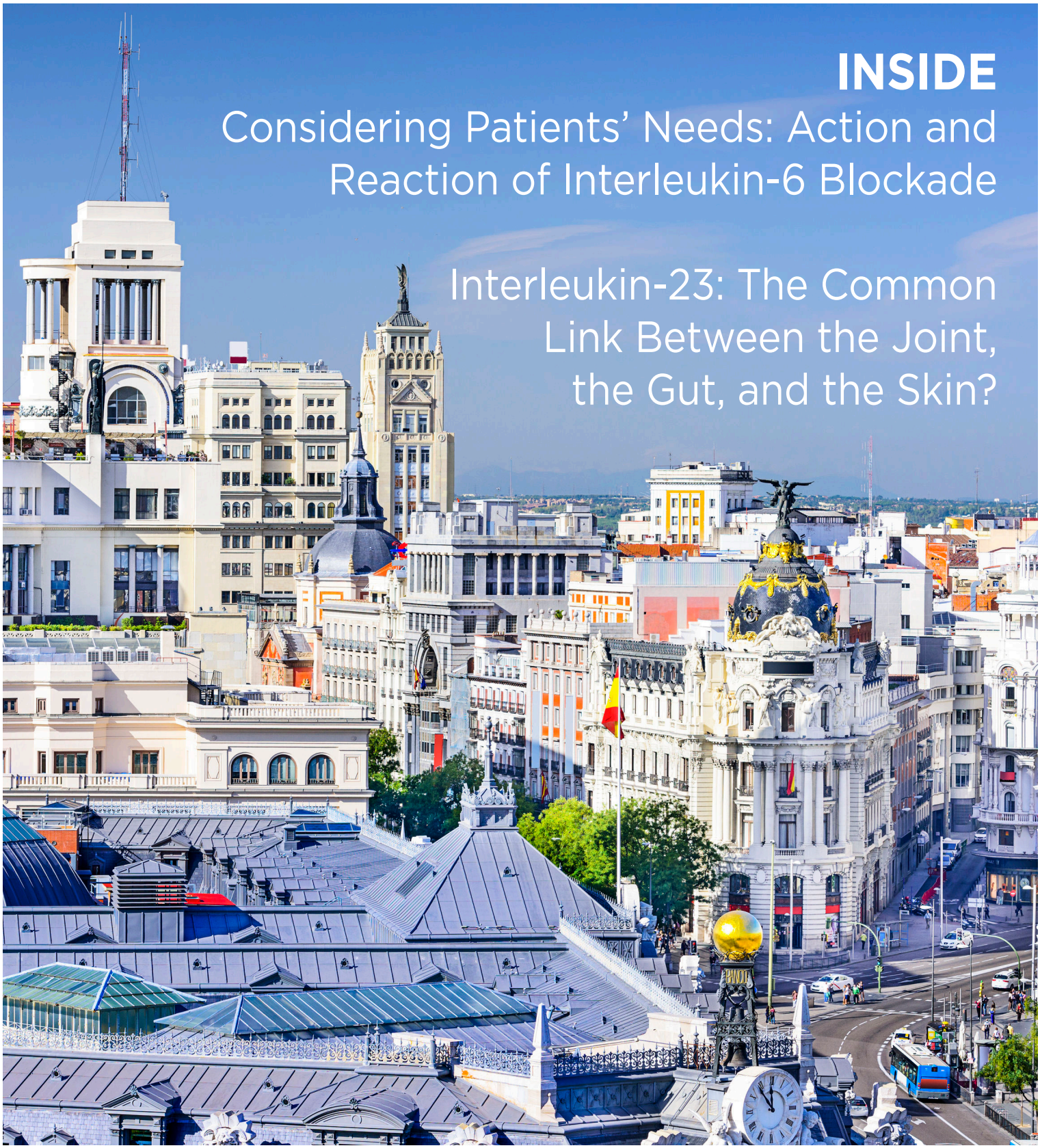
EMJ EUROPEAN MEDICAL JOURNAL

RHEUMATOLOGY

EMJ Rheumatol. 2017 Suppl 13 • europeanmedical-journal.com



INSIDE

CONSIDERING PATIENTS' NEEDS: ACTION AND REACTION OF INTERLEUKIN-6 BLOCKADE

This symposium took place on 14th June 2017, as a part of the European League Against Rheumatism (EULAR) 18th Annual European Congress in Madrid, Spain

Chairperson

Costantino Pitzalis[1]

Speakers

Josef S. Smolen,[2] Ernest Choy[3]

1. Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

2. Division of Rheumatology, Department of Medicine, Medical University of Vienna; Department of Medicine, Hietzing Hospital, Vienna, Austria

3. Head of Rheumatology and Translational Research, Institute of Infection and Immunity; Director of Arthritis Research UK and Health and Care Research Wales CREATE Centre; Cardiff University, Cardiff, UK

Disclosure: Prof Pitzalis has received grants and research support from AbbVie, AstraZeneca/MedImmune, Bristol Myers Squibb, Celgene, Janssen/Johnson & Johnson, Pfizer, Roche/Genentech/Chugai, and UCB, and has received honoraria or consultation fees from Janssen; he is also a consultant for several pharmaceutical and biotechnology companies. Prof Smolen has received grants and research support from AbbVie, Janssen, Lilly, MSD, Pfizer, and Roche, and has received honoraria or consultation fees from AbbVie, Amgen, AstraZeneca, Astro, Celgene, Celtrion, Glaxo, ILTOO, Janssen, Lilly, MedImmune, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi, and UCB. Prof Choy has received research grants and served as a member of advisory boards and speaker bureaus of Abbott Laboratories, Allergan, Amgen, AstraZeneca, Biogen, BMS, Boehringer Ingelheim, Celgene, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring Pharmaceutical, GSK, Hospira, ISIS, Jazz Pharmaceuticals, Janssen, MedImmune, Merrimack Pharmaceutical, MSD, Napp, Novimmune, Novartis, Pfizer, Regeneron, Roche, R-Pharm, Sanofi-Aventis, Synovate, Tonix, and UCB.

Acknowledgements: Writing assistance was provided by Nicole Rossides, ApotheCom, London, UK.

Support: The publication of this article was funded by Janssen Pharmaceutica NV. The views and opinions expressed are those of the authors and not necessarily Janssen Pharmaceutica NV.

Citation: EMJ Rheumatol. 2017;5[Suppl 13]:2-9.

MEETING SUMMARY

The symposium discussed mechanisms of interleukin (IL)-6 blockade for the treatment and management of patients with rheumatoid arthritis (RA). Prof Smolen provided a clinical update of the latest efficacy and safety data on various anti-IL-6 drugs, including sirukumab. He noted that all anti-IL-6 drugs were efficacious in treating physical and mental symptoms of RA. When the efficacy of anti-IL-6 antibodies was compared between drugs, targeting the IL-6 ligand was similar to targeting its receptor. Prof Pitzalis described the pathophysiology of IL-6 in RA and the reason for targeting IL-6. Lastly, Prof Choy outlined the importance of measuring patient-reported outcomes to monitor symptom improvement and evaluate the impact of IL-6 on mental functioning. Because IL-6 modulates the hypothalamic pituitary axis, fatigue and depression are common in patients with RA. Evidence suggests that the inhibition of IL-6 activity reduces symptoms of fatigue and depression in patients with RA, and that improvement in mental health occurs independently, rather than as a consequence of improvement in physical functioning.

Welcome and Introduction

Professor Costantino Pitzalis

The objective of the symposium was to explain the mechanism behind IL-6 dysfunction in RA pathophysiology, review novel RA therapies and their effect on structural damage and patient-reported outcomes, and consider the use of IL-6 inhibitors in patients with RA to manage psychological symptoms.

The Role of Interleukin-6 in Rheumatoid Arthritis Pathophysiology and Structural Damage

Professor Costantino Pitzalis

IL-6 is a keystone cytokine responsible for the pathogenesis of RA,[1] a chronic systemic inflammatory condition driven by synovitis, which causes joint damage,[2,3] bone erosion, and joint narrowing due to cartilage damage. IL-6 mediates effects both at the local and systemic level,[2,3] evident by the high levels of IL-6 in both the synovial fluid and serum of patients with the disease.[2]

At the systemic level, IL-6 plays a key role in the aberrant immune responses leading to autoimmunity in RA. IL-6 drives T follicular helper cells and the differentiation and maturation of B-cells into plasmablasts and plasma cells. IL-6, together with transforming growth factor-beta (TGF-β) and IL-23, also drives the activation and differentiation of T helper (Th)17 cells, which are highly pathogenic. Thus, IL-6 contributes to the activation of the immune system that, following stimulation by still not fully determined arthritogenic antigens, leads to breach of tolerance (particularly to citrullinated antigens) and the production of autoantibodies; the presence of these antibodies is a disease indicator, and they can circulate for years unnoticed without causing any symptoms until a 'second hit' reaches the synovial membrane in the joint. At the joint level, a complex immunological cascade is activated in which IL-6 again mediates critical aspects of the immune system, including the activation of macrophages, the differentiation of specific T cell and B cell subsets, and the subsequent activation of synovial fibroblasts and the osteoclasts that lead to joint damage (Figure 1).

