The Journal of Rheumatology 2022;49 Suppl 1:26–31
doi:10.3899/jrheum.211325
First Release February 15 2022

The Journal of Rheumatology

Clinical Controversies in Psoriatic Disease: The Use of IL-17i/IL-23i Versus TNFi as First-line Advanced Therapy in Psoriatic Arthritis

Deepak R. Jadon[1], Arthur Kavanaugh[2], and Ying Ying Leung[3]

ABSTRACT. Psoriatic arthritis (PsA) is a complex, heterogeneous disease, with disease activity in various domains. In recent years, many novel treatments with diverse mechanisms of action have been introduced into the clinical setting. Numerous factors go into the choice and sequencing of different therapies for individual patients. At the 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting, a point/counterpoint debate was held addressing therapeutic choices. Specifically, the question addressed was whether interleukin (IL)-17/IL-23 inhibitors or tumor necrosis factor inhibitors are the appropriate initial therapy for patients with PsA.

Key Indexing Terms: GRAPPA, psoriatic arthritis

Introduction

The availability of novel agents with distinct mechanisms of action for the treatment of patients with psoriatic arthritis (PsA) has permitted greater choice and allowed for improved outcomes. However, PsA is a heterogeneous condition with varied levels of disease activity across multiple domains. With a paucity of head-to-head (H2H) studies to date, and in the absence of definitive data that would allow for "personalized medicine" for individual patients, the multiplicity of treatment options can present challenges for patients and providers as regards sequencing therapeutic choices. At the 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting, a point/counterpoint debate was held addressing therapeutic choices. The debate question was as follows: In the treatment of patients with psoriatic arthritis, should inhibitors of interleukin (IL)-17 (IL-17i) or IL-23 (IL-23i) be used before inhibitors of tumor necrosis factor (TNFi)?

As part of the supplement series GRAPPA 2021, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

DRJ acknowledges that this research was supported by Cambridge Arthritis Research Endeavour (CARE) and the National Institute for Health Research Cambridge Biomedical Research Centre (BRC-1215-20014). YYL is supported by the National Medical Research Council, Singapore (NMRC/CSA-Inv/0022/2017).

[1]D.R. Jadon, MBBCh, MRCP, PhD, Rheumatology Research Unit, Department of Medicine, University of Cambridge, Cambridge, UK; [2]A. Kavanaugh, MD, Division of Rheumatology, Allergy and Immunology, University of California, San Diego, California, USA; [3]Y.Y. Leung, MB, ChB, MD, Department of Rheumatology, Singapore General Hospital, and Duke-NUS Medical School, Singapore.

DRJ received research grants, education grants, and/or honoraria from pharmaceutical companies, including AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Fresenius Kabi, Galapagos/Gilead, GSK, Celltrion, Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, and UCB. AK is consultant to AbbVie, Amgen, Eli Lilly, Janssen, Novartis, and UCB. YYL received honoraria from AbbVie, DKSH, Janssen, Novartis, and Pfizer.

This paper does not require institutional review board approval.

Address correspondence to Dr. D.R. Jadon, Rheumatology Research Unit, Department of Medicine, University of Cambridge, Cambridge CB2 0QQ, UK. Email: dj351@medschl.cam.ac.uk

Accepted for publication December 7, 2021.

Proponent Evidence

Dr. Deepak Jadon presented evidence for the proponent argument, that IL-17i or IL-23i should be used as the first-line advanced therapy for patients with PsA, ahead of TNFi therapy. This proposal is based upon 8 key themes: (1) the IL-17/23 axis is very important in PsA; (2) IL-17i optimizes more clinical disease domains through better skin responses, with equitable musculoskeletal efficacy, and do so even in patients with milder skin psoriasis (PsO); (3) using IL-17i avoids the need for concomitant methotrexate (MTX) prescription; (4) IL-17i and IL-12/23i persistence has been shown to be better than TNFi; (5) first-line use of IL-17i and IL-12/23i aligns with the emerging concept of "getting immunotherapy right first time"; (6) IL-17i and IL-23i are unique in having emerging randomized controlled trial (RCT) evidence for efficacy in axial PsA (axPsA); (7) IL-17i and IL-12/23i have less frequent dosing than TNFi; and (8) few or no safety signals have been reported with IL-17i and IL-12/23i compared with TNFi for tuberculosis (TB), demyelination, and paradoxical immune reactions.

