IL-17 INHIBITION IN SPONDYLOARTHRITIS: A TARGETED APPROACH IN PSORIATIC ARTHRITIS

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MEETING SUMMARY

Prof Philip Mease introduced psoriatic arthritis (PsA) with a particular emphasis on disease symptoms and an update on the status of current disease management. Erik Lubberts described the interleukin (IL)-17 pathway and its role in the pathogenesis of PsA. Prof Iain McInnes reviewed the clinical evidence for the efficacy of IL-17 inhibition in PsA. Prof Désirée van der Heijde brought the symposium to a close with a presentation on the clinical impact of joint structural damage and strategies for its prevention in PsA.

Psoriatic Arthritis: Where Are We In 2015?

Professor Philip Mease

The prevalence of PsA in the United States and Europe ranges from 0.1-0.3% of the total population (depending upon case definition),[1,2] with a comparatively lower prevalence seen in other parts of the world such as China and Argentina.[3,4] Several relatively recent studies of patients with psoriasis show that 20-30% also have PsA.[5-12] In one such population study,[12] following confirmation of psoriasis by a dermatologist, patients were referred to a rheumatologist for evaluation regardless of their musculoskeletal symptoms.

	Peripheral arthritis	Skin and nail disease	Axial disease*	Dactylitis	Enthesitis
NSAIDs	X		X		
Intra-articular steroids	X				
Topicals		X			
Physiotherapy			X		
Psoralen UVA/UVB		X			
DMARDs (MTX, CsA, SSZ, LEF)	X	X			
Biologics (anti-TNF agents)	X	X	X	X	X

Figure 1: Treatments for psoriatic arthritis: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) evidence review.[22]

*Based on data from ankylosing spondylitis trials (used as surrogate for PsA spondylitis).

CsA: cyclosporin A; LEF: leflunomide; MTX: methotrexate; UVA/UVB: ultraviolet A/B; NSAIDs: nonsteroidal anti-inflammatory drugs; SSZ: sulfasalazine; TNF: tumour necrosis factor; PsA: psoriatic arthritis; DMARDs: disease-modifying anti-rheumatic drugs.

Of approximately 1,000 patients found to have psoriasis, 30% were diagnosed with PsA. Furthermore, 41% of those with PsA were not aware that they had the condition, highlighting the importance of identifying such patients. PsA can present in several heterogeneous clinical manifestations including peripheral arthritis, enthesitis, dactylitis, and spondylitis, necessitating a highly patient-centric approach to diagnosis and assessment of the severity of PsA and patient management to ensure that treatment adequately benefits each domain.

CASPAR (Classification Criteria for Psoriatic Arthritis)[13] represents the most current diagnostic criteria for PsA. This system results in high diagnostic specificity and sensitivity (99% and 94%, respectively)[13] and highlights the need to take into account several factors, including musculoskeletal and skin disease elements, in PsA diagnosis. Clinical deformities and damage that result in functional disability are seen in 20% of patients with PsA.[14] Furthermore, after 10 years, 55% of patients will develop deformation of five or more joints.[15] Of those patients diagnosed with early PsA, a quarter have at least one erosion on presentation at the clinic and almost half will develop erosive disease within 2 years of diagnosis.[16] Predictors of long-term development of erosive disease include initial presentation with numerous tender or swollen joints and the presence of digital dactylitis.[17-19]

Delaying diagnosis exacerbates progressive deterioration, with as short as a 6-month delay in consultation potentially leading to detrimental outcomes for the patient.[20] There is also evidence of increased mortality rates in patients with PsA, the causes of which are similar to those for the population as a whole; however, improvements in mortality rates have been shown in recent years, which may be attributed to the availability of more effective treatments.[21] Clearly, improvements in screening and diagnosis are unmet needs within PsA that could be improved through increased awareness of the disease among dermatologists, primary care physicians, and patients.