IL-6 has widespread effects due to its extensive production by multiple cells and the broad expression of IL-6 receptors.[5] Importantly, the IL-6 receptor α chain is primarily based in haematopoietic cells while the β chain, the glycoprotein 130 (GP130), is widely expressed also on non-haematopoietic and stromal cells. For example, IL-6 mediates chronic synovitis and pannus formation, and together with the RANK ligand, triggers osteoclastogenic pathways[1] contributing to subchondral bone erosions and joint damage. Evidence has shown that sirukumab (an antibody that binds to the IL-6 ligand) is effective in preventing structural damage progression. Markers of bone destruction (e.g. C1M, C3M, C4M) were reduced, while markers associated with cartilage regeneration and bone turnover were increased (e.g. β-isomerised C-terminal telopeptides of Type I collagen (CTX-1) and the N-terminal-Mid fragment of osteocalcin).[6]

Downstream effects outside the joint include IL-6 targeting the liver and inducing acute phase reactants (e.g. C-reactive protein [CRP], an important measure of disease activity in patients with RA, and hepcidin), which interferes with iron homeostasis leading to hypoferraemia and anaemia commonly seen in chronic diseases.[7]

Another example is the inflammation mediated by IL-6 that can increase cardiovascular disease risk.[7] Systemic inflammation tends to exacerbate prior cardiovascular risk factors, which is why inflammation in RA is linked to accelerated atherosclerosis.[8] Elevated IL-6 levels are also associated with increased mortality in patients with acute coronary syndrome and increased risk of myocardial infarction in healthy men, regardless of whether RA inflammation was present.[8]

Lastly, the influence of IL-6 on the hypothalamic–pituitary axis has been associated with fatigue and mood changes.[9] High levels of IL-6 in the blood are associated with high levels of IL-6 in the brain, since it can cross the blood–brain barrier.[10,11] Following inflammation, not only can high levels of IL-6 be found within the brain, but also widespread GP130 expression.[12] Furthermore, proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and IL-1 (and also toll-like receptors), can induce *de novo* production of IL-6 from microglia, astrocytes, endothelial receptors, and certain types of neurons.[12]

IL-6, together with TNF-α and IL-1, activate a homeostatic pathway that begins with the release of corticotropin-releasing hormone and arginine vasopressin in the paraventricular nuclei of the brain.

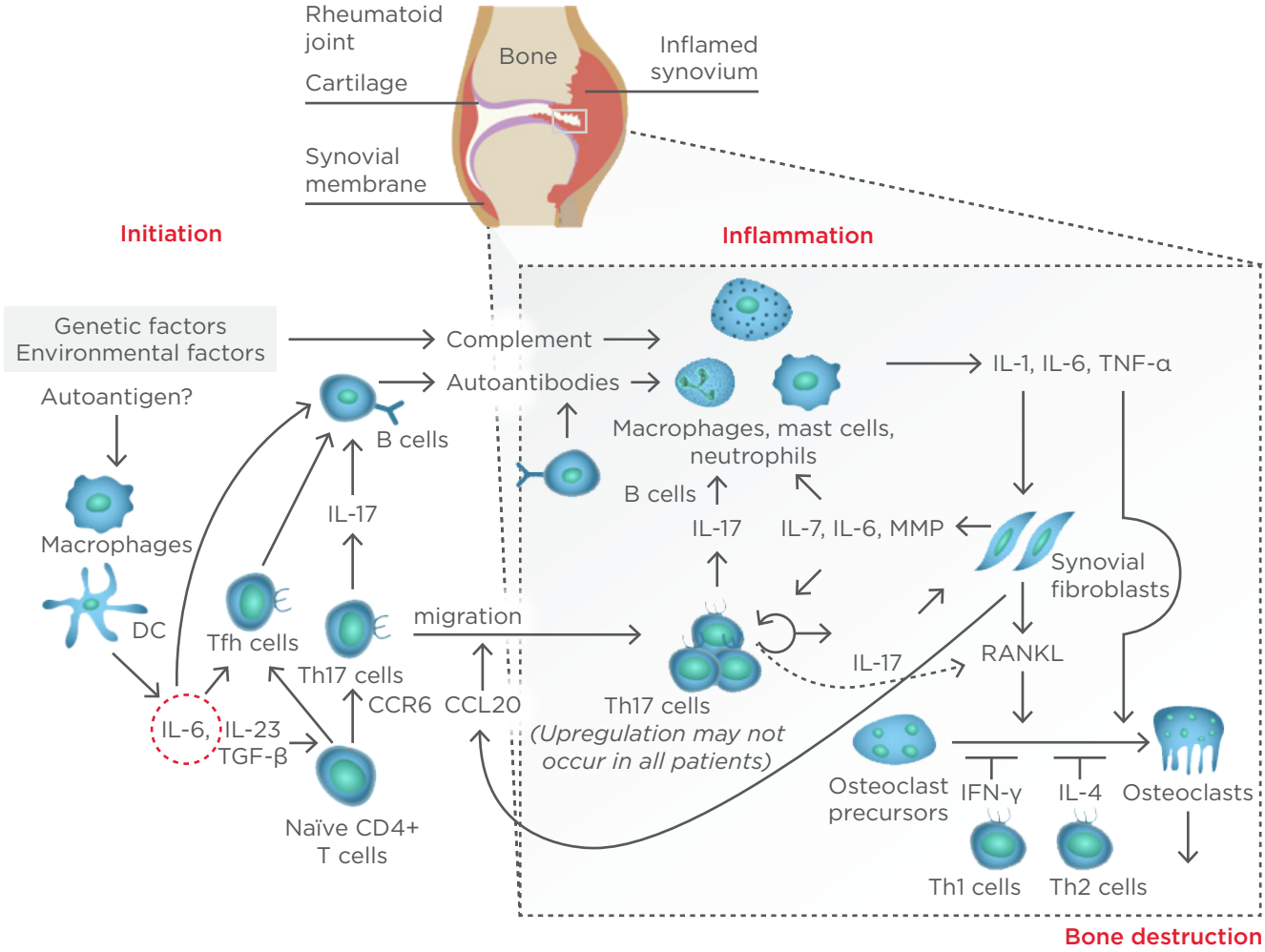


Figure 1: Pathogenesis of rheumatoid arthritis.
CCL20: chemokine ligand 20; CCR6: chemokine receptor Type 6; DC: dendritic cell; IFN-γ: interferon gamma; IL: interleukin; MMP: matrix metalloproteinases; RANKL: receptor activator of nuclear factor kappa-B ligand; Tfh: T follicular helper; TGF-β: transforming growth factor-beta; Th: T helper; TNF-α: tumour necrosis factor-alpha. *Adapted from Komatsu et al.*[4]

Corticotropin is then released and activates the adrenal release of cortisol, which then attempts to turn off the expression of proinflammatory cytokines. IL-6 has an effect of the locus coeruleus (the principal site for synthesis of noradrenaline), which may lead to fatigue and low mood state (Figure 2).[9,13]

Interleukin-6 Blockade: A Clinical Update

Professor Josef S. Smolen

IL-6 is a ubiquitous cytokine in the immune system. The majority of IL-6 receptors are membrane-bound[3,14] and cannot transduce signals on their own. IL-6 transduction occurs via multimerisation of the membrane and soluble-bound forms of IL-6 receptors (cleaved from membrane-bound receptors by ADAM17) and GP130, and subsequent activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways, which leads to cell survival, cell growth, cell proliferation, cell-cycle progression, increased protein synthesis, and drug resistance;[15] all of which are key to inflammation (Figure 3).

The IL-6 ligand, its receptors, and GP130, are all potential targets for the treatment of RA. Antibodies developed as potential treatments bind to different targets in the IL-6 signalling pathway; some antibodies bind to the IL-6 receptor, others to the IL-6 ligand, and a few can inhibit IL-6 signal transduction. This section outlines evidence that anti-IL-6 antibodies are efficacious treatments for patients with the disease. Generally, response rates decrease in patients with increasing history of

treatment and stronger medication (e.g. anti-TNF-α drugs), regardless of whether they are undergoing active therapy or placebo, because they are more resistant to treatment. However, there is evidence to suggest that all anti-IL-6 drugs mentioned in this summary are efficacious in managing RA regardless of prior treatment history. Furthermore, they have similar efficacy and safety profiles regardless of their mode of action. Therefore, this section summarises data on the efficacy and safety of four anti-IL-6 antibodies: tocilizumab, sarilumab, clazakizumab, and sirukumab.