1. The IL-17/23 axis is important in PsA. Research and clinical practice experience have demonstrated the importance of the IL-17/23 axis in psoriatic disease (PsD), including PsA. Animal models show the pathogenesis of enthesitis stemming from highly specific entheseal-resident T cells, influenced by IL-23, in a manner that can be independent of TNF.[1] McGonagle et al have summarized the literature on differential cytokine effects in PsA, cutaneous PsO (PsC) and ankylosing spondylitis (AS).[2] They concluded that while TNF is moderately important in PsA,

PsC, and AS, IL-17A is far more important. It was also concluded that IL-23 is more important than TNF in PsC. In rheumatoid arthritis (RA), TNF-mediated synovitis is important, but in PsA we observe enthesitis, osteoproliferation, ankylosis, osteolysis, and osteoporosis.[2,3] These pathologies involve novel cells such as γδ T cells, invariant natural killer T cells, and mucosal-associated invariant T cells, which are most associated with the IL-17/23 axis.[2,3]

Biological models must be confirmed in the clinical environment. The ECLIPSA study was a prospective, open-label RCT in which PsA patients with active enthesitis were randomized 1:1 to either IL-12/23i (ustekinumab [UST]) or TNFi.[4] The RCT's primary endpoint of resolution of enthesitis was achieved in 74% of 46 patients who completed treatment with an IL-12/23i vs only 42% of those treated with TNFi, as measured by the Spondyloarthritis Research Consortium of Canada index (score = 0) at week 24 ($P = 0.02$). The IL-12/23i group achieved superior secondary endpoint responses compared with TNFi for enthesitis ($P = 0.01$) and skin PsO ($P = 0.03$), but not for arthritis ($P = 0.95$).[4] Another 52-week prospective, open-label feasibility study explored the regression of peripheral subclinical enthesopathy in therapy-naïve patients treated with UST (IL-12/23i) for moderate-to-severe chronic plaque PsO.[5] A total of 70 patients were studied, and within 12 weeks, suppression of ultrasound-measured subclinical enthesitis using UST was demonstrated, and maintained to week 52. Such comprehensive studies have not been performed with TNFi in PsC or PsA.

2. IL-17i optimizes more clinical disease domains than TNFi. Two H2H RCTs of IL-17i (secukinumab [SEC][6] and ixekizumab [IXE][7]) vs TNFi (adalimumab [ADA]) have shown comparable efficacy for musculoskeletal indices, but IL-17i was far more efficacious for skin indices. Since those publications, further results have emerged and will be presented here. At the European Alliance of Associations for Rheumatology (EULAR) 2021 annual congress, data from the EXCEED study[6] showed SEC to be statistically more likely than ADA to improve physician global assessment of disease activity as early as week 24 ($P = 0.002$) and maintained to week 52 ($P = 0.02$). SEC and ADA were no different in terms of improvement in disability (as measured by the Health Assessment Questionnaire–Disability Index) or quality of life (as measured by the 36-item Short Form Health Survey physical component summary or mental component summary).[8]

There is a notable lack of RCTs using musculoskeletal ultrasound to demonstrate the efficacy of TNFi. The randomized, placebo-controlled, phase III ULTIMATE RCT enrolled 166 disease-modifying antirheumatic drug (DMARD)-inadequate responders (IRs) and biologic-naïve PsA patients with active ultrasound synovitis, clinical synovitis, or clinical enthesitis, and randomized them to SEC or placebo.[9] The primary endpoint of mean change in the ultrasound Global Outcome Measure in Rheumatology in Clinical Trials–EULAR Synovitis Score (GLOESS) at week 12 was higher with SEC than placebo (mean change −9 vs −6; $P = 0.004$), and difference evident from as early as week 1. Key secondary endpoints, including American College of Rheumatology (ACR) 20 and ACR50 responses, were also achieved. This novel ultrasound-based RCT study proved that the IL-17i, SEC, attains a rapid and significant objective reduction in synovitis in patients with PsA.[9]

Results from the SPIRIT-H2H study show that IL-17i should not just be reserved for PsA patients with moderate-to-severe PsO.[10] Even in the patients with less severe PsO, IXE was statistically more likely than ADA to achieve minimal disease activity (MDA; 45.7% vs 34.6%; $P \leq 0.05$) and very low disease activity (14.1% vs 10.4%; treatment by subgroup interaction $P \leq 0.10$) at week 24.[10]

3. IL-17i use avoids the need for concomitant MTX prescription. The ability to use IL-17i monotherapy is a major advantage over the common practice to combine MTX with monoclonal TNFi therapy. Not having to coprescribe MTX improves the risk of adverse effects, frequency of blood test monitoring, and polypharmacy, and Dr. Jadon's clinical practice experience is that patients would prefer not to be taking MTX.