With regards to availability and efficacy of treatments for PsA, a Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) evidence review[22,23] showed that non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroids display some efficacy in patients with mild disease; however, to alleviate symptoms of moderate-to-severe disease, systemic treatments must be used (Figure 1).

Most disease-modifying anti-rheumatic drugs (DMARDs) have been shown to improve symptoms in the joints of patients with PsA, without improving skin manifestations of the disease. Methotrexate, however, has shown some efficacy for both joint and skin symptoms.[24,25] Although there are few studies of methotrexate in PsA, the randomised, placebo-controlled Methotrexate in

Psoriatic Arthritis (MIPA) study[26] showed no significant effect of methotrexate on several composite musculoskeletal indices after 6 months of treatment. Several studies of anti-tumour necrosis factor (TNF) therapies in PsA have shown efficacy in the musculoskeletal domain as well as in the management of skin disease. With regards to other outcomes, anti-TNF treatments have also resulted in statistically significant improvements in enthesitis, dactylitis, physical function, and qualityof life (QoL).[25,27]

Despite the availability of NSAIDs, DMARDS, and anti-TNF therapies, significant unmet needs remain in PsA. Improved methods of assessment of disease activity are needed to reflect clinical outcomes. Additional biomarkers are needed to facilitate this assessment; at present, the use of the inflammation biomarker, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are generally used. However, CRP and ESR are reported as normal in up to 50% of patients with PsA despite the presence of clinically active disease,[28,29] thus limiting their use. Novel markers are therefore needed to aid diagnosis and assessment of disease activity and to predict structural damage. Furthermore, additional measures are needed which enable clinicians to treat to targets such as minimal disease activity or remission. Currently available treatments may have safety and tolerability issues and some patients show a lack of or diminished sustainability of response. Thus, there is a need for new medicines with novel modes of action and different safety and tolerability profiles, which lead to sustained benefits in patients with PsA.

Treatments for rheumatoid arthritis (RA) have been investigated in patients with PsA; amongst these, IL-1 inhibitors, rituximab, abatacept, the IL-6 receptor inhibitor tocilizumab, and the Janus kinase (JAK) inhibitor tofacitinib are still being evaluated, but have shown some degree of efficacy for PsA.[25,30] Recently-approved treatments for PsA include the IL-12/23 inhibitor ustekinumab and the phosphodiesterase 4 (PDE-4) inhibitor, apremilast.

Novel treatments currently under investigation in patients with PsA include secukinumab and ixekizumab, which are direct IL-17 inhibitors. Treatments are also in development to target IL-23, which is involved in stimulation of T_H17 cell differentiation and activation. Inhibitors of IL-23 include guselkumab, tildrakizumab, and BI655066, which are being assessed for psoriasis, PsA, and ankylosing spondylitis. In addition, several dual inhibitors of IL-17 and TNF are also in development for PsA.[25,30]

Understanding the Pathophysiology of Psoriatic Arthritis: The Role of IL-17

Doctor Erik Lubberts

IL-17A is the key effector pro-inflammatory cytokine in the IL-17 family; it can exist as a homodimer or as a heterodimer complexed with IL-17F. Receptor binding (IL-17 receptor A [IL-17RA]/IL-17RC) results in conformational changes, nuclear factor (NF)-κB activation, and increased transcription of growth factors and cytokines including IL-6/IL-8.[31] IL-17 is produced by T_H17 cells, a novel T helper cell subset, which differentiate from naïve T cells in the presence of polarising cytokines (IL-1 and IL-23 are important in this role for humans).[32] T_H17 cells are also known to produce IL-17F and IL-22. T_H17 cytokines are required for defence against extracellular pathogens such as fungal infections; however, they have also been implicated in cell-mediated inflammation and autoimmune diseases.[32] In addition to T_H17 cells, IL-17A is also produced by multiple lineages of the innate immune system, including mast cells, neutrophils, dendritic cells, γδT cells, macrophages, and natural killer cells.[32] IL-17R signalling has been suggested as a critical pathway in the transition of acute synovitis into chronic destructive arthritis,[33] potentially driven by an IL-17-induced pro-inflammatory feedback loop as a result of an increase in IL-17/TNFα-producing T_H17 cells in peripheral blood in early RA. Further work is warranted to determine whether targeting IL-17 in addition to TNFα may result in neutralisation of T_H17 activity.[34-36]

