication have been shown to reduce adherence in patients with chronic conditions (43). In patients with psoriasis, age <55 years, lower income levels, and lack of insurance were associated with difficulty in obtaining biologics (44). Younger age and income level were determined to be independent risk factors, while lack of insurance was correlated with lower income.

Sensitivity analysis of income levels found that difficulty in obtaining biologics was associated with income <$100,000, <$60,000, and <$40,000. A study of patients with rheumatoid arthritis receiving biologics found that although out of pocket expenses were low for most individuals, adherence was significantly decreased for patients with high out of pocket expenses (45). If the cost of biologics is preventing adherence, patients can be referred to support programs offered by pharmaceutical companies such as the StelaraSupport™ Instant Savings Program (46).

Antidrug antibody formation

At present, the role of antidrug antibodies (ADAs) in treatment decisions is not well defined. While immunogenicity can be informative when considering switching therapy, the decision to switch should ultimately be based on clinical efficacy and safety (37). It is often not practical to measure ADA levels as part of routine evaluations because although enzyme-linked immunosorbent assays are commercially available, there are no standard criteria for interpreting results and understanding the assay's specificity and sensitivity needs to be taken into account because of potential drug interference (20,47).

Failure or loss of clinical response to certain biologic therapies may be related to the formation of ADAs (37). ADA levels are inversely proportional to serum drug concentration, and high ADA levels have been shown to reduce the efficacy of adalimumab and infliximab (37,47,48). However, ADAs to etanercept are not associated with clinical response, and the significance of ADAs to ustekinumab has yet to be determined (37,48,49). Formation of ADAs to infliximab can also adversely affect tolerability, as studies have shown that infliximab ADA levels are correlated with acute and delayed infusion reactions, including rash, pruritus, headache, nausea, fever, hypertension, and arthralgia (37,49). In contrast, ADAs to adalimumab and etanercept do not appear to increase risks for adverse effects (37).

TNFα ADAs do not cross-react; thus, antibodies to one drug do not predict ADA formation to a different TNFα inhibitor (37). In rheumatoid arthritis, switching to etanercept from infliximab or adalimumab has been shown to improve clinical outcomes in patients with ADAs (37).

A lack of ADAs in nonresponders with adequate serum drug concentration may indicate that a patient did not respond to the drug's mechanism of action (49). Thus, a nonresponsive patient without ADAs to one TNFα inhibitor may be unlikely to respond to a different TNFα inhibitor (49).

Serum drug levels may provide more insight than ADA levels when trying to determine possible reasons for treatment failure and whether switching is warranted (49). If a nonresponder has a low trough serum drug concentration, treatment intensification can be considered before switching therapies, whereas if a nonresponder has a high serum drug concentration, switching to another agent (with the same or different mechanism of action) should be considered. In addition, measuring serum levels of certain biologics early in the course of treatment can provide insight into long-term outcomes. In a cohort of 56 patients with chronic plaque psoriasis initially treated with adalimumab or etanercept, Mahil et al. (47) found that serum adalimumab concentration at 4 weeks was predictive of treatment response at 6 months; however, serum etanercept levels at 4 weeks were not associated with response at 6 months.

Need for a washout period

Recommendations differ on the need for a washout period when switching from one biologic to another. The 2009 British Association of Dermatologists guidelines recommend not to overlap biologic therapies and to have a washout period of 4 times the drug's half-life between therapies (6). However, there are no data available to support this recommendation (50), and a more recent consensus from the Progressive Psoriasis Initiative (PPI) (12) questions the value of a long washout period between treatments. The PPI consensus (12) stated that the risk for psoriasis flares is generally greater than the risk for any adverse effects associated with overlapping biologic therapies. While a theoretical risk for increased susceptibility to infection has been proposed if washout time is not adequate between biologic therapies, data supporting such a risk are minimal (50).

Further, consensus from the Transitioning Therapies program (18) recommends against a washout period unless a safety concern arose with the previous therapy that needs to resolve before initiating a new treatment. Instead, the new biologic should be initiated when the next dose of the previous biologic is due (18). Special consideration may be required when transitioning from ustekinumab to another biologic because ustekinumab maintenance doses are

only given every 8–12 weeks. If psoriasis signs and symptoms are poorly controlled, administration of a different biologic 2–4 weeks after the last dose of ustekinumab can be considered (18).

Demographic characteristics

Certain patient demographic and clinical characteristics should be considered when selecting therapies that will minimize treatment failure. For example, overweight and obese patients may have better outcomes with infliximab or ustekinumab than with other biologics because dosing for these agents is based on body weight (20,23,51). Gender may also affect the pharmacokinetic properties of different biologics. It has been observed that adalimumab has a shorter half-life in female versus male patients (47) and that male gender was associated with a reduced likelihood for infliximab treatment failure (51).