Posthoc subgroup analysis of the open-label, rater-blinded SPIRIT-H2H RCT demonstrated that IXE monotherapy is as good as IXE-MTX combination therapy at week 52 for articular endpoints (ACR50).[11] However, ADA articular efficacy was markedly improved when combined with MTX (ACR50 response improved from 42% to 56%), although this result was still not better than IXE monotherapy at week 52. The same pattern was observed for other endpoints, including MDA, Disease Activity Index for Psoriatic Arthritis, enthesitis resolution, and dactylitis resolution, with greater magnitude for skin scores.[11]

4. IL-17i and IL-12/23i persistence is better than TNFi. In Dr. Jadon's clinical experience, patients wish for their treatments to be effective (efficacious) and to continue being effective (persistence), thereby reducing anxiety relating to eventual treatment failure.

Drug survival results from the British Dermatology Registry have shown that the probability over time of remaining on ADA is far lower than in UST or SEC.[12] In a total of 9652 patients studied, the overall drug survivals of ADA, SEC, and UST in year 1 were 0.78 (95% CI 0.77–0.79), 0.88 (95% CI 0.86–0.91), and 0.88 (95% CI 0.87–0.89), respectively. The adjusted hazard ratios (aHR) for discontinuation of ADA and SEC compared with UST were 2.11 (95% CI 1.76–2.54) and 0.67 (95% CI 0.40–1.11), respectively. Subanalyses for the presence of PsA predicted for drug survival in the ADA and SEC cohorts, with aHR of 0.67 (95% CI 0.51–0.88 and 0.70 (95% CI 0.40–1.24), respectively, but for discontinuation in the UST cohort, with an aHR of 1.42 (95% CI 1.12–1.81).[12]

Results from the Psoriasis Longitudinal Assessment and Registry corroborate these findings, with 5-year drug survival being far poorer for the 3 TNFi therapies (infliximab [IFX] HR 2.73, ADA HR 4.16, etanercept [ETN] HR 4.91) compared with UST (all $P \leq 0.001$). The results were independent of first-, second-, or third-line use of advanced therapy.[13] Within the constraints of statistical power, analyses in patients with concurrent PsA reflected observations in the overall PsO patient population.

These results are all in keeping with Dr. Jadon's clinical practice experience of persistence with these therapies.

5. Getting it right first time. The concept of "getting it right first time" is gaining traction in immunotherapy. The better efficacy of IL-17i and IL-23i in TNF-naïve patients might not be because biologic-naïve patients are preselected responders. Instead, it might be because failure with the first biologic therapy primes the immune system to respond less well to subsequent biologics—and perhaps also to more readily develop antidrug antibodies.

The p19-IL-23i guselkumab showed good—but still lower—efficacy, as measured by ACR20/50/70 response rates in TNFi-naïve compared with TNFi-IR patients in the DISCOVER-1 RCT of guselkumab vs placebo in patients with active PsA to week 52.[14] The same pattern was observed in an RCT of SEC vs placebo.[15] These results give credence to the approach of "getting immunotherapy right first time" (GiRFT).

6. IL-17i has emerging RCT evidence for efficacy in axPsA. Dr. Jadon is not aware of any dedicated RCTs testing the efficacy of TNFi in patients with axPsA. Instead, we extrapolate axial spondyloarthritis (axSpA) data to our patients with axPsA, despite there being much evidence that they are pathologically and clinically different.