Evidence for elevated IL-17A/IL-17R signalling in PsA has been demonstrated by several studies. Huffmeier et al. showed that susceptibility to PsA is associated with single nucleotide polymorphisms in *TRAF3IP2* (*ACT1*), which encodes a molecule downstream of the IL-17RA. Elevated IL-23p19/IL-23R and IL-17A/IL-17R expression in psoriatic skin and synovial fluid from patients with PsA,[37-40] as well as increased frequencies of IL-17$^+$ and IL-22$^+$ CD4$^+$ T cells in the peripheral blood of patients with psoriasis and PsA,[41] have been observed. In the synovial membranes of patients with PsA, CD4$^+$ T cells predominate over CD8$^+$

cells, whilst $CD8^+$ cells predominate over $CD4^+$ cells in the synovial fluid of these patients.[42,43] Furthermore, Menon et al.[44] demonstrated a previously unrecognised contribution of $IL\text{-}17^+/CD8^+$ T cells to the pathogenesis of PsA, with levels of these cells showing a correlation with disease activity and radiographic erosion in patients with PsA.[44] These pathways are also thought to contribute to skin inflammation and enthesis, with IL-17 and IL-22 acting via $IL\text{-}23R^+$ resident/IL-23-responsive T cells.[45]

Long-term joint inflammation results in bone erosion in 67% of patients with PsA; however, evidence of new bone formation is also characteristic of PsA, in the form of syndesmophytes, enthesophytes, and the presence of ankyloses (peripheral bony fusion).[14,46] In addition, IL-17 is a potent stimulator of osteoclastogenesis;[47] degradation of Type I collagen in synovium and bone by IL-17 has been demonstrated,[48] and IL-17 in combination with TNFα increases osteoclastic resorption *in vitro*.[49] Potential pathways involved in the formation of bone include the Wnt signalling pathway, the transforming growth factor-beta/bone morphogenic protein pathway, the prostaglandin E2 pathway, and perhaps the balance between IL-23, IL-17, and IL-22.[50,51]

In summary, IL-17A represents the main effector cytokine within the IL-17 family. Elevated levels are found in the skin and synovium of patients with PsA, identifying this as a key cytokine involved in the pathophysiology of skin inflammation, psoriasis, and PsA. IL-17 is involved in the perpetuation of a pro-inflammatory feedback loop between T cells and synovial fibroblasts that may lead to persistent synovitis, and has been shown to be involved in enthesitis and, to some extent, osteoclastogenesis and bone erosion in patients with PsA. The role played by IL-17 in bone formation in these patients is evolving.

IL-17 Inhibition in Psoriatic Arthritis: Current Evidence and Future Perspectives

Professor Iain McInnes

PsA is a heterogeneous disease with a variety of clinical manifestations, which include uveitis, enthesitis, synovitis, osteitis, and disease of the skin and nails. In order for the immune system response to result in such a range of outcomes, the extent of this response must be context-dependent. Consequently, a very different immune response is seen in the gut to that seen in the skin and in the eye, for example. Therefore, when considering clinical evidence for the use of interventional treatments for PsA, expectations of the same magnitude of response in different tissues may not be met, despite the affected tissues having the same underlying pathogenesis.

Publication of new guidelines for the treatment of PsA is imminent; however, currently, the treatment pathway for PsA is to start with methotrexate or another DMARD, before moving to an anti-TNF treatment in patients with persistently high disease activity. Ustekinumab, an anti-IL-23 antibody, is an option in patients who fail to respond or are intolerant of anti-TNF treatments. Several new treatment options are also in development for PsA, including inhibitors of IL-17 and inhibitors of JAK (Figure 2);[52-54] however, it is currently unclear how these will fit into the traditional treatment paradigm for this disease.