Tocilizumab

Tocilizumab is an antibody that can bind to both membrane and soluble-bound forms of IL-6 receptors. Results from various trials have shown a statistically significant greater rate of American College of Rheumatology response criteria (ACR)50 and ACR70 (percent scores in relation to changes in RA symptoms) responses in patients who received tocilizumab, regardless of prior medication (methotrexate, disease-modifying anti-rheumatic drugs [DMARD], or anti-TNF-α). For example, data from a pooled analyses of trials (AMBITION,[16] LITHE,[17] OPTION,[18] and RADIATE[19]) matched prior findings: ACR70 responses were reported in 28% of methotrexate-naïve responders, 19% of DMARD-insufficient responders, and 12% of anti-TNF-α-insufficient responders.

Results have also shown radiographic benefit, reduction in disease progression, and improvement in quality of life. The LITHE trial showed that patients who received tocilizumab combined with methotrexate had higher Genant-modified Sharp scores (measure of erosion and joint space narrowing) at Week 52, with a statistically significant difference of 0.3 in each dose group (4 mg/kg and 8 mg/kg) compared to 1.1 in the placebo group. More specifically, both doses resulted in a lower value in both erosion and joint space narrowing numerical scores, which implies that tocilizumab is associated with reduced bony and cartilaginous destruction.[17] The OPTION trial[18] showed that both dose groups of tocilizumab combined with methotrexate showed a greater reduction in Health Assessment Questionnaire (HAQ) score (measure of health-related quality of life) than patients who took methotrexate as monotherapy in the control group, which did not reach the minimal clinically important difference of -0.22 before Week 12.

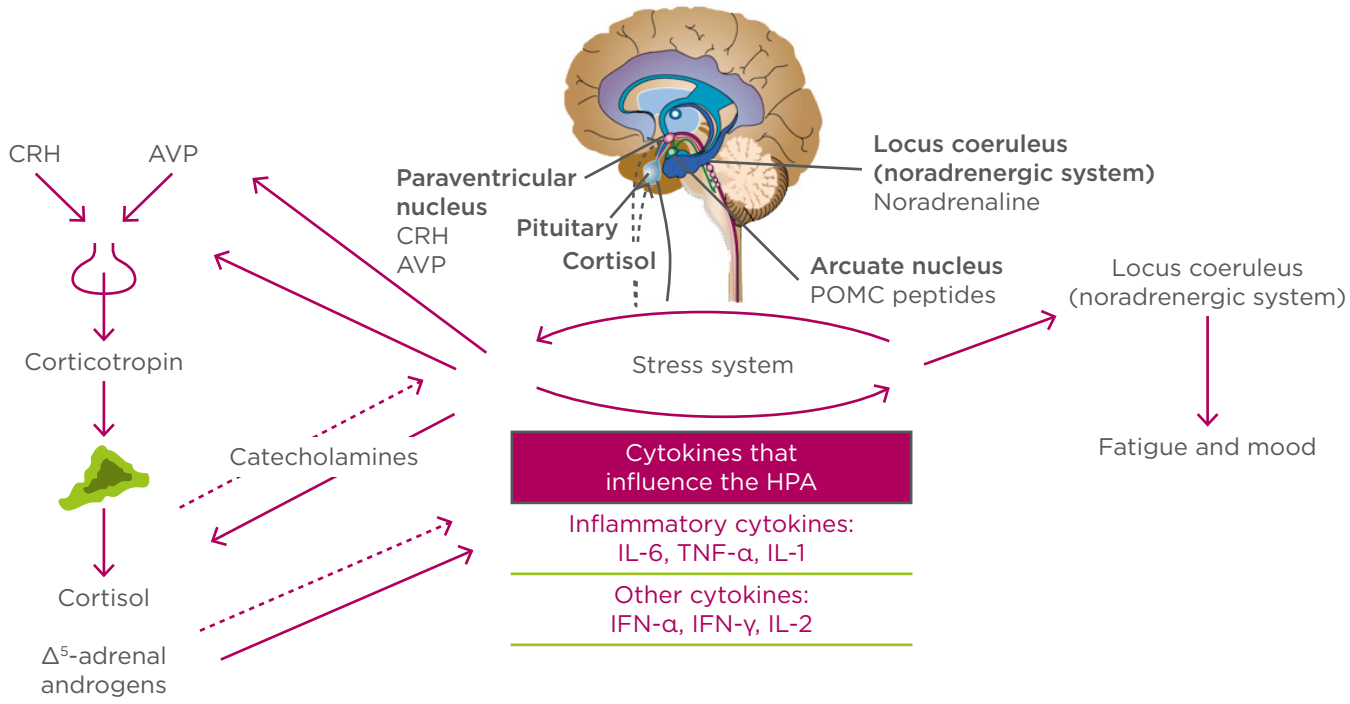


Figure 2: Cytokines affect fatigue and mood in rheumatoid arthritis by influencing the hypothalamic pituitary adrenal axis.

AVP: arginine vasopressin; CRH: corticotropin-releasing hormone; HPA: hypothalamic-pituitary-adrenal axis; IFN-γ: interferon-gamma; IL: interleukin; POMC: proopiomelanocortin; TNF-α: tumour necrosis factor-alpha. *Adapted from Chrousos[9] and Tsigos and Chrousos.[13]*

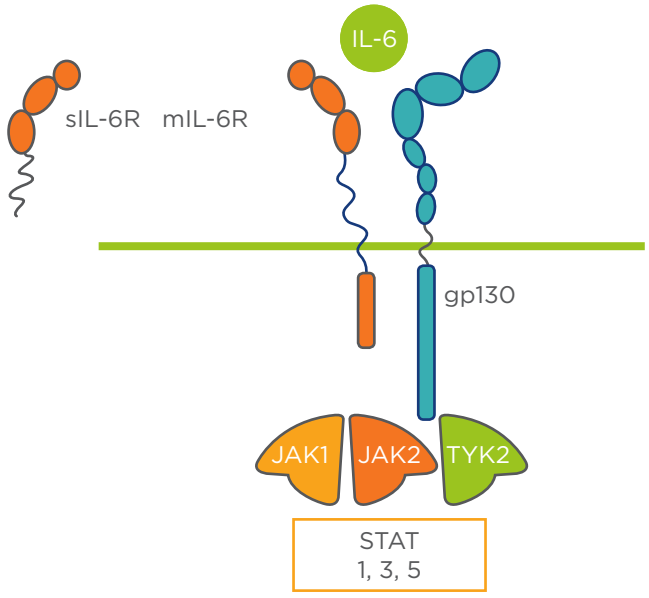


Figure 3: The interleukin-6 pathway.
IL: interleukin; gp130: glycoprotein 130; JAK: Janus kinase; mIL-6R: membrane interleukin-6 receptor; sIL-6R: soluble interleukin-6 receptor; STAT: signal transducers and activators of transcription; TYK: tyrosine kinase 2.

Further to this result, the SURPRISE trial[20] showed that, in patients who did not respond to methotrexate treatment, the rate of DAS28 remission (measure of disease activity reduction) was higher when tocilizumab was combined with methotrexate than when tocilizumab was used as monotherapy. The rate of disease activity score in 28 joints (DAS28) remission at Week 24 was 69.6% in the group that received combination therapy, compared to 55.0% in the group that received tocilizumab as monotherapy, a statistically significant difference. This implies that tocilizumab works best in combination with methotrexate. This finding is supported by the FUNCTION trial,[21] which showed that the number of ACR50 and ACR70 responses were higher in the group that received the combination therapy compared with the two groups that received either of them as monotherapy.

Sarilumab

Sarilumab is an anti-IL-6 receptor antibody like tocilizumab, so they were both expected to have a similar efficacy profile. Results from the MOBILITY trial[22] showed that methotrexate-insufficient responders exhibited higher rates of ACR20, ACR50, and ACR70 responses and lower progression of erosion and joint space narrowing (measured by the modified Total Sharp score) when they were treated with sarilumab combined with methotrexate, compared with those who were given placebo combined with methotrexate. The incidence of ACR70 response was 25% for 200 mg of sarilumab, 20% for 150 mg, and 7% for placebo, which is in line with data from methotrexate-naïve participants in tocilizumab. In another study,[23] anti-TNF-insufficient responders (i.e. patients who are more resistant to treatment effects than methotrexate-insufficient responders) who were given sarilumab combined with conventional synthetic DMARD had ACR70 response rates of 16.3% for sarilumab 200 mg, 19.9% for 150 mg, and 7.2% in placebo, which is again in line with tocilizumab results. In conclusion, sarilumab has a similar efficacy profile to tocilizumab, potentially due to their common mode of action.