The MAXIMISE (Managing Axial Manifestations in PsA with Secukinumab) trial was a dedicated phase IIIb, double-blind, placebo-controlled, multicenter, 52-week trial testing SEC in axPsA.[16] Among the total cohort of 498 patients with PsA, excellent Assessment of SpondyloArthritis international Society (ASAS) 20 and ASAS40 responses were observed in patients with axPsA treated with SEC vs placebo; these were not dissimilar to the responses seen in RCTs of SEC dedicated to axSpA. The clinical improvements in symptoms and signs were also corroborated by statistically significant and objective improvements in the Berlin magnetic resonance imaging score for the spine and sacroiliac joints.[17]

Pooled data from the guselkumab DISCOVER-1 and DISCOVER-2 RCTs were subanalyzed for PsA patients with proven radiological sacroiliitis. There were more significant improvements in axial indices in the guselkumab group compared with placebo-treated patients with axPsA as measured by the Bath Ankylosing Spondylitis Disease Activity Index 50 and Ankylosing Spondylitis Disease Activity Score responses, as early as week 24 and maintained to week 52.[18]

In the first study of its kind, a dedicated phase IV multicenter RCT (ClinicalTrials.gov: NCT04929210) evaluating the safety and efficacy of guselkumab (p19-IL-23i) in biologic-naïve patients with active axPsA began in 2021 and will complete in 2024.[19]

7. IL-17i and IL-12/23i have less frequent dosing than TNFi. Currently, IL-17i, IL-23i, and IL-12/23i have far less frequent dosing (every 4 weeks, 8 weeks, and 12 weeks, respectively) than TNFi (every 1–2 weeks). Patients with PsA are often relatively young, looking after younger and/or older family members, employed, and possibly traveling for work. Although yet to be studied, the infrequent administration of IL-17i, IL-23i, and IL-12/23i will surely be a favorable factor in patient adherence to medication.

8. There are fewer safety signals with IL-17i and IL-12/23i. In national registries[12] and long-term extension studies of RCTs, fewer adverse safety signals have been reported with IL-17i and IL-12/23i compared with TNFi in terms of TB incidence/reactivation, central nervous system demyelination, and paradoxical immune reactions such as paradoxical PsO. The absence of signals for TB with IL-17 might, in time, permit their use in populous underserved TB-endemic areas, thereby contributing to various initiatives to reduce global health inequalities.

Summary of proponent evidence. To summarize, the IL-17/23 axis is very important in PsD and should be the focus of our treatments. We therefore need to change our approach to GiRFT rather than through trial and error, during which time patients suffer. IL-17i have been shown to optimize more disease domains, through better skin responses and equitable musculoskeletal efficacy. IL-17i have proven efficacy as measured by ultrasound, and excellent musculoskeletal efficacy in patients with milder skin PsO; therefore, IL-17i should not be reserved only for those with moderate-to-severe skin PsO. IL-17i use avoids the need for concomitant MTX, which is a major benefit for our patients. Persistence appears much better with IL-17i and IL-12/23i than with TNFi. There are emerging dedicated RCTs testing IL-17i and IL-23i in patients with axPsA—data that TNFi simply do not have. The infrequent dosing and fewer safety signals with IL-17i and IL-12/23i should not be undervalued.

Opponent Evidence

Dr. Ying Ying Leung reviewed the opponent evidence for this question. The reasons why IL-17i should not be used ahead of TNFi are based on 4 lines of evidence. First, evidence does not support IL-17i being superior in musculoskeletal domains compared to TNFi. Second, other than for skin PsO, IL-17i do not have efficacies in treatment of other extraarticular manifestations of PsA. Third, evidence supporting efficacy regarding cardiovascular outcomes are stronger for TNFi. Fourth, with the availability of biosimilar versions, TNFi are more accessible than IL-17i.

Following the approval of the first TNFi for the treatment of PsA in January 2002 (ETN), 4 other TNFi (IFX, ADA, certolizumab pegol [CZP], and golimumab) have been approved for PsA, with biosimilars now available for 3 of these TNFi. To date, there has been more than 20 years of experience in the use of TNFi in PsA, with accepted efficacy and clinical effectiveness, whereas the first IL-17i (SEC) was approved only in 2016 for treatment of PsA, representing a newer class of treatment option. The efficacies of IL-17i and TNFi for musculoskeletal domains in PsA seems to be very comparable. In the systematic review on efficacy of treatments for peripheral arthritis in PsA by the GRAPPA peripheral arthritis working group, both TNFi and IL-17i were shown to have superior efficacies for active arthritis in PsA compared to placebo for a bundle of outcomes including ACR20/50/70, physical function, pain, quality of life, and structural damage.[20] Using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology,[21] there was a moderate level of evidence showing no statistical significant differences between IL-17i and TNFi in various outcomes. Thus far, there are 2 H2H RCTs comparing clinical efficacy of IL-17i with TNFi. In the EXCEED trial, the efficacy