The pivotal Phase III trials with the anti-TNF biologics adalimumab,[55] etanercept,[56] infliximab,[57] golimumab,[58] and certolizumab pegol[59] have shown that 50-60% of patients with PsA achieve an American College of Rheumatology 20% improvement criteria (ACR20) response, demonstrating significant long-term improvements in this and associated endpoints including skin symptoms, physical function, and QoL. Registry data show that around half of patients stay on anti-TNF therapy for around 5 years,[60] and these studies reveal a well-established safety profile in PsA in addition to significant long-term improvements in ACR20 responses and radiographic endpoints. Anti-TNF treatment has been associated with an increased risk of infection. In addition, intolerance to treatment or an inadequate response has been observed in some patients together with decreasing drug survival rates with long-term therapy.

Several other novel drugs have been investigated in PsA; these include apremilast which is a PDE-4 inhibitor currently approved for the treatment of PsA. Following 16 weeks of treatment with apremilast, 40% of patients achieved an ACR20 response. In addition, apremilast was shown to be well-tolerated, and continued dosing to Week 24 maintained or further improved the signs and symptoms of PsA.[61]

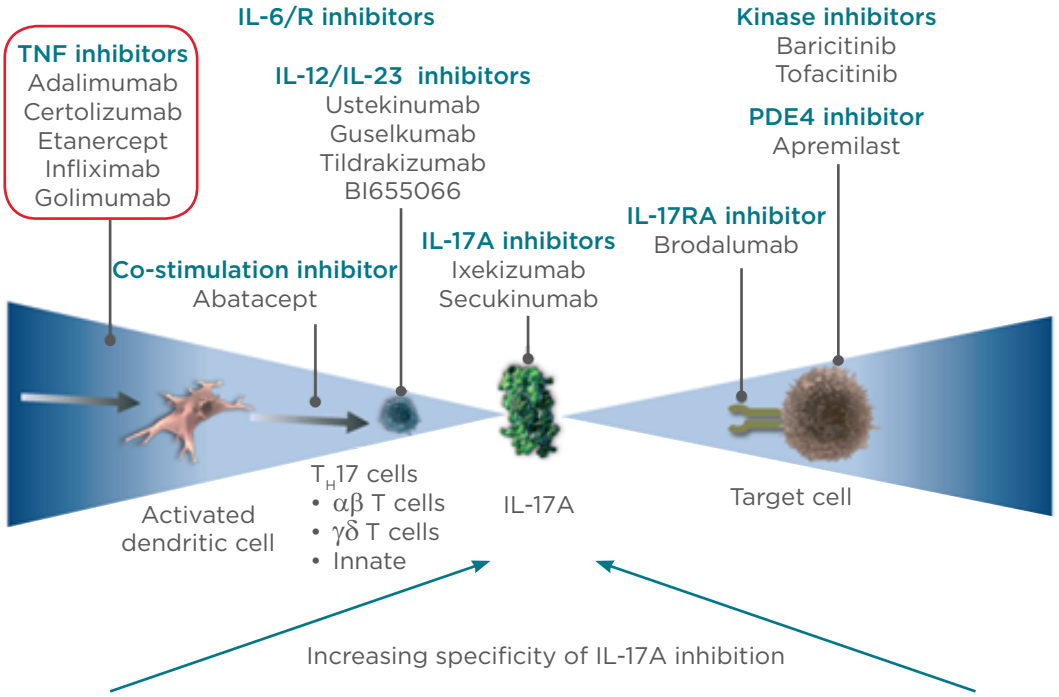

Figure 2: Pathogenesis-driven treatment for psoriatic arthritis.
PDE4: phosphodiesterase Type 4; T_H17: T helper 17 cell; IL: interleukin; TNF: tumour necrosis factor.