Clazakizumab

Clazakizumab is an antibody that binds to the IL-6 ligand, so although it has a different mechanism than the previous two drugs, results show similar efficacy to anti-IL-6 receptor antibodies. A Phase IIb trial[24] showed greater ACR20 response rates at Week 12 in patients who received clazakizumab combined with methotrexate, compared with those who received clazakizumab as monotherapy, but both types of therapy showed better response rates than those in the placebo plus methotrexate group. Adalimumab (an anti-TNF drug) combined with methotrexate was just as effective a treatment as 25 mg of clazakizumab combined with methotrexate, and both produced the highest response rates out of all the groups (76.3% and 78.0%, respectively). Therefore, clazakizumab as a monotherapy has less efficacy compared with clazakizumab combined with methotrexate and an anti-TNF drug combined with methotrexate.

Sirukumab

Sirukumab is another antibody that binds to the IL-6 ligand. In a Phase II trial,[25] the ACR50 response rate at Week 12 was higher across all doses of sirukumab compared to the placebo group, with 100 mg of sirukumab taken every 2 weeks showing a statistically significant difference of 26.7% of participants compared to 3.3% of participants in the placebo group. A Phase III programme comprising several studies and this section will focus on the key findings of the SIRROUND-D trial and the SIRROUND-T trial.

The SIRROUND-D trial consisted of 104 weeks of therapy with 16 weeks follow-up for participants who failed to respond to DMARD. The primary endpoints were ACR20 response rate at Week 16 and change in van der Heijde Sharp score from baseline to Week 52, which is a measure of structural damage. For both primary endpoints, both doses of sirukumab showed statistically superior results compared to the placebo group; in fact, both doses were associated with an 80% reduction in progression rate of structural damage compared to the placebo group (0.5 versus 3.7, respectively).[25] The statistical significance also applied to ACR50 response rate, physical function,[26] and mean change in fatigue and quality of life (measured with SF-36) at Week 24.[27] In terms of physical function, the placebo group did not meet the minimal clinical significant difference (0.22) and both groups of sirukumab exceeded it two-fold.

The SIRROUND-T trial,[28] which consisted of 52 weeks of therapy, with 16 weeks of follow-up for participants that failed to respond to TNF inhibitors, showed the same results as SIRROUND-D. ACR20 and ACR50 response rates, physical function, and quality of life at Week 16 were significantly higher in both sirukumab groups compared to the placebo group and, in terms of physical function, the placebo group did not meet the minimal clinical significant difference, whereas both groups of sirukumab exceeded it. In a pre-specified subgroup analysis, a similar response rate was shown regardless of prior therapy and the number of drugs that patients failed to respond to. Patients who failed to respond to more than one had lower response rates than those who failed to respond to only one, regardless of whether they were undergoing active treatment or placebo, but the ACR20 response rate at Week 16 was still 40% for those who had received two prior TNF inhibitors, and 36–39% for those who failed three. Lastly, a post-hoc analysis showed statistically higher ACR20 response rates at Week 16 even among participants who failed TNF inhibitors and tocilizumab, which implies that IL-6 ligand inhibitors work even if IL-6 receptor inhibitors fail.

Safety data on sirukumab gathered from pooled randomised clinical trial data[28] show similar results to what have been reported in previous studies on the topic. Serious infections are more likely with sirukumab than with placebo, but not more likely than other similar agents. This is because IL-6, as well as having proinflammatory side effects, also has homoeostatic effects on the immune system. For example, IL-6 is a key growth factor in the bone marrow, so inhibition of IL-6 may lead to neutropaenia, which is associated with rare but serious infection.

In summary, sirukumab, an anti-IL-6 ligand antibody, showed efficacy regarding clinical, functional, and structural outcomes, as well as physical function and quality of life. Its safety profile is within expectations based on prior data of IL-6 receptor inhibitors (primarily tocilizumab).

The Biology Behind Patient-Reported Outcomes in Rheumatoid Arthritis

Professor Ernest Choy

Current regulations (e.g. from the U.S. Food and Drug Administration [FDA]) require patient-reported outcomes to be measured as key endpoints in clinical trials.[29] A systematic review carried out at John Hopkins University, Baltimore, Maryland, USA,[30] showed that the top three patient-reported domains that were measured by randomised clinical trials (RCT) were physical function (65 RCT; measured by HAQ-Disability Index [HAQ-DI), pain (30 RCT; measured by pain 100 mm Visual Analogue Scale [VAS] for pain), and patient global VAS (27 RCT; measured by VAS 100 mm). Fatigue and health-related quality of life were also frequently measured.

Fatigue

Fatigue is measured frequently across studies because it is a common symptom across many chronic physical and mental illnesses. A cross-sectional study of 238 patients with RA[31] showed that the mean fatigue score was 49 mm on the VAS; 54% of patients scored >50 mm and 84% of patients had clinically relevant fatigue defined by a fatigue score of ≥20 mm. Fatigue score was correlated with disease activity (r=0.48; measured by DAS28), degree of pain (r=0.68), and HAQ score (r=0.51), which may be due to reduced ability to carry out daily activities with increased fatigue.

A conceptual framework created by OMERACT of the manifestation of fatigue in patients with RA[32] showed that the cause of fatigue in this disease is multi-factorial and there are components of fatigue that may not necessarily be related to RA, such as components related to general inflammation or components more broadly related to cognitive,

personal, or socio-environmental factors. Another finding was that patients are more prone to fatigue if they suffer from anxiety or depression. Evidence from the Cochrane meta-analysis comparing both TNF inhibitors and non-TNF agents shows that blocking inflammation reduces fatigue;[33] thus, one significant component that drives fatigue in many patients with RA is inflammation.

Depression

Depression is commonly reported in people with RA. A German study measured the prevalence of depression in patients with RA by using four different measures of depression to capture its different aspects, including mood changes and low mood levels.[34] Consequently, prevalence of depression ranged from 18.5–49.5%, and all prevalence rates were higher than the general population. Furthermore, all four measures showed a correlation between depression scores and the DAS28 score ($p<0.001$), implying a correlation between depression and the level of inflammation. A Japanese study supports this correlation when using the Beck Depression Inventory to measure mood changes by showing that depression was correlated with CRP levels.[35]

Depression is very common in sufferers of chronic inflammatory diseases in general, and blocking inflammation can improve depression independently rather than as a result of improved physical functioning. A meta-analysis showed that TNF inhibitors were associated with reduced depression compared with placebo. More specifically, TNF inhibitors were more effective in reducing depression than standard DMARD.[36] A meta-analysis of four studies showed that sirukumab was linked with improved prevalent depressed mood and anhedonia independently of improvement in physical function.[37] Therefore, the difference in patient-reported mood level remains significant even when the data control for improvement in disease activity.

It is possible that patients with endogenous depression may actually be suffering from an inflammatory disease. A meta-analysis supports this hypothesis, with findings that people with endogenous depression had higher levels of IL-6 levels and TNF-α levels.[38] It is also possible that blocking cytokines can reduce depressive symptoms in patients with endogenous depression. The SIRROUND-D trial reported that the physical component score from a 36-item short form survey (SF-36 [a widely used measure of health-related quality of life]) was correlated with changes in the HAQ score. This was reflected by improvement in the mental component score from SF-36 as well; in fact, all four aspects of the score reached or exceeded the minimally important clinical difference for each of these domains.[39] The same result was shown in the SIRROUND-T trial.[28] This concludes that both doses of sirukumab improved fatigue in tandem with physical functioning compared with placebo, with no difference in improvement between doses. Another finding was that the mental health aspect of the mental component score improved independently of change in vitality, role-emotional, and social functioning, which supports the hypothesis that inhibiting IL-6 activity can improve depression independently of improvement in physical functioning.

Biological Explanation

The reason for the close relationship between IL-6 activity and mental functioning is that IL-6 can pass through the blood–brain barrier[10,11] and influence activity in the hypothalamic–pituitary axis, which regulates stress responses and other bodily responses such as the immune system. Via mechanisms not yet understood, IL-6 within the hypothalamic–pituitary axis can lead to fatigue and mood changes.[9,13] In summary, evidence from patient-reported outcomes suggests that cytokines are implicated in the pathogenesis of fatigue and depression in RA, and that inhibiting cytokines can reduce fatigue and depression.

REFERENCES

1. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012;18(13 Suppl):S295-302.

2. Yoshida Y, Tanaka T. Interleukin 6 and rheumatoid arthritis. Biomed Res Int. 2014;2014:698313.

3. Rose-John S et al. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: Role in inflammation and cancer. J Leukoc Biol. 2006;80(2):227-36.

4. Komatsu N, Takayanagi H. Inflammation and bone destruction in arthritis: Synergistic activity of immune and mesenchymal cells in joints. Front Immunol. 2012;3:77.