of SEC was compared to ADA in 853 patients with active PsA, showing no statistically significant difference between arms at week 52.[22] In the SPIRIT H2H trial, IXE was superior to ADA with the primary composite endpoint of ACR50 and Psoriasis Area and Severity Index 100 response at week 24[7]; however, the superiority was driven by the superior skin response for IXE. IXE was noninferior to ADA in achieving ACR20/50/70, swollen and tender joint counts, pain, and physical function.[10] Some caveats should be highlighted in the interpretation of these H2H studies. First, in the EXCEED trial, a higher dose of SEC (300 mg monthly) was used rather than the usual 150 mg monthly to achieve the outcomes, whereas in the SPIRIT H2H trial, 17.5% of patients had severe PsO and received a higher dose of IXE. In both H2H studies, the efficacy of IL-17i in enthesitis and dactylitis was not statistically significantly different compared to ADA. The efficacies of IL-17i and TNFi for axSpA are also comparable. Currently, there are no published H2H RCTs comparing IL-17i and TNFi for axial outcomes. RCTs in axSpA or AS showed superior efficacies for both IL-17i and TNFi compared to placebo. In the updated GRAPPA recommendation, strong recommendation is given equally for IL-17i and TNFi for peripheral arthritis, axial, enthesitis, and dactylitis domains.[23]

Network metaanalysis is a technique for comparing ≥ 3 interventions simultaneously in a single analysis using both direct and indirect evidence across a network of studies.[24] If done properly and if based on strong data, network metaanalysis can provide robust information for comparisons between pairs of interventions that have never been evaluated within individual RCTs. Several network metaanalyses comparing efficacies of biological treatments in PsA have come to a similar and consistent conclusion: the efficacies of IL-17i and TNFi for musculoskeletal domains in PsA were similar, whereas IL-17i have superiority over TNFi for skin domain.[25,26,27] The superiority of IL-17i over TNFi in the PsO domain is consistent with H2H studies for PsO.[7,28] IL-23i, which blocks the proximal signaling in the IL-23/Th17 pathway, has also shown to have superiority over TNFi in H2H studies in PsO.[29,30]

TNFi, particularly the monoclonal antibodies, are effective for the extraarticular domains of PsA. Although SEC given at a high dose was more superior than the standard dose in 1 RCT,[31] SEC failed to meet the primary endpoints for noninfectious uveitis in 3 RCTs.[32] In 2 phase II RCTs for Crohn disease, IL-17i (brodalumab and SEC) did not meet the primary endpoints and actually caused exacerbation of disease and more adverse events.[33,34]

PsA is associated with cardiovascular (CV) comorbidities, and the control of inflammation is associated with positive CV effect. Preliminary studies are emerging to show the association of IL-17i with better results in vasomotor studies and carotid plaques on ultrasound in PsO.[35] These soft outcomes provide indirect evidence of the association of IL-17i and lower atherosclerosis burden. On the other hand, more direct evidence from event rates supporting the beneficial CV effect from TNFi in PsA has become available. A large longitudinal cohort study based on a health claim dataset in PsO has shown fewer CV events in 9148 TNFi users compared to 8581 MTX users at 12 months (HR 0.55, $P < 0.01$), and every 6 months of cumulative exposure to TNFi were associated with an 11% reduction in risk of CV events ($P = 0.02$).[36] A metaanalysis pooling data from 5 studies (49,795 patients with PsA/PsO) found a significant lower relative risk (RR) of CV events with TNFi compared to both topical treatments (RR 0.58, 95% CI 0.43–0.77) or MTX (RR 0.67, 95% CI 0.52–0.88).[37]

With more than 20 years of experience in studies and use of TNFi, the adverse event profile of TNFi is much more established than for newer agents. RCTs designed for evaluation of efficacy are not adequately powered to compare adverse events. Real-life patients who are not eligible for RCTs often have more comorbidities and are more prone to adverse events.[38] Long-term postmarketing surveillance and real-world data from various source and registries are invaluable in assessing drug safety. The long-term safety of ADA in 29,967 adult patients, representing 56,916 patient-years of exposure from global clinical trials across multiple indications, has demonstrated no new safety signals compared to those originally reported.[39] The most frequently reported serious adverse event was infection (3.7/100 person-years [PY]). The rates of serious adverse events of interest remained low and consistent with data derived from other registries.[40,41,42] For instance, prospective data from the US Corrona RA registry on 2798 new initiators of ADA have found a low incidence rate per 100 PY for serious infections.[43] Although the risk of TB may be substantially lower for IL-17i, the comparative risk of infection is similar for TNFi and IL-17i. In a retrospective cohort study of commercially insured patients with PsA or PsO with 11,560 new treatment episodes for biologics between 2015 and 2018 in the US, no increased risk of infection with IL-17i compared with TNFi was found (HR 0.89, 95% CI 0.48–1.66).[44]