Patients with high levels of C-reactive protein and low levels of albumin (markers for inflammation) may have accelerated drug clearance due to increased reticuloendothelial system-mediated drug catabolism (47). Genetic heterogeneity and polymorphisms are also assumed to cause differences in drug metabolism that likely determine why some patients fail to respond to one biologic but may respond to others (20). However, until these characteristics are better understood, routine genetic testing is not recommended when determining psoriasis treatment strategies and goals (20).

Variants of psoriasis

The presence of variant forms of psoriasis may aid in selecting a biologic agent. A prospective trial of 64 patients found that guttate psoriasis with plaque psoriasis was a significant predictor for infliximab treatment failure (51). Santos-Juanes et al. (33) reported rapid improvement of erythrodermic psoriasis with ustekinumab in 2 patients that had failed previous treatment with phototherapy, cyclosporine, efalizumab, methotrexate, etanercept, adalimumab, and infliximab. Similarly, a patient with erythrodermic psoriasis who had failed numerous previous therapies showed a dramatic response to infliximab (52).

Published literature evaluating switching psoriasis treatments

Table 2 summarizes findings from the clinical literature evaluating switching from a conventional systemic agent to a biologic or from one biologic to a second biologic. Results from these studies overwhelmingly support that switching is a well-tolerated, viable option that can significantly improve outcomes for patients who experience treatment failure on a given therapy. In all of the studies identified, the majority of patients who switched treatment achieved the study's primary endpoint for psoriasis improvement (e.g., PASI 50/75/90 or PGA of 0/1, depending on the study). Notably, response rates were high when patients who experienced treatment failure with one TNFα inhibitor were switched to a second TNFα inhibitor, indicating that this is a reasonable treatment sequence (61).

Data from psoriasis registries also provide valuable insight into the real-world effectiveness of switching treatments. An observational, longitudinal analysis of data collected in the Swedish National Registry for Systemic Treatment of Psoriasis (PsoReg) from 2007 to 2011 found that biologic-naïve patients who switched from a conventional systemic agent to a biologic agent ($n = 267$) experienced significant improvements in the clinical severity of skin signs and symptoms and in health-related quality of life (21). Mean PASI score improved from 13.6 before switching to 5.7 after switching; mean DLQI score improved from 10.9 to 5.0; and mean EuroQoL 5-Dimension (EQ-5D) score improved from 0.68 to 0.80 (all $p < 0.001$) (21). Another small study of psoriasis registry data from the University Hospital of La Coruña, Spain, found that of 35 patients who failed on etanercept and were switched to adalimumab, 82.9% (29/35) achieved PASI 50 after 12 weeks of treatment (66). These findings further support that variation in response is common between different anti-TNFα agents, and failure on one anti-TNFα agent does not predict failure on subsequent anti-TNFα agents (66). A 1-year observational study using data from the Dermbio Danish registry on biologic treatment ($N = 179$) found that efficacy of ustekinumab was not significantly different in anti-TNFα-naïve patients compared with patients who failed to respond to 1–3 previous anti-TNFα agents (~80% of patients achieved PASI 75) (67).

In addition to these registry studies and the treatment switching studies described in Table 2, the pivotal phase 3 trials in the ustekinumab clinical development program, PHOENIX 1 and PHOENIX 2, included a substantial proportion of patients who were previously treated with another biologic agent (37.9–51.2%) (68,69).

Table 2. Summary of Studies Reporting on Switching to Biologic Therapy to Treat Moderate-to-severe Plaque Psoriasis