Targeting IL-6 has resulted in little response in the skin, although a single Phase II study has shown provisional efficacy in the articular domain. Of the treatments targeting IL-12/IL-23 (ustekinumab, guselkumab, toldrakizumab, BI655066), data are only publicly available for ustekinumab, which is approved for the treatment of PsA. Data from the PSUMMIT Phase III clinical study of ustekinumab in anti-TNF-naïve patients (PSUMMIT I) or those who had previously received treatment (PSUMMIT 2; one-third of participants were anti-TNF-experienced) showed that just under 50% of participants achieved an ACR20 response.[62,63] Although the PSUMMIT 2 study was not designed to compare anti-TNF-experienced/naïve patients, treatment with ustekinumab was effective in patients who were inadequate responders to anti-TNF therapy, although the response was lower than that seen in patients who were anti-TNF-naïve. In addition, ustekinumab was shown to improve enthesitis and dactylitis.[62,64]

Direct targeting of IL-17 has been shown to be an effective treatment for psoriasis. In the Phase III FIXTURE study, greater efficacy was seen with secukinumab, an anti-IL-17A antibody, versus etanercept over a period of 52 weeks in patients with moderate-to-severe plaque psoriasis. Both 150 mgand 300 mg doses of secukinumab resulted in rapid and sustained responses in terms of the co-primary endpoints (a 75% reduction in the mean psoriasis area-and-severity index [PASI] score [PASI 75] and the Investigator's Global Assessment 2011 modified version [IGA mod 2011]), which were significantly higher than those seen for etanercept or placebo.[65] In the Phase III CLEAR study, secukinumab showed greater efficacy versus ustekinumab in both PASI 90 and PASI 100.[66]

Consequently, secukinumab has also been investigated in patients with PsA. FUTURE 1 and FUTURE 2 were randomised, placebo-controlled, multicentre Phase III studies designed to assess the efficacy and safety of secukinumab in patients with active PsA compared with placebo. FUTURE 1 used intravenous administration of secukinumab (10 mg/kg) for 24 weeks followed by subcutaneous administration of a maintenance dose (75 or 150 mg) during the 2-year follow-up phase of the study. This was in contrast to the study design of FUTURE 2, in which subcutaneous secukinumab (75, 150, or 300 mg) was administered over 24 weeks followed by a 5-year follow-up phase using the same doses. For both FUTURE 1 and FUTURE 2, secukinumab significantly improved the ACR20 response after 24 weeks,[67,68] with approximately half of patients in each study achieving ACR20. Of note in FUTURE 2 was the

inclusion of a 300 mg dose of secukinumab which gave a similar response to the 150 mg group.[67,68] In FUTURE 2, when patients were stratified by prior anti-TNF treatment, secukinumab showed clear efficacy irrespective of whether patients were anti-TNF-naïve or inadequate responders to anti-TNF therapy (ACR20 responders: anti-TNF-naïve 58.2% [p<0.0001], 63.5% [p<0.0001], and 36.9% [p<0.01] versus 15.9% [secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively]; anti-TNF inadequate responders 45.5% [p<0.01], 29.7% [not significant (ns)], and 14.7% (ns) versus 14.3% [secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively]).[68] Similarly, the FUTURE 2 study demonstrated that efficacy was seen with or without concomitant use of methotrexate (ACR20 responders: co-treatment with methotrexate 54.4% [p<0.001], 47.7% [p<0.01], and 44.7% [p<0.05] versus 20.0% [secukinumab 300 mg; 150 mg; and 75 mg versus placebo respectively]; no methotrexate treatment 53.6% [p<0.0001], 53.6% [p<0.0001], and 15.4% (ns) versus 10.4% [secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively]).[68] Higher percentages of patients showed improvements in resolution of both dactylitis and enthesitis with secukinumab versus placebo: 56.5% (p<0.01), 50.0% (p<0.01), and 30.3% (ns) versus 14.8% for dactylitis; and 48.2% (p<0.01), 42.2% (p<0.05), and 32.4% (ns) versus 21.5% for enthesitis (secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively, at Week 24).[68] With regards to physical function, in both FUTURE 1 and FUTURE 2 rapid improvements were seen in Health Assessment Questionnaire Disability Index (HAQ-DI) with secukinumab (150 mg and 75 mg in FUTURE 1, and 300 mg and 150 mg in FUTURE 2) versus placebo.[67,68]

