

CLINICAL MANAGEMENT RECOMMENDATIONS

Transitioning Between Biologics

Ronald Vender, MD, FRCPC¹

¹Dermatrials Research Inc., Hamilton, ON, Canada

ABSTRACT

Background: Transitioning between biologics has become an important part of practice.

Objective: Patients with moderate to severe plaque psoriasis who are on biologics can have efficacy failures, as well as safety concerns. This would often necessitate a change of biologic, which may be within the same class or to a different class. A change due to an adverse event from the presently used biologic may resolve or require treatment until a new biologic is introduced, which may pose some delay in the initiation of the subsequent biologic.

Methods: A review of the literature and guidelines published were performed.

Results: A practical guide to transitioning between biologics are presented

Limitations: There are no randomized placebo-controlled trials comparing transitioning to different biologics to determine the best method of transitioning.

Conclusion: Transitioning between biologics is an option for those patients requiring such a change either for safety or efficacy reasons.

INTRODUCTION

Transitioning between biologics, also known as switching or changing between biologics, is not a new phenomenon. Since biologics for moderate to severe psoriasis have been available, physicians have been required to think about how, when, what and whom to switch. A treating physician, along with the patient, must have an agreed-upon treatment target or goal. The ultimate goal, in most

cases, however, could be complete disease clearance, although PASI 75 has been considered an acceptable goal by previous authors.¹ In order to achieve this, or at least as close as possible with the tools available, continuous, discussions, assessments and potential modifications should be done during patient visits. These modification strategies include dose adjustments, reduction of dose intervals, adjuvant topical or systemic therapies, or changing the biologic.¹ This short paper focuses on the last strategy:

changing, switching or transition between biologics.

TIME FOR SOMETHING NEW

When considering a change, one must also consider the functional impairment of the patient, comorbidities, as well as treatment risks.² For instance, not all biologics are indicated for psoriatic arthritis, while others must be used with caution in patients with inflammatory bowel disease (a known comorbidity associated with psoriasis). Some biologics can be administered via alternative devices (e.g. auto-injectors) to simplify self-injection in patients that may have dexterity issues.

Primary non-response, secondary non-response, adverse events, and the patient-physician decision may also be factors for switching therapy.³ Primary non-response is also well known as a primary failure. This can occur in a small percentage of patients with any biologic. In the past, a PASI response of less than 75% improvement was considered primary failure if the success was not seen in the first six months of treatment. More recently, due to the greater efficacy of newer biologics, a PASI response of less than 90% improvement may be considered a primary failure. This can be considered as early as the first 8-12 weeks.^{4,5} Some treating physicians may be a bit more patient and stretch it to the first 4-6 months. While a lack of initial efficacy during the induction period may be considered primary failure, given the variation of induction periods with many biologics, this may be an inadequate time to reach a conclusion.

Secondary non-response is also known as secondary failure, where there is a loss of efficacy over time. Several possible contributing factors include a patient's

weight, previous biologic failures, and comorbidities (e.g. psoriatic arthritis, diabetes, hypertension and cardio-metabolic disease). Occasionally, optimization of the biologic, such as increasing the dose or shortening the intervals between treatments, may boost efficacy. A new concept of re-induction may also help to reverse a secondary failure.^{6,7}

Adverse events may necessitate a change in biologics as well. Examples include the development of tuberculosis, multiple sclerosis, congestive heart failure, recurrent candidiasis and/or sinusitis and injection site reactions. Lastly, patient-physician decision, such as a request for switching for reasons other than efficacy or safety, can occur. However, undisclosed non-adherence may be thought of as non-response to treatment and could lead to switching therapies unnecessarily.^{8,9}

WASHOUTS

There are differences of opinions as to whether washouts are required in-between different biologics. Appropriate washout periods minimize the potentially adverse safety effects of treating with two immunomodulatory agents at once. Evidence against a washout appreciates the risk to the patient's quality of life of waiting for 4 half-lives between biologics. The latter may outweigh any perceived benefit.^{10,11} The risk for psoriasis flares is generally greater than the risk for any adverse effects associated with overlapping biologic therapies.¹² 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.¹³

