The Journal of Rheumatology 2024;51 Suppl 2:89–92
doi:10.3899/jrheum.2024-0293
First Release July 15 2024

The Journal of Rheumatology

GRAPPA Debate: Targeted Small Molecules Versus Biologics as First-Line Systemic Therapy After Conventional Therapy for Moderate-to-Severe Psoriasis

Wilson Liao[1], April W. Armstrong[2], and Kristina Callis Duffin[3]

ABSTRACT. In this debate at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting, arguments were made contrasting the first-line use of oral targeted small-molecule drugs vs biologic therapy for the treatment of moderate-to-severe psoriasis (PsO) after failure of conventional therapy. Arguments in favor of small-molecule drugs included good efficacy and safety, patient preference, cost savings, global health equity, and environmental stewardship. Arguments in favor of biologics included superior efficacy, excellent safety, availability of long-term data, pediatric regulatory approvals, and potential benefit for comorbidities. By the end of the debate, there was recognition of significant pros and cons of each approach. Both small-molecule drugs and biologic therapy are valuable options for PsO treatment, and their use can be tailored toward specific individuals or healthcare systems.

Key Indexing Terms: biologic therapy, GRAPPA, psoriasis, psoriatic arthritis, small-molecule inhibitor, therapeutic

Introduction

Psoriatic disease treatments have advanced recently, with newer therapies (biologics, small-molecule inhibitors) that can be used beyond conventional treatments (eg, topical steroids and phototherapy) and systemic agents (eg, methotrexate, acitretin, cyclosporine, fumarates, leflunomide, and sulfasalazine).[1] Biologic therapies are protein-based treatments that target specific immune pathways and cytokines relevant to psoriasis (PsO) and psoriatic arthritis (PsA). Examples include tumor necrosis factor inhibitors (TNFi; etanercept, adalimumab, infliximab, certolizumab pegol, golimumab), interleukin 17 inhibitors (IL-17i; secukinumab, ixekizumab, brodalumab, bimekizumab), IL-12/23i (ustekinumab), and IL-23i (guselkumab, risankizumab, tildrakizumab). Targeted small-molecule drugs are small chemical compounds that target specific immune molecules. Examples include phosphodiesterase 4 inhibitors (PDE4i; apremilast), Janus kinase inhibitors (JAKi; tofacitinib, upadacitinib), and tyrosine kinase 2 inhibitors (TYK2i; deucravacitnib). Clinicians treating moderate-to-severe PsO are often faced with a choice of using biologic agents or targeted small-molecule drugs. In a debate moderated by Dr. April Armstrong at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting, Dr. Wilson Liao argued in favor of small-molecule drugs for the treatment of moderate-to-severe PsO (and PsA when present) after failure of conventional therapy. The counterargument in favor of biologic therapy was presented by Dr. Kristina Callis Duffin.

As part of the supplement series GRAPPA 2023, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

[1]W. Liao, MD, Department of Dermatology, University of California San Francisco, San Francisco, California; [2]A.W. Armstrong, MD, MPH, Division of Dermatology, University of California Los Angeles, Los Angeles, California; [3]K. Callis Duffin, MD, MS, Department of Dermatology, Spencer Fox Eccles School of Medicine, University of Utah, Salt Lake City, Utah, USA.

WL has received research grant funding from Amgen, Janssen, Leo, Novartis, Pfizer, Regeneron, and Trex Bio. AWA has served as a research investigator, scientific advisor, or speaker for AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Mindera, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, and Pfizer. KCD has served as a consultant (received honoraria) for AbbVie, Amgen/Celgene, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Stiefel, and CorEvitas; as a speaker for Novartis; and as an investigator for AbbVie, Amgen/Celgene, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, Novartis, Pfizer, Regeneron, Stiefel, and UCB.

This paper does not require institutional review board approval.

Address correspondence to Prof. W. Liao, Department of Dermatology, University of California San Francisco, Box 0808, San Francisco, CA 94143, USA. Email: wilson.liao@ucsf.edu.

Accepted for publication March 17, 2024.

Oral small-molecule inhibitors as first-line agents after conventional therapy

Even in the current era of biologic therapy, conventional systemic therapies (methotrexate, acitretin, cyclosporine, fumarates, leflunomide, and sulfasalazine) are accepted worldwide by dermatologists and rheumatologists as appropriate first-line therapy for moderate-to-severe PsO and PsA.[1] Dr. Liao argued that if biologics are a truly superior option, they would have supplanted conventional systemic therapy. He argued that newer oral small molecules can be considered more effective, safe, and evolved versions of conventional systemic therapy.