Secukinumab demonstrated a good safety and tolerability profile in a pooled analysis of the FUTURE 1 and 2 studies.[67,68] The most common adverse events (AEs) for both secukinumab and placebo were nasopharyngitis, upper respiratory tract infections, and headache. The incidence of serious adverse events (SAEs) including inflammatory bowel/Crohn's disease, *Candida* infections, neutropaenia, major adverse cardiac events, and malignancy was low with secukinumab. Overall exposure-adjusted AE/SAE incidence rates across the entire safety period (mean/maximum exposure: 358.1/721 days for secukinumab and 128.6/233 days for placebo) were 210.3/9.0 and 319.6/13.6 per 100 patient-years with secukinumab and placebo, respectively.[69]

In summary, TNF inhibitors have improved outcomes for patients with PsA; however, a significant unmet need remains, particularly for patients who have an inadequate response or intolerance to anti-TNF therapy. Treatment with the PDE-4 inhibitor apremilast or the IL-12/IL-23 inhibitor ustekinumab has shown efficacy in patients with PsA, offering novel therapeutic options. In addition, inhibition of IL-17A with secukinumab has shown significant efficacy in psoriasis and PsA in Phase III trials, and may offer a promising new approach.

Recent Advances in Joint Structural Damage Assessment in Psoriatic Arthritis

Professor Dr Désirée van der Heijde

Structural damage due to PsA is highly prevalent and can occur early in the disease course, with 30-50% of patients presenting with erosions to joints after 2 years[70] and 35-75% of patients in established hospital cohorts showing erosions.[15,71] Joint damage is progressive and increases with duration of the disease.[72] PsA results in bone resorption as well as bone formation and these processes can occur in the same patient, with erosion clearly visible alongside periostitis due to bone formation. Bone erosions resulting from PsA are more destructive than those seen in RA and, ultimately, can result in loss of integrity of the entire joint. Structural damage takes several forms, from shortening of fingers to complete ankyloses of joints.

Several methods of radiological scoring have been developed and validated for damage assessment. The four main methods described (PsA Steinbrocker [Toronto]; PsA Ratingen Score; PsA Sharp method; PsA Sharp/van der Heijde [mTSS]) were all originally developed and tested in patients with RA and adapted for use in PsA. The addition of distal interphalangeal joints (DIPs) of the hands as a scoring site to these methods may be relevant for PsA alongside scoring of new bone formation, pencil-in-cup deformities, and gross osteolysis (GO).[73]

The IMPACT 2 study describes results from two readers making assessments of the number of joints with pencil-in-cup deformities arising in patients after 24 weeks of treatment with the TNF inhibitor infliximab versus placebo.[73] Overall,

few joints showed pencil-in-cup deformities and neither reader reported increases in the incidence of this deformity type over the length of the study in any of the treatment groups. There were also no new joints with GO over the trial period. Evidently, new joints with pencil-in-cup deformations and GO do not occur frequently enough to be used as outcome measures in PsA clinical trials with a length of 24 weeks. In addition, the inclusion of DIPs of the hands to the scoring system does not improve its sensitivity, but are still included because of the frequent involvement in PsA.[73,74]