Study	*N*	Design	Previous therapies	Key results
Switching to etanercept				
Mazzotta et al. (53)	124	Observational study	Cyclosporine, PUVA, retinoids, corticosteroids, fumaric acid esters, MTX, infliximab, efalizumab	PASI 75 was achieved at week 24 by 75.3% of patients not previously treated with biologics and by 65.2% of those who had previously received biologic therapy
Switching to infliximab				
PSUNRISE (54,55)	215	Prospective, open-label, multicenter study	Etanercept ± MTX or cyclosporine	65.4% of patients achieved PGA 0 or 1 scores at week 10; response at week 26 was 61.3% Switching to infliximab was associated with improvements in HRQoL as measured by DLQI, EQ-5D, SF-36, and disease activity VAS
TANGO (56)	38	Multicenter, single-arm, observational, phase 4 study	Etanercept	71% Of patients achieved PASI 75 at week 10; mean BSA reduction from baseline to week 10 was 65% ($p < 0.001$) DLQI improved from 13 at baseline to 0 at week 24 ($p < 0.001$); Skindex-29 component scores for symptoms, emotional state, and social functioning decreased from baseline to week 24 ($p < 0.001$)
Switching to adalimumab				
BELIEVE Subanalysis (57)	730	16-Week double-blind, randomized controlled trial	Prior failure, intolerance, or contraindication to ≥2 systemic therapies	At week 16, 61.7% of patients who previously received anti-TNFα therapy achieved PASI 75 compared with 71.7% of anti-TNFα-naïve patients ($p = 0.095$) PGA 0 or 1 response rates were 65.4% for anti-TNFα-naïve patients, 57.1% for patients previously treated with etanercept, and 47.2% for patients previously treated with infliximab From baseline to week 16, mean DLQI scores decreased from 13.8 to 4.5 in patients who previously received anti-TNFα therapy and from 14.0 to 3.4 in anti-TNFα-naïve patients ($p = 0.199$ for anti-TNFα-experienced versus naïve patients at week 16)
PROGRESS (58,59)	152		Etanercept, MTX, or NB-UVB phototherapy	52% of patients achieved PGA 0 or 1 at week 16 (61% of patients switched from

Table 2. *Continued*

Study	*N*	Design	Previous therapies	Key results
		Prospective, open-label, multicenter, phase 3b study		MTX, 48% of patients switched from NB-UVB, and 49% of patients switched from etanercept) For patients that achieved PGA 0 or 1 at week 16, the median time to achieving this clinical success was 56 days Mean BSA decreased from 11.8% at screening to 4.5% at week 16 Mean PASI scores decreased by 3.1–6.1 points from screening to week 4, depending on prior therapy group DLQI decreased by 3.8–7.0 points from screening to week 16, depending on prior therapy group Sleep Problem Index II scores increased by an average of 5.2 points from screening to week 16; Sleep Problem Index I scores increased by 4.9 points from screening to week 16 Work productivity and pain scores improved
Bissonnette et al. (60)	85	Unblinded, open-label study at 12 centers in Canada	Etanercept primary or secondary efficacy failure	After 24 weeks of treatment with adalimumab, 46% of patients achieved PGA 0 or 1 In patients with primary etanercept treatment failure ($n = 50$), mean BSA was reduced by 42% at week 12, and 40% achieved PASI 75 In patients with secondary etanercept treatment failure (loss of efficacy; $n = 35$), mean BSA was reduced by 61% at week 12, and 31% achieved PASI 75
van Lümig et al. (61)	30	Analysis of data from 2 prospective registries in the Netherlands	Etanercept	54% of patients achieved PASI 75 at week 48 Improvements were observed for the majority of patients regardless of the reason for switching (primary or secondary failure, or intolerance)
Papoutsaki et al. (62)	30	Open-label, non-randomized prospective study	Unresponsive or had contraindications to MTX, cyclosporine, retinoids, and PUVA, and failed	83% (25/30) of patients switched to adalimumab after failure with other biologics

Table 2. *Continued*

Study	*N*	Design	Previous therapies	Key results
			to respond to efalizumab, etanercept, and infliximab	achieved PASI 75 at week 24; 77% (23/30) achieved PASI 90 No differences were observed based on previous biologic treatment
Woolf et al. (63)	14	Single-center, retrospective, open-label, case cohort study	Etanercept	64% (9/14) of patients achieved PASI 50 at follow-up (median week 16) Of these 9 patients, 4 achieved PASI 75 and 1 achieved PASI 90 Mean DLQI decreased from 13.1 to 8.2, with 62% of patients experiencing ≥5-point improvement
Yamauchi and Mau (64)	12	Case series	Etanercept secondary failure (achieved PASI 75 but lost response over time)	5/8 Patients whose scores had decreased to between PASI 50 and PASI 75 on etanercept were able to re-establish PASI 75 by week 12 on adalimumab; the other three patients saw improvements but did not regain PASI 75 response Of four patients whose scores had decreased below PASI 50, two re-established PASI 75 response within 12 weeks and two had between PASI 50 and PASI 75
Switching to ustekinumab				
TRANSIT (65)	489	52-Week phase 4, open-label, parallel-group, randomized clinical trial	MTX	77% of patients who switched to ustekinumab after failing on MTX achieved PASI 75 at week 52 At week 52, 61% of patients had a ≥5-point reduction in DLQI score from baseline; 65% had a DLQI of 0 or 1
Downs (50)	10	Observational case series	Primary or secondary treatment failure with an anti-TNFα agent	PASI 90 was achieved by 70% (7/10) of patients switched to ustekinumab; the other three patients achieved PASI 75

BSA, body surface area; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; MTX, methotrexate; NB-UVB, narrowband ultraviolet B; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PUVA, psoralen plus ultraviolet A; SF-36, Short Form-36; TNF, tumor necrosis factor; VAS, visual analog scale.