One strong point to support TNFi is the availability of effective and safe biosimilars.[45] Disparities in the usage of biologics across countries have been well recognized and availability of agents affects optimal control of PsA.[46,47] Cost and local healthcare policies continue to be relevant barriers to biologic use.[46] Data are emerging to show the effect of biosimilars in bridging the unmet need of undertreatment for patients with active disease.[48]

Although IL-17i represents a new and exciting class of therapeutics in PsA, it may be important to reflect on its RR and benefits compared with TNFi. The key considerations would be whether it is time to push back TNFi in the treatment of PsA, with its long history of usage and accepted efficacies across multiple domains (peripheral arthritis, axial, enthesitis, dactylitis, skin, and nails), including extraarticular manifestations, inflammatory bowel disease, and uveitis. Apart from superiority of IL-17i in the PsO domain, evidence thus far supports equivalent efficacies for IL-17i and TNFi for peripheral arthritis, enthesitis, dactylitis, and axial domains. In addition, TNFi has stronger evidence for its beneficial effects on CV outcomes and proven safety in reproductive health, particularly for CZP. IL-17i may be safer for patients living in localities with high prevalence of TB, yet the risk of serious infection seems to be comparable between the 2 drug classes. In addition, the optimal therapeutic options

should be considered with the appropriate patient characteristic profile. For example, for patients with severe PsO or history of TB, IL-17i may be a good choice. Whereas patients with inflammatory bowel disease, uveitis, or high CV risk, TNFi would be a better option. The choice of biological treatment should be a shared decision between doctor and patient considering risks vs benefits according to the individual's characteristics.

One last word in the debate for optimal first-line strategic therapy for PsA: it is important to remember that there are 30–40% of patients who do not have adequate or meaningful responses regardless of the class of drug given, at least for the musculoskeletal domains. Studies from gene and immune cell signatures revealed possible phenotypes within patients classified as having PsA: the cutaneous, entheseal, and synovial predominant phenotypes. Activation and amplification of the IL-23/Th-17 axis plays a key role in cutaneous and entheseal predominant phenotypes, while the Th-1 pathway is still important in the predominant synovial phenotype.[49] A small RCT by Miyagawa et al[50] provided strong proof of concept for better prediction of response with better phenotyping. Patients with PsA were stratified according to Th-17 or Th-1 predominate subtype by flow cytometry of peripheral blood to undergo strategic therapies of SEC or UST vs TNFi. The study team demonstrated a significantly higher efficacy in ACR20, Disease Activity Score in 28 joints–low disease activity (LDA), and Simplified Disease Activity Index–LDA for patients randomized to the strategic therapy arm rather than the standard biologic therapy arm.[50] With advances in technology, we are getting closer to better understanding the pathological pathways mediating PsD and facilitating the choice of the best therapeutic options according to biomarkers that could predict treatment response. Until we have these properly validated predictive biomarkers to assist our decision making, and while evidence supports equivalent efficacies and harms for TNFi vs IL-17i, perhaps the best way forward is to let the clinicians and patients make the decision according to their risk/benefit preferences.

Conclusion

PsA is a complex, heterogeneous disease that can manifest activity across various domains. In recent years, many novel treatments with diverse mechanisms of action have been introduced into the clinic. Indeed, we have learned about the immunopathophysiology of the disease from clinical studies of various targeted therapies. While we have different potential therapies, at present it is not possible to predict a priori what would be the best drug for an individual patient. In the end, the decision for choice of biologic DMARD should be shared between doctor and patient, with consideration for patient characteristics and preference.