GUIDELINES

There are many published guidelines for treating psoriasis, however very few provide guidance on how to transition between biologics. The guidelines from Spanish Academy of Dermatology and Venereology (AEDV) recommend that when switching to consider the following: presence or absence of active joint disease, the clinical characteristics of the patient (weight, risk of infection, comorbidities, and contraindications related to specific biologic agents), the mechanism of action, the appropriateness of the dosage and route of administration, the additional cost of induction therapy and other pharmacoeconomic considerations, the relative risk of infections and immunogenicity and the response of the new biologic with previous exposure or failures of other biologics. However, no guidance was given on exactly how to transition.¹⁴

The joint AAD-NPF Guidelines suggest switching biologics when there is no definitive response to treatment with anti-IL12/23, anti-IL17s and anti-IL23s ascertained after 12 weeks of continuous therapy, anti-TNFs after 12-16 weeks of continuous therapy and Infliximab after 8-10 weeks. If clinically needed, it is suggested, to switch to a different biologic agent with the possibility of improved efficacy, safety, and/or tolerability. They warn that not all switches may result in improvement. The duration of the interval between discontinuation of previous medication and initiation of a biologic may depend on the treatment that is being discontinued, disease severity, and response to prior treatment, therefore, should be assessed on a case-by-case basis. Similar to AEDV Guidelines, no direction on exactly how to switch is discussed.¹⁵

The National Institute for Health and Care Excellence (NICE) Guidelines, recommend a switch if there is 1) no adequate response to a first biologic (at 10 weeks after starting infliximab, 12 weeks for etanercept, ixekizumab, secukinumab and brodalumab, and 16 weeks for adalimumab, ustekinumab, or guselkumab; primary failure) or 2) psoriasis initially responds adequately but subsequently loses this response (secondary failure), or 3) the 1st biologic cannot be tolerated or becomes contraindicated. Again, there is no guidance on how to transition.¹⁶

The most definitive guidelines on transitioning between biologics belong to the British Association of Dermatologists (BAD).⁷ They suggest the following transitioning options: No washout period or a non-standard washout period (greater than or less than three months or four half-lives). An overlap of biologic therapy or bridging with standard systemics may also be considered. No studies comparing strategies for transitioning between biologic therapies were included in the clinical review. In those that used shorter, non-standard washout periods, there did not appear to be an increased safety risk. The BAD guidelines note factors that influence transitioning therapy strategies: drug pK/pD of the drug being stopped and the one to be started, the patient's clinical history, the disease severity and the underlying risk of infection (if biologics are overlapped). Finally, recommendation R27 suggests the following: When transitioning to a new biologic therapy (from a previous biologic therapy) consider using: a 1-month washout period or the length of the treatment cycle (whichever is longer) between the last dose of the current biologic therapy and the planned date of biologic initiation.

HOW TO TRANSITION

When switching due to efficacy, one can use no washout by switching at the next scheduled dose of the failed biologic based on the minimal or shortest dosing interval of the failed biologic with the standard induction dose schedule followed by standard maintenance dosing of the subsequent biologic.⁶ However, when switching due to safety issues, one may need to use a necessary treatment-free interval until safety parameters have normalized or stabilized.⁶

The washout period for biologics is usually considered to be four half-lives of the reference drug. It is important to realize that the pharmacodynamic effects of the biologic may not necessarily correlate with the pharmacokinetic effects.^{7,11,17} When no washout period is required then the guide in Table 1 is suggested. Note the table accounts for usual dosing, but if patients are switched without washouts of the prior drug, adverse outcomes have not been reported - i.e. they could stop a drug on one day and take another the next day.

TABLE 1. The Guide based on minimum dosing intervals

Failed Biologic	Could start a new biologic in...
Etanercept	1 week ¹
Adalimumab	2 weeks ¹
Infliximab	2-4 weeks ¹
Certolizumab	2 weeks ²
Ustekinumab	4 weeks ²
Secukinumab	2 weeks ²
Ixekizumab	2 weeks ²
Brodalumab	2 weeks ²
Guselkumab	4 weeks ²
Tildrakizumab	4 weeks ²
Risankizumab	4 weeks ²

¹Mrowietz, U., de Jong, E., Kragballe, K., et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2014;28: 438-453. ²Extrapolated from Mrowietz, U., de Jong, E., Kragballe, K., et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2014;28:438-453.