With regards to other treatments, the effect of a number of anti-TNF therapies on structural damage in patients with PsA has been assessed. Following treatment with five different anti-TNF therapies over 24 weeks, very little change from baseline in mTSS was seen, in contrast to an increase from baseline seen with placebo over the same period. These results were sustained over 52 weeks. A systematic review and meta-analysis of the five randomised controlled trials[75] showed a greater proportion of patients with no radiographic progression at Week 24 (84.5% versus 68.8% for anti-TNF and placebo, respectively), with an odds ratio for progression of 2.7 (anti-TNF treatment versus placebo). In addition, no difference in efficacy was seen among anti-TNF treatments.[75] With regards to the effect of methotrexate on radiographic progression in patients with PsA, data from placebo-controlled studies have yet to be published. Similarly, data are lacking to assess methotrexate versus anti-TNF treatment versus the combination: methotrexate + anti-TNF treatment. Data to assess the effect of methotrexate + anti-TNF therapy are limited and restricted to post-hoc analyses from randomised studies of anti-TNF therapies; hence no additive effect of co-medication with methotrexate and anti-TNF treatment has been demonstrated.[75]

A preplanned, integrated analysis of combined radiographic data from the PSUMMIT 1 and PSUMMIT 2 Phase III, randomised controlled trials of ustekinumab versus placebo was carried out in patients with active PsA.[76] Overall, treatment with ustekinumab resulted in a significantly lower change from baseline in mTSS than placebo.[76] Data from the Phase III FUTURE I study of secukinumab versus placebo in patients with PsA showed significantly less radiographic progression for secukinumab 150 and 300 mg doses versus placebo at Week 24 as assessed by mTSS, a significantly lower change from baseline in erosion score for both secukinumab doses versus placebo, and a significantly lower change from baseline in joint space narrowing score for the intravenous 75 mg secukinumab group. The inhibition of mTSS over 24 weeks was seen irrespective of prior use of anti-TNF treatments.[77] In addition, the mean change from baseline in mTSS was lower for secukinumab versus placebo irrespective of concomitant methotrexate use.[77] Secukinumab demonstrated sustained inhibition of radiographic progression through Week 52.[77]

As seen for RA, preventing the progression of structural damage in order to limit irreversible damage and disability is pertinent for PsA.[78] Hence, EULAR guidelines state that the primary goal of treatment for patients with PsA is to maximise long-term, health-related QoL through control of symptoms, prevention of structural damage, normalisation of function, and social participation; abrogation of inflammation is an important component in achieving these goals.[79] In addition, if patients are seen later in the course of their disease then they are likely to have a higher rate of structural damage.[80] With regards to treatment targets for PsA, clinical remission and inactive disease are important, taking into consideration extra-articular manifestations.[81] It is apparent that structural damage is frequently observed in patients with PsA, which can often have a major impact on function, QoL, and mortality. Treatment with anti-TNF treatments, ustekinumab or secukinumab, can lead to inhibition of the progression of structural damage for these patients.

Summary

In the current treatment pathway for patients with PsA, methotrexate (or an alternative DMARD) is used for initial treatment. When further therapy is required, anti-TNF treatments have demonstrated efficacy in patients with PsA and have also been shown to inhibit structural damage. However, for those patients who show an inadequate response or intolerance to anti-TNF treatments, alternative treatment options are limited.

Novel biologic treatments have demonstrated efficacy in patients with PsA, including the PDE-4 inhibitor apremilast and the IL-12/IL-23 inhibitor ustekinumab. The pro-inflammatory cytokine IL-17 has been shown to play a key role in the pathophysiology of skin inflammation and psoriasis, and is also strongly implicated in synovitis,

enthesitis, and bone erosion in PsA.IL-17 inhibition has demonstrated encouraging results, with the IL-17A inhibitor secukinumab showing superior efficacy versus etanercept (an immunosuppressive human TNF receptor/p75 Fc fusion protein) and versus ustekinumab in psoriasis, as well as significant efficacy versus placebo in PsA. In addition, treatment with secukinumab has been shown to slow the progression of structural deterioration in patients with PsA. As the development of biologic treatmentsfor PsA continues, it remains to be seen how these novel treatment options fit into the traditional treatment paradigm for this disease.

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