Second, Dr. Liao noted the good efficacy of small-molecule

drugs for treating PsO based on clinical trial data. In PsO phase III trials, achieving a target static physician global assessment (sPGA) of 0/1 (clear/almost clear) at week 24 was ~54% for the TYK2i deucravacitinib and ~30% for the PDE4i apremilast, which is comparable to the efficacy achieved by biologics such as the TNFi adalimumab and etanercept.[2,3] In PsA phase III trials, an American College of Rheumatology 20% improvement (ACR20) target was achieved in ~68% of subjects at week 52 for the JAKi tofacitinib and ~73% at week 24 for the JAKi upadacitinib, which were both noninferior to adalimumab.[4,5] Small-molecule drugs exhibit decreased immunogenicity relative to biologic agents and can have broader mechanisms of action with multiple inflammatory cytokines targeted.

Third, Dr. Liao noted the excellent safety profile of small-molecule drugs. Apremilast does not require any routine laboratory monitoring and can be safely used in patients with cancer or HIV, or in those who are immunosuppressed.[6] Deucravacitinib has a low rate of serious infection (1-2%) or herpes zoster reactivation (1%), with no clinically meaningful laboratory abnormalities.[2,3] Although tofacitinib and upadacitinib have black box warnings, the data contributing to these warnings were largely in patients with rheumatoid arthritis (RA), who tend to be older and have more comorbidities than patients with PsA. The risks associated with tofacitinib and upadacitinib can be managed by carefully selecting appropriate patients and using laboratory monitoring, as rheumatologists and dermatologists have done for decades with cyclosporine, methotrexate, and acitretin.[7]

Fourth, it was noted that many patients prefer oral therapies over injectable therapies[8] and that oral therapies avoid many negative aspects of biologic therapies such as injection-site pain, possible anaphylaxis, loss of drug due to misfire, refrigeration requirement, difficulty with travel, and the hassle of disposal.

Finally, Dr. Liao noted that small-molecule drugs are more cost-effective in some healthcare systems compared to biologics.[9,10] Small-molecule drugs may be more globally and racially equitable (eg, for non-North American or European countries) since small-molecule drugs are easier to synthesize, store, and obtain regulatory approval, whereas biologic therapies are expensive to manufacture, distribute, store, and have a costly regulatory approval pathway. From an environmental standpoint, plastic biologic injectable devices lead to biohazard waste that can negatively affect the environment.[11]

Biologics as first-line agents after conventional therapy

Dr. Callis Duffin presented several arguments in favor of first-line biologics for PsO. Biologic therapies for moderate-to-severe PsO are effective, targeted, and are administered at longer intervals, making them more convenient. They have excellent safety profiles and have excellent data in support of efficacy in special populations, particularly children, but also including individuals with malignancy, viral hepatitis, and immunosuppression. There are now 12 biologic agents approved in many countries for moderate-to-severe plaque PsO.

The primary reason to use biologics as first-line therapy for PsO is their superior efficacy. Although small-molecule inhibitors like deucravacitinib and apremilast have comparable efficacy to older-generation biologics (etanercept, adalimumab, and ustekinumab), the newer-generation IL-17i and IL-23i demonstrate much higher rates of achieving PGA 0/1 (clear/almost clear) or Psoriasis Area and Severity Index (PASI) 90.[12-14] All biologics except etanercept have clear superior efficacy by PASI75 and PASI90 at primary endpoints, with some demonstrating high rates of sustained PASI90 through 5-year extension trials.[15]

Biologics are a relatively new class of therapy compared to historical drugs like topicals, phototherapy, and conventional oral medications. When they were first on the market, biologics were tiered last in the therapeutic ladder, largely related to their unknown long-term safety and cost.[16,17] Now, after more than 2 decades of experience, clinical trial data from long-term extensions and registries such as the Psoriasis Longitudinal Assessment and Registry (PSOLAR) and ESPRIT demonstrate that there are no cumulative or unanticipated risks.[18-20] Additionally, IL-12/23i and IL-23i have excellent safety profiles without risk of some of the rare concerns with biologics (eg, multiple sclerosis with TNFi, inflammatory bowel disease with IL-17i, reactivation of latent tuberculosis with TNFi).[21-24] Despite early concerns around heart disease, long-term studies show that many biologics, particularly TNFi, are protective against cardiovascular (CV) events.[25-29] Similarly, concerns regarding increased cancer risk observed in the RA population have not been replicated in most studies of patients with PsO.[30,31] Oral JAKi are considered contraindicated in patients with CV disease or risk of venous thromboembolism.[27,28] Early data for deucravacitinib suggest less concern about these CV adverse events, but long-term data are not yet available.[29]

