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BIOLOGIC TREATMENT AND PSORIATIC ARTHRITIS: A REVIEW FOR THE DERMATOLOGIST

In busy dermatology practices, assessing for psoriatic arthritis (PsA) on top of discussing the diagnosis and management options for psoriasis (PsO) can be a challenge. Interestingly, data suggests that dermatologists are poor in evaluating for PsA in their PsO patients. In a study evaluating the prevalence of PsA in dermatology clinics, nearly one third of patients with plaque-type psoriasis were found to have PsA.¹ Moreover, about 40% of those were newly diagnosed with PsA and had not been given a diagnosis of PsA before. This suggests that dermatologists are possibly missing cases of PsA. Dermatologists are uniquely positioned to diagnose PsA early and prevent worsening of the patient's rheumatologic disease. PsO typically appears 7-12 years before PsA² and 64.5% of patients had PsO diagnosed prior to a diagnosis of PsA.^{3,4} By comparison only 19.4% of patients were diagnosed with PsA before a PsO diagnosis. Even a 6-month delay in symptom onset to the first visit with a rheumatologist was associated with worsening peripheral joint erosion and worse long-term physical function.⁵

Clinical clues for early detection of PsA in PsO patients

Clinical clues in PsO patients that suggest a higher risk of PsA include presence of scalp lesions (3.9x), nail dystrophy (2.9x), intertriginous psoriasis (2.4x), severe disease (2.2x), and ≥ 3 body sites of involvement (2.2x).⁶ First degree relatives with PsA incur an increased relative risk of 39-fold for

the PsO patient to develop PsA ($p < 0.01$). Basic screening questions for PsA have been described and include inquiring about joint pain, morning stiffness (>30 min upon waking), and back pain (axial involvement; pain/stiffness that improves with movement). A positive response to 2 or more screening questions should trigger a more complete PsA assessment. Assessment of dactylitis, enthesitis (specifically pain at the Achilles tendon and lateral epicondyle insertion points), and synovitis is relatively fast and may help to identify patients that may have PsA that may benefit from a rheumatology referral. Investigations that may be considered prior to rheumatologic referral are C-reactive protein (CRP)⁷ and X-ray of the affected joints.

Biologics in PsA

The therapeutic armamentarium for PsO has exploded within the last 15 years. We now have multiple agents that can be used to treat PsO and achieve clear or near clear results. But what about our patients with concurrent PsA? The American College of Rheumatology (ACR) criteria 20/50/70 is a composite measure of PsA efficacy that can be used to roughly gauge treatment efficacy. It can be considered in some respects to the Psoriasis Area and Severity Index (PASI) 50/75/90. Beyond the ACR, perhaps the best outcome measure for efficacy of biologics in PsA is assessment of the drug's ability to halt radiographic progression. Currently available agents

(anti-TNF α agents, anti-IL12/23 agents, anti-IL17a agents, and anti-IL23 agents) have shown great efficacy for PsO but differential efficacy for the treatment of PsA, including prevention of radiographic progression and treatment of axial disease. Multiple anti-TNF α 's and IL-17a's have demonstrated halting of radiographic bone progression. Figure 1 represents a summary of efficacy of various biologics for PsO and PsA.

Anti-TNFs and PsA

Anti-TNF α agents were the first biologic agents on the market for treatment of PsO and PsA. Five TNF α inhibitors (etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab) are currently approved in Canada and other countries for use in PsA. The efficacy of the drugs for PsA is comparable, and given the breadth of agents available, the choice of agent can be tailored to patient preferences for route (subcutaneous versus intravenous), frequency of administration, and potential cost to the patient. Meta-analyses and clinical trials have extensively documented the efficacy of anti-TNF α agents in patients with PsA.⁸ Studies have shown efficacy of etanercept,⁹⁻¹¹ infliximab,¹²⁻¹⁵ adalimumab,¹⁶⁻²¹ golimumab,^{22,23} and certolizumab pegol^{24,25} compared to placebo. Monotherapy with a TNF α inhibitor was superior to methotrexate monotherapy after controlling for multiple variables in a retrospective trial.²⁶ In summary, the various

trial efficacy data included reduced arthritis activity (ACR20 responses in 50 to 65% of patients within three months), delayed radiographic progression; improved physical function and quality of life measures. Other features of PsA, such as enthesitis and dactylitis are also improved in patients treated with TNF α inhibitors.