5. Calabrese LH, Rose-John S. IL-6 biology: Implications for clinical targeting in rheumatic disease. Nat Rev Rheumatol. 2014;10(12):720-7.

6. Dasgupta B et al. The effect of sirukumab plus methotrexate on circulating biomarkers of joint

destruction in moderate to severe rheumatoid arthritis patients from the SIRROUND-D Phase 3 study. Ann Rheum Dis. 2017;76(Suppl 2):94.

7. Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: The interleukin-6 receptor. Rheumatology (Oxford). 2010; 49(1):15-24.

8. Choy E et al. Cardiovascular risk in rheumatoid arthritis: Recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. Rheumatology (Oxford). 2014;53(12):2143-54.

9. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332(20):1351-62.

10. Banks WA et al. Penetration of interleukin-6 across the murine blood-brain barrier. Neurosci Lett. 1994;179 (1-2):53-6.

11. Russo I et al. Effects of neuroinflammation on the regenerative capacity of brain stem cells. J Neurochem. 2011;116(6):947-56.

12. Erta M et al. Interleukin-6, a major cytokine in the central nervous system. Int J Biol Sci. 2012;8(9):1254-66.

13. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53(4):865-71.

14. Heinrich PC et al. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J. 2003; 374(Pt 1):1-20.

15. Burger R. Impact of interleukin-6 in hematological malignancies. Transfus Med Hemother. 2013;40(5):336-43.

16. Jones G et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69(1):88-96.

17. Fleischmann RM et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. J Rheumatol. 2013; 40(2):113-26.

18. Smolen JS et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): A double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-97.

19. Emery P et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: Results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.

20. Kaneko Y et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). Ann Rheum Dis. 2016;75(11):1917-23.

21. Burmester G et al. Tocilizumab in combination therapy and monotherapy versus methotrexate in methotrexate-naïve patients with early rheumatoid arthritis: Clinical and radiographic outcomes from a randomized, placebo-controlled trial. Arthritis Rheum. 2013; 65(Suppl 10):2767.

22. Genovese MC et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: Results of a Phase III study. Arthritis Rheumatol. 2015; 67(6):1424-37.

23. Fleischmann R et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol. 2017;69(2):277-90.

24. Weinblatt ME et al. The efficacy and safety of subcutaneous clazakizumab in patients with moderate-to-severe rheumatoid arthritis and an inadequate response to methotrexate: Results from a multinational, Phase IIb, randomized, double-blind, placebo/active-controlled, dose-ranging study. Arthritis Rheumatol. 2015;67(10):2591-600.

25. Smolen JS et al. Sirukumab, a human anti-interleukin-6 monoclonal antibody: A randomised, 2-part (proof-of-concept and dose-finding), phase II study in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2014;73(9):1616-25.

26. Takeuchi T et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis despite disease-modifying anti-rheumatic drug treatment: Results of a randomized, double-blind, placebo-controlled study. Annals of the Rheumatic Diseases. 2016;75(Suppl 2):717.

27. Bingham C III et al. Treatment with sirukumab, an anti-il6 cytokine monoclonal antibody, improves fatigue and health-related physical and emotional well being in patients with active rheumatoid arthritis refractory to conventional or biologic therapy: Results of 2 global, placebo-controlled, Phase 3 trials. Arthritis Rheumatol. 2016;68 (Suppl 10).

28. Aletaha D et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): A randomised, double-blind, placebo-controlled, parallel-group, multinational, Phase 3 study. Lancet. 2017;389(10075):1206-17.

29. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: Patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:79.

30. Orbai AM et al. Patient reported outcomes in rheumatoid arthritis clinical trials. Curr Rheumatol Rep. 2015;17(4):28.

31. Pollard LC et al. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology (Oxford). 2006;45(7): 885-9.

32. Hewlett S et al. Fatigue in rheumatoid arthritis: Time for a conceptual model. Rheumatology (Oxford). 2011;50(6): 1004-6.

33. Almeida C et al. Biologic interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev. 2016(6):Cd008334.

34. Englbrecht M et al. Validation of standardized questionnaires evaluating symptoms of depression in rheumatoid arthritis patients: Approaches to screening for a frequent yet underrated challenge. Arthritis Care Res (Hoboken). 2017;69(1):58-66.

35. Kojima M et al. Depression, inflammation, and pain in patients with rheumatoid arthritis. Arthritis Rheum. 2009;61(8):1018-24.

36. Kappelmann N et al. Antidepressant activity of anti-cytokine treatment: A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry. 2016.

37. Sun Y et al. Improvement in measures of depressed mood and anhedonia in two randomized, placebo-controlled Phase III studies of sirukumab, a human anti-interleukin-6 antibody, in patients with rheumatoid arthritis. Ann Rheum Dis. 2017;76(Suppl 2):250.

38. Dowlati Y et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446-57.

39. Thorne C et al. Favorable effects of sirukumab treatment on physical function and reductions in morning stiffness in patients with active rheumatoid arthritis and an inadequate response to disease-modifying anti-rheumatic drugs. Abstract: AB0341. European League Against Rheumatism (EULAR) congress, 8-11 June, 2016.

INTERLEUKIN-23: THE COMMON LINK BETWEEN THE JOINT, THE GUT, AND THE SKIN?

This symposium took place on 16th June 2017, as a part of the European League Against Rheumatism (EULAR) 18th Annual Congress in Madrid, Spain

Chairpersons

Dennis McGonagle,[1] Frank Behrens[2]

Speakers

Dennis McGonagle,[1] Frank Behrens,[2] Silvio Danese[3]

1. University of Leeds, Leeds, UK
2. Goethe University, Frankfurt, Germany
3. Humanitas University, Rozzano, Italy

Disclosure: Prof McGonagle has received grant/research support from Pfizer, MSD, Janssen, Celgene, and AbbVie. He has also received honoraria or consultation fees from Pfizer, MSD, Janssen, Celgene, UCB, Abbvie, and Novartis and has participated in speaker bureaus sponsored by Pfizer, MSD, Janssen, Celgene, AbbVie, and Novartis. Dr Behrens has received grant/research support from AbbVie, Janssen, Pfizer, Roche, Chugai, and Novartis. He has also received honoraria or consultation fees from AbbVie, Pfizer, Roche, Chugai, UCB, BMS, Celgene, MSD, Novartis, Biotest, Janssen, Genzyme, Lilly, and Sandoz. Prof Danese has received honoraria or consultation fees from AbbVie, AstraZeneca, Johnson & Johnson, MSD, Mundipharma, Takeda Millennium, Salix Pharmaceuticals, and Pfizer. He has also participated in speaker bureaus sponsored by AbbVie, AstraZeneca, Johnson & Johnson, MSD, Mundipharma, Takeda Millennium, Salix Pharmaceuticals, and Pfizer.
Acknowledgements: Writing assistance was provided by Reg Gomez, ApotheCom, London, UK.
Support: The publication of this article was funded by Janssen Pharmaceutica NV. The views and opinions expressed are those of the authors and not necessarily those of Janssen Pharmaceutica NV.
Citation: EMJ Rheumatol. 2017;5[Suppl 13]:10-16.

MEETING SUMMARY

Prof McGonagle introduced the symposium and briefly described the aims of the meeting. Dr Behrens first discussed how findings from relevant psoriasis and psoriatic arthritis (PsA) registries can be applied to improve daily practice, and reflected on the real-life effectiveness of biologic therapies in the treatment of PsA. Prof McGonagle then followed with a discussion describing the key immunological pathways involved in psoriasis and PsA, evaluating the key similarities and differences in tissue and cytokine pathobiology in both conditions. Prof Danese then concluded the symposium by presenting on the pathophysiology of the interleukin (IL)-23 pathway in inflammatory bowel disease (IBD), reviewing the latest data for IL-23 inhibitors in treating IBD.