Many of the biologics also have data supporting safety and efficacy in special populations for either PsO or PsA, including children and women who are pregnant or breastfeeding.[32,33] Drugs approved by the US Food and Drug Administration for use in children for plaque PsO include etanercept, secukinumab, ixekizumab, and ustekinumab; adalimumab and infliximab are also approved for children with juvenile idiopathic arthritis and related indications.[34] The structure of certolizumab pegol, a Fab fragment of a monoclonal antibody, has been shown to cross the placenta or into breast milk at negligible levels.[32,33]

One commonly cited barrier to biologic use is that they must be administered by subcutaneous injection or intravenously. This barrier is easily overcome with patient education[35] and the realization that the infrequency of dosing (weekly, monthly, bimonthly, or quarterly) often outweighs the daily or twice-daily administration of oral therapies. Aside from injection-site reactions, which are common and inconsequential, biologics are not associated with significant rates of day-to-day adverse effects. This is in contrast to the oral drug apremilast, which causes headaches, nausea, and diarrhea in 10% to 30% of patients, subsequently leading to discontinuation in up to 10% of patients well before any efficacy is achieved.[36]

Discussion

Both small-molecule drugs and biologic therapy are valu-

able options for PsO treatment, and their use can be tailored toward specific individuals or healthcare systems. Apremilast has distinct safety and administration advantages over biologics; however, apremilast is not more advantageous when considering efficacy, time to onset of therapeutic benefit, or day-to-day adverse effects. Deucravacitinib offers improved efficacy with fewer short-term adverse effects compared to biologics, but it has limited long-term data and no real-world registry data to support its long-term safety with regard to more serious and uncommon adverse effects like venous thromboembolism. Cost, local/regional formulary policies, access, refrigeration, and needle waste will always be cited as barriers to first-line biologic use. However, moderate-to-severe PsO often demands biologic therapy, even as first-line therapy before conventional therapies. We hope that this debate highlights the range of issues and trade-offs that must be considered when selecting treatment for patients with psoriatic disease. At the end of the debate, a show of hands suggested that more people agreed that oral therapy should be the first-line therapy after conventional therapy, and Dr. Liao was declared the winner of the contest.

ACKNOWLEDGMENT

We thank DerMEDit (www.dermedit.com) for editing services in preparation of this manuscript.