IL-12/IL-23p40 Inhibitors and PsA

Ustekinumab is a monoclonal antibody that targets the shared p40 subunit of IL-12 and IL-23 with high affinity. In the PSUMMIT-1 trial, the week 24 data showed significantly more ustekinumab patients achieved ACR20 than placebo at a dose of 90mg and 45 mg (ACR20 50% and 42% respectively versus placebo 23%).²⁷ In another phase III randomized controlled trial, the PSUMMIT-2, efficacy of ustekinumab in PsA patients was seen in patient who were primary failures to TNF α inhibitor therapy.²⁸ Despite having been exposed to anti-TNF α therapy, 44% of the ustekinumab treated patients achieved ACR20 (vs. 20% for the placebo arm), a statistically significant difference. Furthermore, dactylitis, enthesitis, and spondylitis were also ameliorated with ustekinumab and delay in radiographic joint damage was seen.²⁹ Inhibition of radiographic progression was sustained to week 52. Ustekinumab has not been shown to inhibit PsA axial disease progression when a

marker of PsA axial disease was used a surrogate (ankylosing spondylitis data).

IL-17a inhibitors and PsA

IL-17a inhibitors include secukinumab, and ixekizumab which are indicated for PsO and PsA. Randomized control trials have shown efficacy in PsA including prevention of radiographic progression and treatment of axial disease. FUTURE2 trial data showed that significantly greater secukinumab-treated patients (300 and 150 mg), compared with placebo-treated patients, achieved an ACR20 response at week 24 (54%, 51%, and 29% versus 15 %).³⁰ Five-year data was recently published for the secukinumab FUTURE1 trial which shows ACR 20/50/70 data of 71.0%/51.8%/36.3% respectively for secukinumab treated patients.³¹ The FUTURE1 trial showed that secukinumab inhibited structural joint damage through 24 weeks,³² and delayed radiographic progression out to 3 years (data was only collected up to 3 years).³³ The SPIRIT-P1 trial looking at ixekizumab showed ACR 20/50/70 rates of 57.0/33.6/15.0 for the 80mg q4 week dosing at week 24 vs 31.1/4.7/0 for placebo (all statistically significant).³⁴ In biological-naïve PsA patients from the SPIRIT-P1 trial, ixekizumab q2 week dosing or q4 week dosing achieved comparable ACR50 and ACR70 responses and delayed joint structural damage at 24 weeks irrespective of disease-modifying anti-rheumatic drugs (DMARD) or methotrexate use.

Brodalumab is a monoclonal antibody that blocks the IL-17 receptor α subunit, effectively inhibiting IL-17a, -e and -f. In a phase II randomized, double-blind, placebo-controlled study in PsA, brodalumab 140 or 280 mg at week 1, 2, and then every 2 weeks, at 12 weeks achieved ACR 20 response of 37% and 39% respectively, compared to placebo 18%.³⁵ An ACR50 response in 14% of patients at both doses compared with 4% in the placebo group and ACR70 response in 5% of patients.³⁵ Similar rates of improvement were seen in biologic naïve and non-naïve patient groups. In the open extension of this study, the ACR50 response increased to 33%. However, brodalumab was not shown to be effective for dactylitis.³⁶

IL-23s and PsA

Guselkumab is a human monoclonal antibody that binds to IL-23p19 subunit and inhibits the downstream signaling of IL-23. DISCOVER-2, a Phase III study, showed ACR20 of 64% at week 24. However, delay in radiographic bone progression was seen but only the 100mg every 4 week dosing (not 100mg every 8 week dosing as is currently approved for psoriasis).³⁷ Guselkumab is thus the first IL-23 agent to show delayed radiographic progression in a large phase 3 cohort.

Risankizumab is a humanized monoclonal antibody that targets the IL-23p19 subunit and selectively inhibits IL-

23. Phase II data showed promising results with an ACR20 up to 62% at week 16 in risankizumab-treated patients (150mg week 0, 4, 16) versus ACR20 of 36% in the placebo patients. As well, pooled rizankizumab treated patients showed no radiographic bone progression seen at week 24. Phase III studies are beginning in the near future.

Tildrakizumab is a humanized monoclonal antibody that binds to the p19 subunit of IL-23 with high affinity and inhibits downstream signaling of IL-23. A Phase IIb trial of 391 patients with PsA who had three or more tender or swollen joints were randomized to receive tildrakizumab 200 mg once every four weeks, 200 mg, 100 mg, 20 mg every 12 weeks, or placebo every four weeks. At week 24, a significantly greater proportion of patients receiving tildrakizumab achieved an ACR20 of 79.5% (at any dose) compared to placebo. However, the placebo score was elevated at 50.6% for reasons that remain unclear (Study presented at the European Congress of Rheumatology (EULAR) annual meeting in Madrid 2019).

Conclusion

The most recent biologics to come to market for the treatment of PsO have had highly efficacious results in clearing cutaneous disease, however, have potentially disparate abilities in treating joint disease. It is imperative for the dermatologist, who may be the first physician to suspect or diagnosis PsA, to

have a working understanding of the differences in biologic efficacy in PsA. Together with a rheumatologist, an appropriate management plan for patients with both PsO and PsA can be tailored.