Comparing Interleukin-12/23 and Anti-Tumour Necrosis Factor 'Real-World' Registry Data in Psoriasis and Psoriatic Arthritis

Doctor Frank Behrens

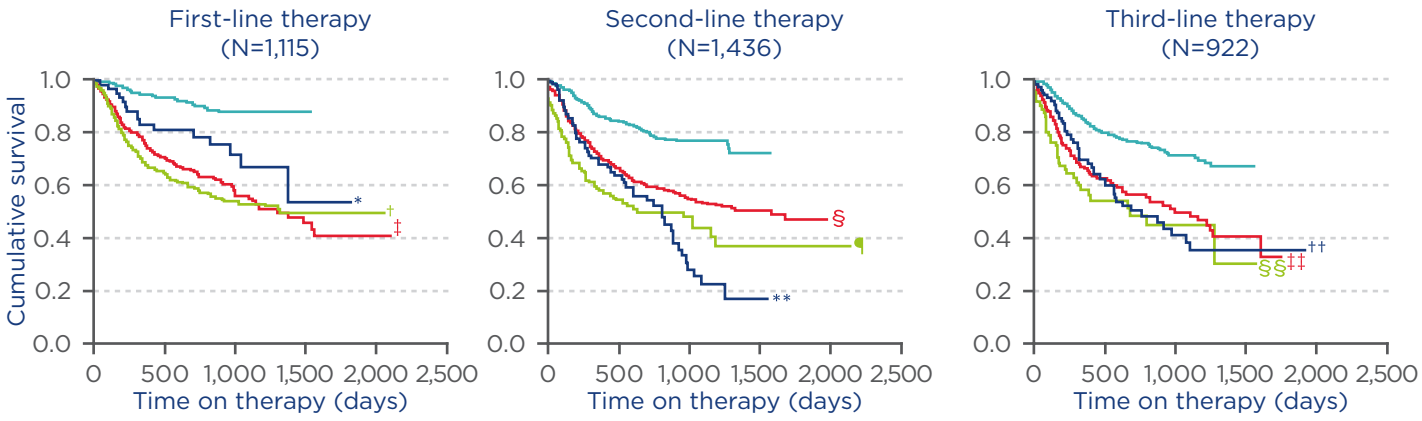
Defining and adhering to therapeutic targets have been shown to be critical for improving treatment outcomes across a number of diseases, including diabetes, hypertension, and rheumatoid arthritis. For spondyloarthropathies (SpA), such as PsA, the treatment target has been defined as remission or, alternatively, low disease activity.[1] This treatment target can be achieved by utilising different outcome measures to formulate an appropriate personalised treatment plan suited to specific patients within clinical practice.

To achieve treatment goals in SpA, firstly the treatment target must be based on a shared decision between the patient and their

rheumatologist. For example, in a randomised controlled trial (RCT) conducted by de Vries et al.,[2] two biologics, infliximab (5 mg/kg intravenously at Weeks 0, 2, 6, 14, and 22) and etanercept (50 mg subcutaneously twice weekly), were compared for the treatment of psoriasis. At Week 24, significantly more patients achieved ≥75% improvement of Psoriasis Area Severity Index (PASI 75) with infliximab (72%) than with etanercept (35%; p=0.01). Additionally, infliximab demonstrated a significant reduction in body surface area (BSA) compared with etanercept. From a rheumatologist's perspective, based on these data, infliximab would be considered the favourable treatment over etanercept. However, in the same study, patients were asked to complete a Treatment Satisfaction Questionnaire for Medication, which assessed the patient's satisfaction with their treatments, based on adverse events, convenience, efficacy, and global satisfaction.[2] Although it was not statistically significant, etanercept scored higher than infliximab with regard to convenience and adverse events, which may be due to its subcutaneous application. Surprisingly, however, there was no significant difference in efficacy satisfaction between the two treatments, despite the significantly greater PASI 75 response with infliximab compared with etanercept.[2] The treatment target should therefore be based on a shared decision between the patient and their rheumatologist. If both views differ, then other goals and different data should be considered to guide the treatment decision.

It should be borne in mind that the primary goal of treating patients with SpA is to maximise long-term health-related quality of life through control of signs and symptoms, avoidance of toxicities, and minimisation of comorbidities.[1] To achieve this goal, physicians can look to RCT and real-world evidence (RWE). RWE is more advantageous in guiding physicians' treatment decisions compared to data obtained from RCT. In RWE, patient treatments are determined by doctors' choices as per standard practice and are not randomised. In addition, non-adherent patients are able to switch treatment and so are likely to remain included in the data, whereas, in RCT, non-adherent patients are taken out of the analysis. RWE also contains a heterogeneous patient population reflecting a realistic scenario, unlike RCT, which contain a number of inclusion and exclusion criteria that artificially create a homogenous treatment group. Given these advantages over RCT, data from psoriasis and PsA registries, which better reflect the real-life effectiveness of biologic therapies, can be applied to improve daily practice.

Several studies using data from registries across the world have compared the efficacy and safety of treatment options for psoriasis and PsA.



*p=0.0014 for infliximab versus ustekinumab (HR: 2.729)

†p<0.0001 for etanercept versus ustekinumab (HR: 4.911)

‡p<0.0001 for adalimumab versus ustekinumab (HR: 4.164)

§p<0.0001 for adalimumab versus ustekinumab (HR: 2.296)

¶p<0.0001 for etanercept versus ustekinumab (HR: 3.219)

**p<0.0001 for infliximab versus ustekinumab (HR: 3.350)

††p<0.0001 for infliximab versus ustekinumab (HR: 2.543)

‡‡p<0.0001 for adalimumab versus ustekinumab (HR: 2.464)

§§p<0.0001 for etanercept versus ustekinumab (HR: 3.041)

Figure 1: Proportion of patients continuing therapy amongst known biologic therapies in psoriasis.[7]
Reasons for stop/switch were similar across biologics.
HR: hazard ratio.

A study from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) assessed the risk of adverse events of special interest with psoriasis treatments in a real-world setting[3] and found that rates of serious infection for infliximab and other biologics were numerically higher compared with ustekinumab. Similarly, a study using data from the prospective Biologisk Behandling i Dansk Dermatologi (DERMBIO) registry in Denmark demonstrated a trend of lower cumulative incidence of serious adverse events, such as infection, cancer, and cardiovascular events, with ustekinumab compared with adalimumab, etanercept, and infliximab.[4] More recently, the SUSTAIN study,[5] conducted in Germany, reported the efficacy, safety, and tolerability of ustekinumab for the treatment of PsA in routine clinical care from both the physician and patient perspective. At Week 16, efficacy of ustekinumab was rated excellent by 32.3% of physicians, and a further 44.8% of physicians rated it as good. Among patients, efficacy of ustekinumab was rated as excellent or good by 34.0% and 40.2%, respectively. With respect to tolerability of ustekinumab at Week 16, it was rated excellent and good by 51.0% and 43.8% of physicians, respectively, and by 55.0% and 37.0% of patients, respectively.[5]

In the treatment of PsA, it is also necessary to measure disease activity and amend therapy in cases of persistently active disease.[1] For example, in a study from the British Association of Dermatologists' Biologic Interventions Register (BADBIR) which assessed drug survival (time to drug discontinuation) of biologics used to treat psoriasis, ustekinumab was shown to have the highest first-course drug survival as compared with adalimumab, etanercept, and infliximab.[6] Similarly, a study from the DERMBIO registry demonstrated that ustekinumab had a significantly longer survival rate than other anti-tumour necrosis factor-alpha (TNF-α) agents.[4] In another study, from the PSOLAR registry, which compared drug survival in patients with psoriasis undergoing first, second, or third-line treatment with ustekinumab, infliximab, adalimumab, or etanercept, significantly shorter times to discontinuation were observed for infliximab (hazard ratio [HR]: 2.73; 95% confidence interval [CI]: [1.48–5.04]; p=0.0014), adalimumab (HR: 4.16; 95% CI: 2.80–6.20; p<0.0001), and etanercept (HR: 4.91; 95% CI: 3.28–7.35; p<0.0001) compared with ustekinumab (reference treatment) for first-line biologic use.[7] Similar results were observed for second and third-line therapies (Figure 1).[7]

In addition to RWE providing physicians with information to guide treatment decisions, it is also important to consider the patient perspective. Taken together, these results demonstrate that optimising treatment scores is not the same as optimising treatment and that outcome measures, along with clinical data, should be carefully taken into consideration when formulating an appropriate personalised treatment plan for patients in clinical practice.

In conclusion, the primary goal in treating psoriasis and PsA is to lower disease activity and maximise long-term health-related quality of life. Real-life data from psoriasis and PsA registries provide useful information and can be used to make informed treatment decisions. Furthermore, outcome measures should be taken into consideration and treatment targets should be based on a shared decision between the patient and their rheumatologist, since optimising treatment scores does not always translate to optimising treatment.