REFERENCES

1. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA 2020;323:1945-60.
2. Armstrong AW, Gooderham M, Warren RB, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PsO-1 trial. J Am Acad Dermatol 2023;88:29-39.
3. Strober B, Thaçi D, Sofen H, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 program for evaluation of TYK2 inhibitor psoriasis second trial. J Am Acad Dermatol 2023;88:40-51.
4. Mease P, Hall S, Fitzgerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017; 377:1537-50.
5. McInnes IB, Anderson JK, Magrey M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. N Engl J Med 2021;384:1227-39.
6. Mease PJ, Hatemi G, Paris M, et al. Apremilast long-term safety up to 5 years from 15 pooled randomized, placebo-controlled studies of psoriasis, psoriatic arthritis, and Behcet's syndrome. Am J Clin Dermatol 2023;24:809-20.
7. Samuel C, Cornman H, Kambala A, Kwatra SG. A review on the safety of using JAK inhibitors in dermatology: clinical and laboratory monitoring. Dermatol Ther 2023;13:729-49.
8. Komine M, Kim H, Yi J, et al. A discrete choice experiment on oral and injection treatment preferences among moderate-to-severe psoriasis patients in Japan. J Dermatol 2023;50:766-77.
9. Wu JJ, Wang CA, Jobson G, et al. Treatment patterns and healthcare costs among patients with psoriasis initiating apremilast or biologics: a retrospective claims database cohort analysis. J Dermatolog Treat 2023;34:2177095.
10. Barbieri M, Loconsole F, Migliore A, Capri S. A cost-effective and budget impact analysis of apremilast in patients with psoriasis in the Italian setting. J Med Econ 2020;23:362-70.
11. Janik-Karpinska E, Brancaleoni R, Niemcewicz M, et al. Healthcare waste-a serious problem for global health. Healthcare 2023;11:242.
12. Reich K, Gordon KB, Strober BE, et al. Five-year maintenance of clinical response and health-related quality of life improvements in patients with moderate-to-severe psoriasis treated with guselkumab: results from VOYAGE 1 and VOYAGE 2. Br J Dermatol 2021;185:1146-59.
13. Blauvelt A, Lebwohl MG, Mabuchi T, et al. Long-term efficacy and safety of ixekizumab: a 5-year analysis of the UNCOVER-3 randomized controlled trial. J Am Acad Dermatol 2021;85:360-8.
14. Papp KA, Blauvelt A, Puig L, et al. Long-term safety and efficacy of risankizumab for the treatment of moderate-to-severe plaque psoriasis: interim analysis of the LIMMitless open-label extension trial up to 5 years of follow-up. J Am Acad Dermatol 2023;89:1149-58.
15. Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev 2023;7:CD011535.
16. Jabbar-Lopez ZK, Wu KCP, Reynolds NJ. Newer agents for psoriasis in adults. BMJ 2014;349:g4026.
17. Loftholm PW. The psoriasis treatment ladder: a clinical overview. J Mod Pharm 2001;8:12-5.
18. Menter A, Thaçi D, Wu JJ, et al. Long-term safety and effectiveness of adalimumab for moderate to severe psoriasis: results from 7-year interim analysis of the ESPRIT registry. Dermatol Ther 2017; 7:365-81.
19. Gottlieb AB, Kalb RE, Langley RG, et al. Safety observations in 12095 patients with psoriasis enrolled in an international registry (PSOLAR): experience with infliximab and other systemic and biologic therapies. J Drugs Dermatol 2014;13:1441-8.
20. Bissonnette R, Gottlieb AB, Langley RG, et al. Signal detection and methodological limitations in a real-world registry: learnings from the evaluation of long-term safety analyses in PSOLAR. Drug Saf 2021;44:699-709.
21. Havrdová E, Belova A, Goloborodko A, et al. Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study. J Neurol 2016;263:1287-95.
22. Segal BM, Constantinescu CS, Raychaudhuri A, et al. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. Lancet Neurol 2008;7:796-804.
23. Nogueira M, Warren RB, Torres T. Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis – time for a paradigm change. J Eur Acad Dermatol Venereol 2021;35:824-34.
24. Choi MG, Ye BD, Yang SK, Shim TS, Jo KW, Park SH. The risk of tuberculosis in patients with inflammatory bowel disease treated with vedolizumab or ustekinumab in Korea. J Korean Med Sci 2022;37:e107.
25. Griffiths C, Reich K, Gooderham M, et al. Long term safety of ixekizumab in patients with moderate-to-severe plaque psoriasis up to 5 years: pooled data from 16 clinical trials. Poster P0372. Paper presented at: EADV Virtual Congress; 2020 October 29-31.
26. Papp KA, Griffiths CEM, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol 2013;168:844-54.
27. Kim BR, Lee KH, Kim J, et al. Association between cardio-cerebrovascular disease and systemic antipsoriatic therapy in psoriasis patients using population-based data: a nested case-control study. J Dermatol 2023;50:1442-9.
28. Choi H, Uceda DE, Dey AK, et al. Treatment of psoriasis with biologic therapy is associated with improvement of coronary artery plaque lipid-rich necrotic core: results from a prospective, observational study. Circ Cardiovasc Imaging 2020;13:e011199.

29. Bristol Myers Squibb. New two-year deucravacitinib data reinforce durable efficacy and consistent safety profile in treatment of moderate to severe plaque psoriasis. [Internet. Accessed March 28, 2024.] Available from: https://news.bms.com/news/details/2022/New-Two-Year-Deucravacitinib-Data-Reinforce-Durable-Efficacy-and-Consistent-Safety-Profile-in-Treatment-of-Moderate-to-Severe-Plaque-Psoriasis/default.aspx
30. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275-85.
31. Vaengebjerg S, Skov L, Egeberg A, Loft ND. Prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. JAMA Dermatol 2020;156:421-9.
32. Clowse ME, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis 2017;76:1890-6.
33. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis 2018;77:228-33.
34. Hebert AA, Browning J, Kwong PC, Duarte AM, Price HN, Siegfried E. Managing pediatric psoriasis: update on treatments and challenges-a review. J Dermatolog Treat 2022;33:2433-42.
35. Boye K, Ross M, Mody R, Konig M, Gelhorn H. Patients' preferences for once-daily oral versus once-weekly injectable diabetes medications: the REVISE study. Diabetes Obes Metab 2021;23:508-19.
36. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol 2015;73:37-49.