WHAT TO TRANSITION TO

In general, reports show that switching between biologics whether within the same class or to a different class can be successful.¹⁷ However, Piaserico et al. noted that individuals who experienced a secondary loss of efficacy to one TNF inhibitor or stopped treatment due to an adverse event were more likely to achieve PASI 75 at week 12 than those who were primary non-responders.³

The first reported transitioning between two anti-IL-17 antagonists showed similar efficacy when brodalumab patients were transitioned to secukinumab with a two-month washout period. There was no primary, secondary, or safety issue in the brodalumab patients. The reason for the switch was due to the abrupt cessation of a clinical trial of brodalumab for administrative reasons.¹⁸

In contrast to Piaserico et al.³, Georgakopoulos et al.¹⁹ showed that the same might not be true for IL-17A antagonists, where efficacy outcomes did not correlate with reason for secukinumab discontinuation and the duration of secukinumab therapy had no effect on efficacy outcomes when switched to ixekizumab in their case series. More specifically, in this Canadian multicentre retrospective study of 17 secukinumab non-responders, there were 4 primary secukinumab non-responders whom all responded to ixekizumab, reaching PASI75 or a physician's global assessment (PGA) of 0 or 1. There were 9 secondary non-responders to secukinumab where 8 of the 9 responded to ixekizumab with a PASI75 or PGA of 0 or 1. There were 4 patients who stopped secukinumab due to intolerance or non-drug related reasons and 3 were able to

achieve a PASI75 or PGA of 0 or 1 on ixekizumab.

Overall, their results suggested that a large proportion of secukinumab non-responders who switched to ixekizumab will experience an improved clinical response regardless of the reason or timing of secukinumab discontinuation. Not all patients who experienced an adverse event to secukinumab will experience the same issue with ixekizumab but could experience new adverse events as well. It may be worth noting, especially with the secondary non-responders, that the primary outcome of this study was taken at the end of the ixekizumab loading phase (week 12), which is obviously a higher dose than during the maintenance phase. As secondary non-responders to secukinumab, they would have also responded well during the induction phase of this biologic and therefore it is still possible that these patients will be secondary non-responders to ixekizumab when observed at later time points on the label maintenance dose.

Gasslitter, I., et al.²⁰ also recently showed successful switching in 26 patients between the three presently available anti-IL-17 agents (secukinumab, ixekizumab and brodalumab). Eighteen patients changed their treatment from secukinumab to ixekizumab and seven patients to brodalumab. Brodalumab was used in 3 cases after the failure of treatment with ixekizumab. In only one case, did the non-response of brodalumab result in a therapy switch to secukinumab. Overall success was seen in over 70% of patients.

Finally, a clinical benefit has also been observed among patients who switched from an anti-IL12/23 inhibitor (ustekinumab) to an anti-IL23 inhibitor (guselkumab). Specifically, a Phase 3 study showed that guselkumab

demonstrated greater efficacy compared with ustekinumab among patients who failed to achieve an Investigator's Global Assessment score of 0 or 1 with ustekinumab therapy. For example, at week 52, greater proportions of patients treated with guselkumab achieved PASI 90 (51.1% vs. 24.1%; $P < 0.001$) and PASI 100 (20.0% vs. 7.5%; $P = 0.003$) compared with the randomized ustekinumab group.²¹ Similarly, a Phase 2 study showed that patients who have been previously treated with ustekinumab, when re-treated with risankizumab, maintained or improved PASI 90 response rates.²²

Overall, regardless of the biologic, switching agents can significantly improve outcomes for patients.²³

CONCLUSION

Transitioning between biologics is now a privilege and a better way to optimize treatment for patients with moderate to severe psoriasis to improve their quality of life.

Conflict of Interest Disclosures: Ron Vender has served on Advisory Board and Consultant and Principal Investigator and Speaker for Abbvie, Amgen, Bausch-Health, Celgene, Centocor, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB

Funding: None

Corresponding Author:
 Ron Vender, MD, FRCPC
 Dermatrials Research Inc.
 707-25 Charlton Ave East
 Hamilton ON
 L8N 1Y2
 Tel: (905) 517-8119
 Email: ron.vender@me.com

References:

1. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res.* 2010;303(1):1-10.
2. Gladman D, Poulin Y, Adams K, et al. Treating Psoriasis and Psoriatic Arthritis: Position Paper on Applying the Treat-to-target Concept to Canadian Daily Practice. *The Journal of Rheumatology.* Apr 2017;44(4):519-534.
3. Piaserico, Stefano et al. Efficacy of switching between tumor necrosis factor- α inhibitors in psoriasis: Results from the Italian Psocare Registry. *J Am Acad Dermatol.* 2014;70(2):257-262.e3.
4. Mrowietz, U. , Steinz, K. and Gerdes, S., Psoriasis: to treat or to manage? *Exp Dermatol.* 2014;23:705-709. doi:[10.1111/exd.12437](https://doi.org/10.1111/exd.12437)
5. Gulliver, W., Lynde, C., Dutz, J. et al. Think beyond the Skin. 2014 Canadian Expert Opinion Paper on Treating to Target in Plaque Psoriasis. *Journal of Cutaneous Medicine and Surgery.* 2015;19(1);22–27. <https://doi.org/10.2310/7750.2014.13151>
6. Mrowietz, U. , de Jong, E. , Kragballe, K. , et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2014;28:438-453.
7. Smith, C., Jabbar-Lopez, Z., Yiu, Z., et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis. *Br J Dermatol.* 2017;177:628-636.
8. Dunbar-Jacob, J. et al. Treatment adherence in chronic disease. *Journal of Clinical Epidemiology.* 54(12);S57-S60.
9. Ahluwalia, V., Rampakakis, E., Movahedi, M. et al. Predictors of patient decision to discontinue anti-rheumatic medication in patients with rheumatoid arthritis: results from the Ontario best practices research initiative. *Clin Rheumatol.* 2017;36:2421. <https://doi.org/10.1007/s10067-017-3805-4>
10. Cather JC, Crowley JJ. Use of biologic agents in combination with other therapies for the treatment of psoriasis. *Am J Clin Dermatol.* 2014;15(6):467-78.
11. Choi, Young M. et al. From the Medical Board of the National Psoriasis Foundation: Perioperative management of systemic immunomodulatory agents in patients with psoriasis and psoriatic arthritis. *J Am Acad Dermatol.* 2016;75(4):798-805.e7.
12. Mrowietz U, Kragballe K, Reich, et al. Definition of treatment goals for moderate to severe psoriasis:

- a European consensus. *J Eur Acad Dermatol Venereol*. 2011;25(Suppl 3):1–13.
13. Downs, A. Observational case series on a group of patients with severe psoriasis who failed to respond to antitumour necrosis factor α biologics and switched to ustekinumab. *Br J Dermatol*. 2010;163:433-434.
 14. Puig, et al. Spanish Evidence-Based Guidelines on the Treatment of Psoriasis With Biologic Agents. Part 1: On Efficacy and Choice of Treatment. *Actas Dermo-Sifiligráficas* (English Edition). Oct 2013;104(8):694-709.
 15. Menter A, Strober B, Kaplan D, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.
 16. National Institute for Health and Care Excellence, NICE Guidelines. Oct 2012-Updated Dec 2017;Sec1.5.3.4 Psoriasis: assessment and management.
 17. Leman, J. and Burden, A. Sequential use of biologics in the treatment of moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2012;167(Suppl 3):12-20.
 18. Vender R. Transitioning Between Brodalumab and Secukinumab in Moderate to Severe Psoriasis: An Early Look. *J Drugs Dermatol*. August 2016;15(8):941-43.
 19. Georgakopoulos JR Phung M, Ighani, A, et al. Efficacy and safety of switching to ixekizumab in secukinumab nonresponders with plaque psoriasis: A multicenter retrospective study of interleukin 17A antagonist therapies. *J Am Acad Dermatol*. July. 2018;79(1):155-57.
 20. Gasslitter, I Kirsten, N., Augustin, M. et al. Successful intra-class switching among IL-17 antagonists: a multicentre, multinational, retrospective study. *Arch Dermatol Res* (2019).
 21. Langley, R. , Tsai, T. , Flavin, S. , et.al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. *Br J Dermatol*. 2018;178:114-123.
 22. Clinical Response Following Re-Treatment with a Selective IL-23p19 Inhibitor Risankizumab (BI 655066) or Switching from Ustekinumab to Risankizumab in Patients with Moderate-to-Severe Chronic Plaque Psoriasis;Papp K, et al. (FC03.04; Oral Session; Thursday, September 29, 2016; 1:45-1:55 p.m. CET).
 23. Hu, Y., Chen, Z., Gong, Y. et al. A Review of Switching Biologic Agents in the Treatment of Moderate-to-Severe Plaque Psoriasis. *Clin Drug Invest*. 2018;38:191.