Immunological Similarities and Differences Between Psoriasis and Psoriatic Arthritis

Professor Dennis McGonagle

Understanding the clinical relevance of enthesitis and the immunology at the enthesis has helped to understand similarities and differences between psoriasis and PsA. Enthesitis is the inflammation of the enthesis and is well recognised in the synovial joints of patients with PsA.[8] Recent findings have shown that the immunopathogenetic inter-relationship between the synovium and entheses is more complex than first imagined and that joint-specific factors found in the synovio-entheseal complex could trigger innate immune responses and may be pivotal players in the phenotypic expression of PsA.[8]

PsA has a wide spectrum of disease severity. The clinical heterogeneity in PsA reflects the substantial genetic heterogeneity. In recent years, many genes that contribute to the pathogenesis of psoriasis and PsA have been identified.[9] As an example, genetics studies have demonstrated that polymorphisms in the TNF-α interactive protein 3 (*TNFAIP3*) gene, which encodes the ubiquitin-modifying protein, A20, an important endogenous regulator of inflammation, are

linked to both psoriasis and PsA[10] and play a role in the development of enthesitis, with the earliest manifestation occurring within the synovio-entheseal complex resident myeloid cells.[11]

In recent years, several animal models have been developed that demonstrate the primacy of enthesitis in SpA-like disease. The most exciting translational model is that of arthritis following systemic overexpression of IL-23 in the liver, which resulted in three cardinal manifestations, namely a primary enthesis, skin rash, and aortic root inflammation.[12] In this particular model, populations of innate lymphoid-like cells (ILC) were documented at the entheses and these were key to driving the disease process.

In humans, Group 3 ILC (ILC3) play a pivotal role in barrier tissues, such as the gut and the skin, two important sites of disease in SpA. A recent study has demonstrated that there is a higher proportion of ILC3 in human entheseal soft tissue compared with peripheral blood (p=0.008), and a similarly higher proportion of activated ILC3 in both entheseal soft tissue and peri-entheseal bone (p=0.01 and p=0.043, respectively, versus peripheral blood).[13] Furthermore, normal entheseal digests stimulated with IL-23/IL-1β upregulated IL-17A transcripts and histological examination of injured/damaged entheses showed retinoic acid receptor-related orphan receptor gamma (RORγ)-expressing cells.[13]

Recent studies in the aforementioned IL-23-dependent murine model have shown that many of the entheseal resident IL-17-producing cells were gamma delta (γ-δ) T cells.[14] This family of innate immune lymphocytes is best recognised for localisation at sites of barriers where stress and injury is common, allowing them to sense damage;[15] they are now recognised as key players in the pathogenesis of IL-23-induced entheseal inflammation. It was recently discovered that γ-δ T cells are present in normal human enthesis and that they constitute a greater proportion of the T cell pool in entheseal soft tissue compared with peripheral blood, making it likely that they represent a tissue-resident population.[16] This is the first description of γ-δ T cells at the human enthesis and offers tentative confirmation of findings in mouse models where these cells play a key role in SpA pathogenesis. This is the first confirmation in humans that across the SpA spectrum of disease, from gut to skin to enthesis, IL-23-dependent innate immune cell populations are present.

RWE has provided a proof-of-concept of the key importance of the IL-12/IL-23 axis in PsA. The PHOENIX 1 study,[17] which examined the long-term efficacy and safety of ustekinumab through 5 years of continuous treatment, demonstrated that initial clinical responses were generally maintained through to Week 244 (PASI 75: 63.4% and 72.0% for patients receiving 45 mg and 90 mg, respectively) (Figure 2).

Subclinical enthesopathy has also been shown to be a commonality between psoriasis and PsA. Ultrasonographic enthesopathy was present in 11.6% of entheses in the psoriasis group and 5.3% of entheses in the control group (p<0.0005).[18] Furthermore, treatment with ustekinumab led to an improvement in subclinical enthesopathy in patients with psoriasis.[19] The data suggest that early intervention with anti-IL-12/IL-23 agents in psoriasis may prevent the evolution of subclinical disease into frank PsA. However, this needs to be evaluated in real-world registry data sets to confirm that PsA evolution can be prevented when the IL-23/IL-17 axis is targeted. In summary, there are strong common genetic and immunological overlaps between psoriasis and PsA; however, these diseases are highly heterogeneous. Emerging data in both preclinical and clinical studies have identified different populations of innate lymphocytes that are critically dependent on the IL-23/IL-17 axis.

The Link Between the Joint and the Gut: A Gastroenterologist's View

Professor Silvio Danese

The link between the joint and the gut was explored from a gastroenterologist's perspective through a patient case study; the patient was female and 48 years old. She had had guttate psoriasis since she was 25 years of age and developed PsA, which affects both knees, 6 years before the study. She was treated with non-steroidal anti-inflammatory drugs and methotrexate at 10 mg/weekly, which was then reduced to 7.5 mg/weekly. She presented with abdominal pain and diarrhoea (4–6 stools/day, although not at night), with mucus but no blood in her stool. Her histopathology results confirmed the diagnosis of Crohn's disease and she was administered steroids and methotrexate (25 mg/weekly). She responded well to her treatment, later continuing on methotrexate and tapering off of the steroids.

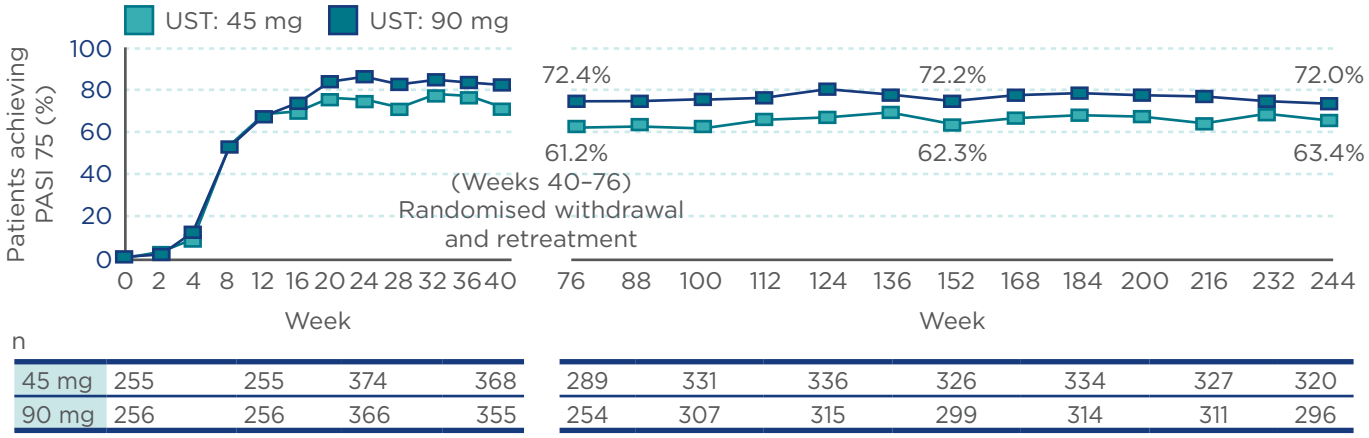


Figure 2: The PHOENIX 1 study: The proportion of patients achieving ≥75% improvement in Psoriasis Area Severity Index efficacy in the overall population through 5 years.

Note: Placebo crossover patients were included at the beginning of Week 24 (i.e. 12 weeks after UST treatment). Analyses were not conducted between Weeks 40 and 76 when the majority of the population was withdrawn from treatment per study design. Analyses resumed at Week 76 when about half of the withdrawn patients had reinitiated UST for ≥12 weeks. Patients who reinitiated treatment after Week 76 were reincluded after ≥12 weeks of retreatment. UST 90 mg is indicated for patients with a body weight of >100 kg.

PASI 75: 75% improvement in Psoriasis Area Severity Index; UST: ustekinumab.

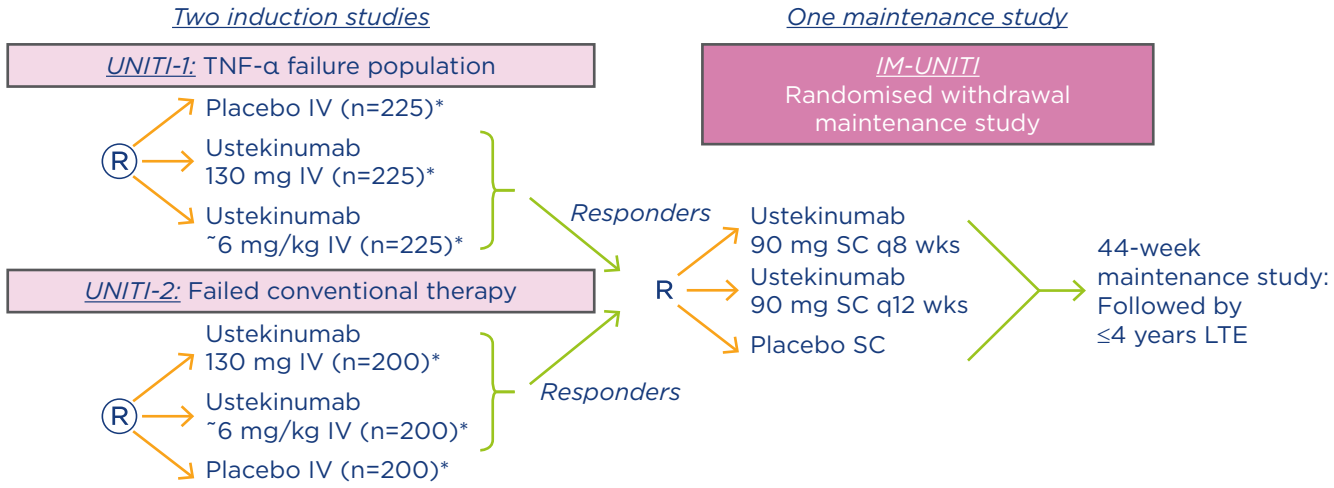


Figure 3: UNITI Phase III Crohn's programme.