Results from these studies support that switching to ustekinumab is effective and well tolerated for most patients, given the high overall PASI 75 response rates at week 12 (67.1% with the 45-mg dose in PHOENIX 1 and 66.7% with the 45-mg dose in PHOENIX 2) and acceptable safety profile of ustekinumab (68,69). Similarly, in the phase 3 ERASURE and FIXTURE studies of the IL-17A antibody, secukinumab, 12.5–29.3% of patients had psoriasis that was poorly controlled with previous a biologic therapy (anti-TNFα or ustekinumab), with up to 7.6% of patients experiencing no response to previous anti-TNFα therapy (15). In these studies, PASI 75 response rates at week 12 ranged from 67.0% to 81.6%, supporting the efficacy of IL-17 inhibition in patients with moderate-to-severe psoriasis, including those who failed on previous biologics (15). Taken together, data from ustekinumab and secukinumab studies indicate that switching to a biologic that acts independently from TNFα can result in significant and dramatic improvements in both biologic-naïve patients and in those who failed to respond to one or more previous biologic agents.

Another possible advantage of switching from a TNFα inhibitor to a non-TNFα-based biologic is reversal of weight gain. Studies of ustekinumab have shown that it is not associated with weight gain (70), unlike anti-TNFα agents, which are associated with mean weight gain of about 1–4 kg (71–73). Results from an observational case series ($N = 10$) by Downs (50) showed that 40% of patients who had experienced weight gain of more than 5 kg with anti-TNFα therapy returned to their normal weight upon switching to ustekinumab. Thus, switching to a biologic that acts independently from TNFα may be preferable for patients who fail to respond to anti-TNFα therapy and who experienced weight gain on that regimen.

While switching biologic treatment is an accepted clinical practice that is effective and well tolerated for the majority of patients, there are still unanswered questions associated with these agents related to their long-term safety and cycling. In addition, it has been observed that a small percentage of patients may experience significant worsening of psoriasis signs and symptoms after switching therapies. In the 16-week open-label, phase 3b PROGRESS study in which patients were transitioned from etanercept, methotrexate, or narrow-band ultraviolet B therapy to adalimumab, 2.6% (4/152) of patients who switched to adalimumab had at least a 125% worsening of PASI scores (58). Bhutani and Koo (74) have also reported isolated cases of psoriasis flares occurring when patients were switched from etanercept to adalimumab. In both of these studies (58,74), the authors reinforce the value of switching therapies in real-world clinical practice, but make the point that clinicians need to be aware that worsening of signs and symptoms is a possibility.

Conclusions

The body of evidence on switching therapies in psoriasis indicate that individuals respond differently to the different biologics approved for treating moderate-to-severe psoriasis, even when the biologics share a mechanism of action targeting TNFα (75). Thus, failure on one agent does not predict future treatment failure with different agents, and prompt alteration of treatment should be a priority for patients who are failing to meet their goals given the wide range of therapies already available and in late-stage clinical development for the management of moderate-to-severe psoriasis.

The availability of multiple biologic therapies with different mechanisms of action will expand the options for switching therapy after failure of an initial biologic. As these new therapies become available, patients' views about their disease are changing and, therefore, better outcomes such as almost complete clearance may be achievable by a substantial proportion of patients (23).

In the past, it was generally accepted that treatment would help manage psoriasis signs and symptoms but that, for most patients, complete clearance was not attainable and some skin lesions would always be present. However, patients are now expecting safe and complete clearance and good tolerability, and are dissatisfied with anything less, especially when they may have experienced complete clearance with pharmacologic treatment in the past. With the evolving landscape of safe and effective biologic agents for the treatment of moderate-to-severe psoriasis, such high expectations are likely to be attainable for many patients. Therefore, an essential component to maximizing treatment success is communication between patients and practitioners to develop realistic treatment goals that, if achieved, will satisfy the patient and improve his or her quality of life.

Acknowledgments

Technical assistance with editing and styling of the manuscript for submission was provided by Oxford PharmaGenesis Inc., and was funded by Novartis Pharmaceuticals Corporation. The authors were fully responsible for all content and editorial decisions and received no financial support or other form of compensation related to the development of this manuscript. The opinions expressed in the manuscript are those of the authors and Novartis Pharmaceuticals had no influence on the contents.

Conflict of interest

Dr. Kerdel has served as a speaker and received research support from Amgen, Janssen, Abbvie, Celgene, and Galderma. He has received research support from Pfizer, Novartis, Astra Zeneca, and Valeant. He has served on the board of directors of Celgene. Dr. Zaiac has no conflicts of interest.

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