REFERENCES

1. Lories RJ, McInnes IB. Primed for inflammation: enthesis-resident T cells. Nature Medicine 2012;18:1018-9.
2. McGonagle DG, McInnes IB, Kirkham BW, Sherlock J, Moots R. The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies. Ann Rheum Dis 2019; 78:1167-78.
3. Schett G, Lories RJ, D'Agostino MA, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731-41.
4. Araujo EG, Englbrecht M, Hoepken S, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. Semin Arthritis Rheum 2019;48:632-7.
5. Savage L, Goodfield M, Horton L, et al. Regression of peripheral subclinical enthesopathy in therapy-naive patients treated with ustekinumab for moderate-to-severe chronic plaque psoriasis: a fifty-two-week, prospective, open-label feasibility study. Arthritis Rheumatol 2019;71:626-31.
6. McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet 2020;395:1496-505.
7. Smolen JS, Mease P, Tahir H, et al. Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52. Ann Rheum Dis 2020;79:1310-9.
8. Goupille P, Behrens F, Coates LC, et al. POS1044. Effect of secukinumab versus adalimumab on ACR core components and health-related quality of life in patients with psoriatic arthritis: results from the EXCEED study [abstract]. Ann Rheum Dis 2021;80 Suppl 1:797-8.
9. D'Agostino MA, Schett G, López-Rdz A, et al. Response to secukinumab on synovitis using power doppler ultrasound in psoriatic arthritis: 12-week results from a phase III study, ULTIMATE. Rheumatology 2021 Sep 16 (Epub ahead of print).
10. Mease PJ, Smolen JS, Behrens F, et al; SPIRIT H2H study group. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naive patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis 2020;79:123-31.
11. Smolen JS, Sebba A, Ruderman EM, et al. Efficacy and safety of ixekizumab with or without methotrexate in biologic-naïve patients with psoriatic arthritis: 52-week results from SPIRIT-H2H study. Rheumatol Ther 2020;7:1021-35.
12. Yiu ZZN, Mason KJ, Hapton PJ, et al; BADBIR Study Group. Drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). Br J Dermatol 2020;183:294-302.
13. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Eur Acad Dermatol Venereol 2016;30:1148-58.
14. Ritchlin CT, Helliwell P, Boehncke WH, et al. SAT0397. Guselkumab, an IL-23 inhibitor that specifically binds to the IL23P19-subunit, for active psoriatic arthritis: One year results of a phase 3, randomized, double-blind, placebo-controlled study of patients who were biologic naïve or TNFA inhibitor-experienced [abstract]. Ann Rheum Dis 2020;79 Supp 1:1148-9.
15. Orbai AM, Husni ME, Gladman DD, et al. POS1050. Secukinumab leads to improvement across psoriatic arthritis manifestations over 2 years regardless of previous exposure to a TNF inhibitor: a post-hoc analysis of FUTURE 5 [abstract]. Ann Rheum Dis 2021;80 Suppl 1:802-3.
16. Baraliakos X, Gossec L, Pournara E, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: results from the double-blind, randomised, phase 3 MAXIMISE trial [abstract]. Ann Rheum Dis 2021;80:582-90.
17. Baraliakos X, Pournara E, Gossec L, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: predictors of response from the double-blind, randomized, phase 3B MAXIMISE