*Subjects randomised to placebo and subjects who are non-responders to ustekinumab are eligible for non-randomised maintenance dosing after completion of the induction study.

IV: intravenous; LTE: long-term extension; q8 wks: every 8 weeks; q12 wks: every 12 weeks; SC: subcutaneous; TNF-α: tumour necrosis factor-alpha.

In April 2015, she complained about joint pain and sleep disturbances; she stopped her methotrexate treatment and was started on adalimumab by her rheumatologist.

By July 2015, the patient's condition had worsened. She had diarrhoea with blood and mucus in her stool, her calprotectin level was 3,800 µg/g, and her C-reactive protein was 5 mg/dL. Her psoriasis worsened and required local treatment, and she developed scleritis, which was controlled by topical steroids. Her joint pain was managed by adalimumab 40 mg/weekly.

In November 2016, a magnetic resonance enterography and an ileocolonoscopy were performed to establish the location and extent of her Crohn's disease. The results demonstrated

active bowel inflammation but no evidence of small bowel disease. Through a multidisciplinary consultation, it was decided to treat the patient with ustekinumab 6 mg/kg via an intravenous, subcutaneous dose at Week 8, and then every 12 weeks thereafter. The patient's condition improved, with her C-reactive protein decreasing to 0.62 mg/dL and her stools reduced to 1–2 per day and were without blood. She had no abdominal pain, no psoriatic lesions, and no ulcers or narrowing of the colon.

UNITI-1 and UNITI-2 are two Phase III randomised, double-blind, controlled studies that compared the effects of a single intravenous dose of ustekinumab (either 130 mg or approximately 6 mg/kg of bodyweight) to a placebo over 8 weeks in patients with moderate-to-severely active Crohn's disease.[20] The UNITI-1 trial included 741 patients who met the criteria for primary or secondary non-response to TNF antagonists or had unacceptable side effects. The UNITI-2 trial included 628 patients in whom conventional therapy had failed or unacceptable side effects occurred. Patients who completed these induction trials then participated in IM-UNITI, which evaluated the efficacy and safety of two maintenance regimens of 90 mg of ustekinumab administered subcutaneously (either every 8 weeks or every 12 weeks) versus placebo (Figure 3).

In both UNITI-1 and UNITI-2, clinical remission, defined as a Crohn's Disease Activity Index (CDAI) score of <150 points, was found at Week 8 to be significantly higher in both of the ustekinumab groups compared with placebo.[20] In IM-UNITI, the percentage of patients who were in remission at Week 44 was significantly higher in the groups that received 90 mg of ustekinumab every 8 weeks or every 12 weeks than in the placebo group, with an absolute difference between treatment every 8 weeks and placebo of 17.2 percentage points, and a difference between treatment every 12 weeks and placebo of 12.9 percentage points.[20]

From a gastroenterologist's view, there is a strong link between the joints and the gut, as extra-intestinal manifestations, such as peripheral arthropathy and arthritis, are prevalent among patients with Crohn's disease and ulcerative colitis.[21,22] Back and joint pain are the most common extra-intestinal symptoms reported by patients with IBD and can significantly lower a patient's quality of life and work productivity.[23] Most patients with IBD are aware of the risk of developing arthritis;[24] however, in a study that investigated self-reported prevalence of musculoskeletal SpA features in a cohort of patients with IBD, a substantial number of patients had not been evaluated by a rheumatologist.[25] This is therefore an area where gastroenterologists and rheumatologists can work more closely together to improve the treatment of immune-mediated inflammatory diseases. In clinical practice, it would be useful to define the red flags that will help clinicians to make a correct diagnosis of IBD-associated SpA.[26] Diagnostic clues for rheumatologists to consider include family history of IBD; clinical symptoms such as clinical diarrhoea, chronic abdominal pain, and weight loss; and history or evidence of perianal fistula/abscess and anaemia. For gastroenterologists, the following diagnostic clues should be considered: chronic back pain (>3 months), peripheral joint pain/swelling, the presence of signs of enthesitis, and history or evidence of dactylitis. Early recognition of extra-intestinal manifestations will also help guide therapy and reduce overall morbidity in affected patients.[27]

In summary, IBD such as Crohn's disease share a commonality with psoriasis and PsA through the IL-23 pathway. Similarly to psoriasis and PsA, clinical studies have shown that inhibiting the IL-23 pathway induces response and remission in patients with moderate-to-severely active Crohn's disease. We should therefore consider how multidisciplinary management can be leveraged to improve the treatment of immune-mediated inflammatory disease.

REFERENCES

1. Smolen JS et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: Recommendations of an international task force. Ann Rheum Dis. 2014;73(1):6-16.

2. de Vries AC et al. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: The Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. Br J Dermatol. 2017;176(3):624-33.

3. Papp K et al. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Drugs Dermatol. 2015;14(7):706-14.

4. Gniadecki R et al. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol. 2015;172(1):244-52.

5. Wendler J et al. Ustekinumab for the treatment of psoriatic arthritis - results of the first interim analysis of non-interventional study SUSTAIN. Ann Rheum Dis. 2017;76(Suppl 2):1322.

6. Warren RB et al. Differential drug survival of biologic therapies for the treatment of psoriasis: A prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.

7. Menter A 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(7):1148-58.

8. McGonagle D et al. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. Arthritis Rheum. 2007;56(8):2482-91.

9. O'Rielly DD, Rahman P. Genetics of susceptibility and treatment response in psoriatic arthritis. Nat Rev Rheumatol. 2011;7(12):718-32.

10. Stuart PE et al. Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. Am J Hum Genet. 2015;97(6):816-36.

11. De Wilde K et al. A20 inhibition of STAT1 expression in myeloid cells: A novel endogenous regulatory mechanism preventing development of enthesitis. Ann Rheum Dis. 2017;76(3):585-92.

12. Sherlock JP et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. Nat Med. 2012;18(7): 1069-76.

13. Cuthbert RJ et al. Brief Report: Group 3 innate lymphoid cells in human enthesis. Arthritis Rheumatol. 2017;69(9): 1816-22.

14. Reinhardt A et al. Interleukin-23-dependent gamma/delta t cells produce interleukin-17 and accumulate in the enthesis, aortic valve, and ciliary body in mice. Arthritis Rheumatol. 2016;68(10): 2476-86.

15. Bonneville M et al. Gammadelta T cell effector functions: A blend of innate programming and acquired plasticity. Nat Rev Immunol. 2010;10(7): 467-78.

16. Cuthbert RJ et al. First description of gamma delta T cells at normal human enthesis. Arthritis Rheumatol. 2017;76(Suppl 2):648.

17. Kimball AB et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. J Eur Acad Dermatol Venereol. 2013;27(12):1535-45.

18. Naredo E et al. High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: A prospective case-control study. Rheumatology (Oxford). 2011;50(10):1838-48.

19. El-Sherbiny Y et al. Type 3 innate lymphoid cells numbers in peripheral blood predict ustekinumab (stelara) therapy responsiveness in psoriatic disease cases with subclinical imaging enthesopathy. Arthritis Rheumatol. 2016; 68(suppl 10):2083.

20. Feagan BG et al. Ustekinumab as induction and maintenance therapy for crohn's disease. N Engl J Med. 2016;375(20):1946-60.

21. Vavricka SR et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106(1): 110-9.

22. Harbord M et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis. 2016;10(3):239-54.

23. van der Valk ME et al. Comparison of costs and quality of life in ulcerative colitis patients with an ileal pouch-anal anastomosis, ileostomy and anti-TNFalpha therapy. J Crohns Colitis. 2015; 9(11):1016-23.

24. Huang V et al. Patient awareness of extraintestinal manifestations of inflammatory bowel disease. J Crohns Colitis. 2013;7(8):e318-24.

25. Stolwijk C et al. Prevalence of self-reported spondyloarthritis features in a cohort of patients with inflammatory bowel disease. Can J Gastroenterol. 2013; 27(4):199-205.

26. Olivieri I et al. Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease. Autoimmun Rev. 2014;13(8):822-30.

27. Ardizzone S et al. Extraintestinal manifestations of inflammatory bowel disease. Dig Liver Dis. 2008;40 (Suppl 2):S253-9.