EULAR 2018 Congress

European League Against Rheumatism

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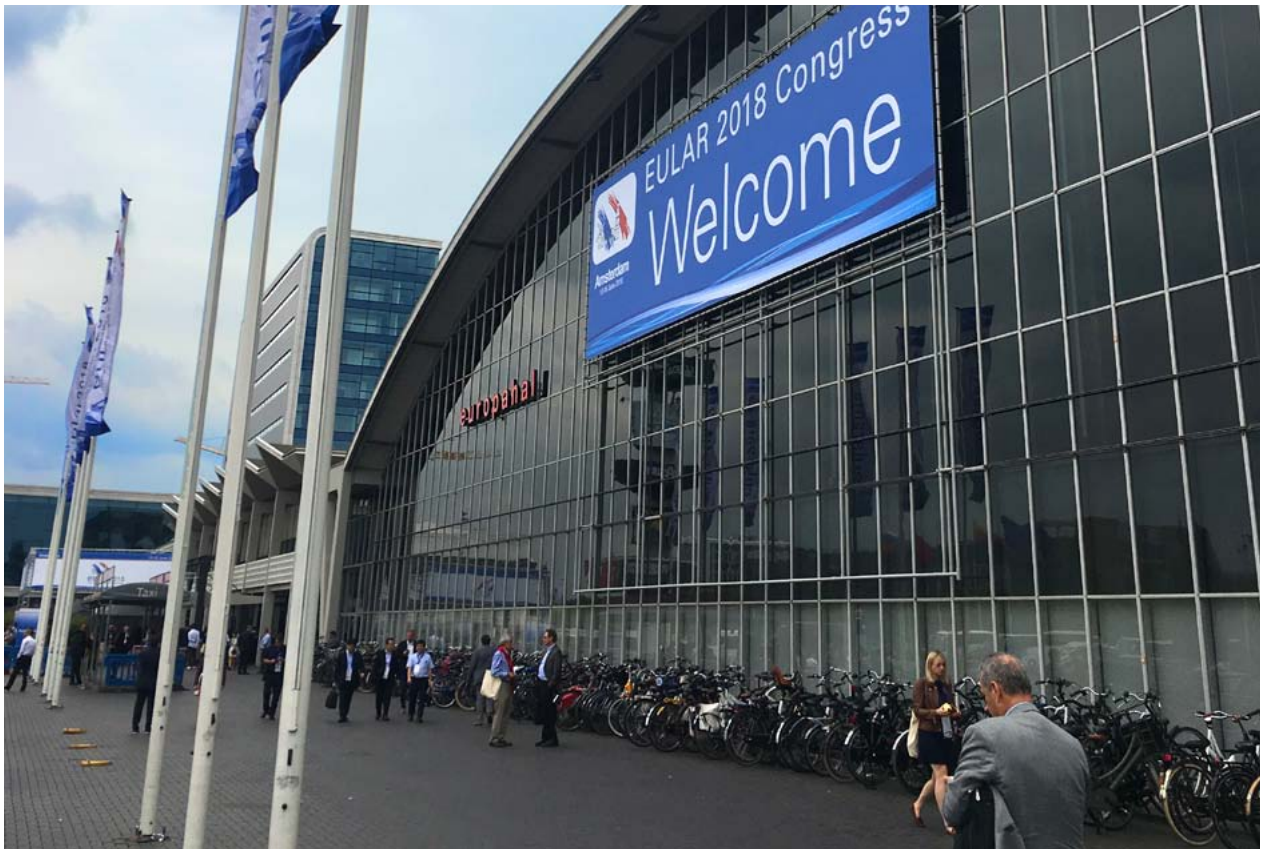
PEER-REVIEWED CONFERENCE REPORT



Switching to Biosimilars Safe and Efficacious

Switching to biosimilar CT-P13 is not inferior to continued treatment with originator infliximab, adding to increasing real-world evidence that switching from originator to biosimilar bDMARDs is safe and efficacious.

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Synergistic Effect NSAIDs + TNFi in Slowing Radiographic Progression AS

Dose-related use of NSAIDs plus TNFi in ankylosing spondylitis patients has a synergistic effect in slowing radiographic progression with the greatest effect seen in high-dose NSAIDs plus TNFi.