trial. Ann Rheum Dis 2021;80 Suppl 1:728.
18. Helliwell P, Gladman DD, Poddubnyy D, et al. Efficacy of guselkumab, a monoclonal antibody that specifically binds to the P19-subunit of IL-23, on endpoints related to axial involvement in patients with active PsA with imaging-confirmed sacroiliitis: week-224 results from two phase 3, randomized, double-blind, placebo-controlled studies. Ann Rheum Dis 2020;79:36-37.
19. Janssen Research and Development. A study of guselkumab administered subcutaneously in bio-naive participants with active psoriatic arthritis axial disease (STAR). [Internet. Accessed January 25, 2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT04929210
20. Leung YY, Korotaeva T, Candia L, et al; GRAPPA treatment recommendations peripheral arthritis working group. Therapies for peripheral joint involvement in psoriatic arthritis: a systematic literature review [abstract]. Ann Rheum Dis 2021;80:1296-7.
21. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
22. McInnes IB, Behrens F, Mease PJ, et al; EXCEED Study Group. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet 2020;395:1496-505.
23. Coates LC, Soriano E, Corp N, et al. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations 2021 [abstract]. Ann Rheum Dis 2021;80 Suppl 1:139-40.
24. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. Intern Emerg Med 2017;12:103-11.
25. Ruyssen-Witrand A, Perry R, Watkins C, et al. Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta-analysis. RMD Open 2020;6:001117.
26. Torres T, Barcelos A, Filipe P, Fonseca JE. A systematic review with network meta-analysis of the available biologic therapies for psoriatic disease domains. Front Med 2021;7:618163.
27. Mease PJ, McInnes IB, Tam LS, et al. Comparative effectiveness of guselkumab in psoriatic arthritis: results from systematic literature review and network meta-analysis. Rheumatology 2021;60:2109-21.
28. Papp KA, Leonardi CL, Blauvelt A, et al. Ixekizumab treatment for psoriasis: integrated efficacy analysis of three double-blinded, controlled studies (UNCOVER-1, UNCOVER-2, UNCOVER-3). Br J Dermatol 2018;178:674-81.
29. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol 2017;76:405-17
30. Reich K, Gooderham M, Thaçi D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet 2019;394:576-86.
31. Letko E, Yeh S, Foster CS, Pleyer U, Brigell M, Grosskreutz CL; AIN457A2208 Study Group. Efficacy and safety of intravenous secukinumab in noninfectious uveitis requiring steroid-sparing immunosuppressive therapy. Ophthalmology 2015;122:939-48.
32. Dick AD, Tugal-Tutkun I, Foster S, et al. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology 2013;120:777-87.
33. Targan SR, Feagan B, Vermeire S, et al. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. Am J Gastroenterol 2016;111:1599-607.
34. Hueber W, Sands BE, Lewitzky S, et al; Secukinumab in Crohn's Disease Study Group. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut 2012;61:1693-700.
35. von Stebut E, Reich K, Thaçi D, et al. Impact of secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. J Invest Dermatol 2019;139:1054-62.
36. Wu JJ, Guérin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-α inhibitors versus methotrexate. J Am Acad Dermatol 2017;76:81-90.
37. Yang ZS, Lin NN, Li L, Li Y. The effect of TNF inhibitors on cardiovascular events in psoriasis and psoriatic arthritis: an updated meta-analysis. Clin Rev Allergy Immunol 2016;51:240-7.
38. Garcia-Doval I, Carretero G, Vanaclocha F, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol 2012;148:463-70.
39. Burmester GR, Gordon KB, Rosenbaum JT, et al. Long-term safety of adalimumab in 29,967 adult patients from global clinical trials across multiple indications: an updated analysis. Adv Ther 2020;37:364-80.
40. Atzeni F, Sarzi-Puttini P, Botsios C, et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimm Rev 2012;12:225-9.
41. Dávila-Seijo P, Dauden E, Descalzo MA, et al. Infections in moderate to severe psoriasis patients treated with biological drugs compared to classic systemic drugs: Findings from the BIOBADADERM registry. J Invest Dermatol 2017;137:313-21.
42. 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.
43. Harrold LR, Griffith J, Zueger P, et al. Longterm, real-world safety of adalimumab in rheumatoid arthritis: analysis of a prospective US-based registry. J Rheumatol 2020;47:959-67.
44. Li X, Andersen KM, Chang HY, Curtis JR, Alexander GC. Comparative risk of serious infections among real-world users of biologics for psoriasis or psoriatic arthritis. Ann Rheum Dis 2020;79:285-91.
45. Smolen JS, Goncalves J, Quinn M, Benedetti F, Lee JY. Era of biosimilars in rheumatology: reshaping the healthcare environment. RMD Open 2019;5:e000900.
46. Baumgart DC, Misery L, Naeyaert S, Taylor PC. Biological therapies in immune-mediated inflammatory diseases: can biosimilars reduce access inequities? Front Pharmacol 2019;10:279.
47. Lucasson F, Kiltz U, Cañete JDD, et al. Are patients with psoriatic arthritis being treated optimally across the world? Disparities in health care for patients with psoriatic arthritis across countries with different GDPs, an analysis of 429 patients from 13 countries. Ann Rheum Dis 2021;80 Suppl 1:183.
48. Al-Herz A, Saleh K, Al-Awadhi A, et al; Kuwait Registry for Rheumatic Diseases (KRRD). Accessibility to biologics and its impact on disease activity and quality of life in patients with rheumatoid arthritis in Kuwait. Clin Rheumatol 2021;40:1759-65.
49. Jadon DR, Stober C, Pennington SR, FitzGerald O. Applying precision medicine to unmet clinical needs in psoriatic disease. Nat Rev Rheumatol 2020;16:609-27.
50. Miyagawa I, Nakayamada S, Nakano K, et al. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. Rheumatology 2019;58:336-44.