References

1. Mease, P. J. et al. Comparative performance of psoriatic arthritis screening tools in patients with psoriasis in European/ North American dermatology clinics. *J. Am. Acad. Dermatol.* 71, 649–655 (2014).
2. Mease, P. J. & Armstrong, A. W. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs* 74, 423–441 (2014).
3. Elmetts, C. A. et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *Journal of the American Academy of Dermatology* 80, 1073–1113 (2019).
4. Scarpa, R. et al. Psoriatic arthritis in psoriatic patients. *Br. J. Rheumatol.* 23, 246–250 (1984).
5. Haroon, M., Gallagher, P. & FitzGerald, O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann. Rheum. Dis.* 74, 1045–1050 (2015).
6. Wilson, F. C. et al. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum.* 61, 233–239 (2009).
7. Cretu, D. et al. Differentiating Psoriatic Arthritis From Psoriasis Without Psoriatic Arthritis Using Novel Serum Biomarkers. *Arthritis Care Res (Hoboken)* 70, 454–461 (2018).
8. Saad, A. A., Symmons, D. P. M., Noyce, P. R. & Ashcroft, D. M. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. *J. Rheumatol.* 35, 883–890 (2008).
9. Mease, P. J. et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 356, 385–390 (2000).
10. Mease, P. J. et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum.* 50, 2264–2272 (2004).
11. Mease, P. J. et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J. Rheumatol.* 33, 712–721 (2006).
12. Van Den Bosch, F. et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. *Arthritis Rheum.* 46, 755–765 (2002).
13. Antoni, C. E. et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *J. Rheumatol.* 35, 869–876 (2008).
14. Antoni, C. et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann. Rheum. Dis.* 64, 1150–1157 (2005).
15. Kavanaugh, A. et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. *Ann. Rheum. Dis.* 65, 1038–1043 (2006).
16. Mease, P. J. et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 52, 3279–3289 (2005).
17. Gladman, D. D. et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum.* 56, 476–488 (2007).
18. Gladman, D. D. et al. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. *Arthritis Res. Ther.* 12, R113–9 (2010).
19. Genovese, M. C. et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J. Rheumatol.* 34, 1040–1050 (2007).
20. Van den Bosch, F. et al. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. *Ann. Rheum. Dis.* 69, 394–399 (2010).
21. Mease, P. J. et al. Impact of adalimumab on symptoms of psoriatic arthritis in patients with moderate to severe psoriasis: a pooled analysis of randomized clinical trials. *Dermatology (Basel)* 220, 1–7 (2010).
22. Kavanaugh, A. et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum.* 60, 976–986 (2009).
23. Kavanaugh, A. et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis Rheum.* 64, 2504–2517 (2012).
24. Mease, P. J. et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann. Rheum. Dis.* 73, 48–55 (2014).
25. van der Heijde, D. et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. *Ann. Rheum. Dis.* 73, 233–237 (2014).
26. Heiberg, M. S. et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. *Ann. Rheum. Dis.* 66, 1038–1042 (2007).
27. McInnes, I. B. et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase

3. multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 382, 780–789 (2013).
28. Ritchlin, C. et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann. Rheum. Dis.* 73, 990–999 (2014).
29. Kavanaugh, A. et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Ann. Rheum. Dis.* 73, 1000–1006 (2014).
30. McInnes, I. B. et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 386, 1137–1146 (2015).
31. Mease, P. J. et al. Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Psoriatic Arthritis: Final 5-year Results from the Phase 3 FUTURE 1 Study. *ACR Open Rheumatol* 2, 18–25 (2020).
32. Mease, P. J. Inhibition of interleukin-17, interleukin-23 and the TH17 cell pathway in the treatment of psoriatic arthritis and psoriasis. *Curr Opin Rheumatol* 27, 127–133 (2015).
33. Kavanaugh, A. et al. Secukinumab for Long-Term Treatment of Psoriatic Arthritis: A Two-Year Followup From a Phase III, Randomized, Double-Blind Placebo-Controlled Study. *Arthritis Care Res (Hoboken)* 69, 347–355 (2017).
34. Mease, P. J. et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann. Rheum. Dis.* 76, 79–87 (2017).
35. Mease, P. J. et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N. Engl. J. Med.* 370, 2295–2306 (2014).
36. Sondag, M., Verhoeven, F., Guillot, X., Prati, C. & Wendling, D. Efficacy of new treatments for dactylitis of psoriatic arthritis: update of literature review. *Clin. Rheumatol.* 38, 591–596 (2019).
37. Deodhar, A. et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 391, 2213–2224 (2018).