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Novel Systemic Sclerosis Drugs

Multiple therapies are being investigated for use in systemic sclerosis, including abatacept, belimumab, lenabasum, pirfenidone, nintedanib and tocilizumab; some of which are expected to provide feasible new options for patients.

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MEDICOM MEDICAL PUBLISHERS

Editor Prof. Dennis McGonagle, University of Leeds, UK

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Letter from the Editor

Prof. Dennis McGonagle

Dear Reader,

The EULAR meeting in Amsterdam in June 2018 brought together over 14,000 medical doctors, allied healthcare professionals, and scientists. The transformative effect of the introduction of biological therapies and their positive long-term, and still emerging, legacy is being increasingly appreciated. Robust evidence showed that rheumatologists "doing their thing" and treating rheumatoid arthritis effectively and early, has benefits beyond the joint, namely the significant long-term reduction of cardiovascular complications. The normalisation of mortality in relationship to the general population raises important issues as to whether rheumatologists need heightened vigilance for cardiovascular complications, especially in well-treated patients.

Drug cost rationalisation with the introduction of biosimilars and both conventional and biological DMARD tapering strategies are ongoing areas of research in RA. The latest evidence supporting the safety of biosimilars is reviewed and studies comparing either conventional or biological DMARD tapering in RA subjects indicated that in the region of 40% of cases relapse at 1 year irrespective of which class of drug was stopped first. It remains to be determined whether longer term tapering strategies will lead to "seesaw" disease control in the face of lower drug costs. Despite the great therapeutic successes in RA, the clinical reality is that many patients remain difficult to treat; a debilitating and heart sink scenario for the patient and doctor. A large international survey addressed this issue and defined fatigue, 2 or more DMARD failures, and moderate corticosteroid dose usage as parameters that experts view as defining this situation. This will certainly be a space to watch in the coming years, especially when these parameters are stacked against hard objective evidence of ongoing inflammation including swollen joint counts and laboratory or imaging evidence of active inflammation.

A link between obesity and psoriatic arthritis is well defined and while recent RA studies are less clear they suggest a link with antibody negative disease; possibly pointing towards mechanistic overlaps with PsA in this RA subgroup. Therapeutic refinements in RA included data on the introduction of only the second anti-IL-6R monoclonal therapy to practice, the demonstration of anti-TNF drug levels and infection risk and the reassuring long-term safety of anti-TNF agents. In spondyloarthritis, emergent evidence suggests that vedolizumab, an integrin blocker with efficacy in IBD, may be ineffective in those cases with concomitant arthritis and even associated with new onset arthritis. These observations were made in cases that generally had previously failed an anti-TNF for IBD. It is interesting to note that this is the diametric opposite of etanercept and anti-IL-17A therapies that are effective for arthritis but not for IBD. Data presented at EULAR also had the pendulum swinging in favour of anti-TNF plus celecoxib in being more effective in preventing new

bone formation in cases of ankylosing spondylitis. On the same topic of bone biology, low bone mineral density as a potential detrimental factor in early SpA was also highlighted. Specifically, in the case of psoriatic arthritis, long-term extension from phase 3 clinical trials showed the continuing benefit of PDE4 inhibition. The generally beneficial effect of the licenced PsA agents on HAQ-DI was also reported, with this particular parameter being considered important on the patient's quality of life.

For those rheumatologists with a particular interest of focus on osteoporosis and osteoarthritis, several interesting areas were covered. One study looked at factors including vitamin D insufficiency and low bone mineral density in axial SpA. Experimental models also showed the role for microRNAs in osteoporosis, which could be potentially exploitable therapeutically in the future. Outcome measures for therapy optimisation are lacking in osteoarthritis. We cover interesting animal model and human data showing how glucosepane, an advanced glycation end-product, may have a role in osteoarthritis monitoring.

In the case of the autoimmune connective tissues diseases, new classification criteria were revealed for SLE. Early evidence for response to baricitinib in SLE was also provided and fits well with the role of the JAK/STAT pathway in regulating type 1 interferon cytokine pathways in disease. Another study showed that ustekinumab, an IL-12/23 blocker, also showed promise in SLE. IL-12 regulates gamma interferon, which was considered a less important interferon family member in SLE, and recent murine studies have also incriminated IL-23 in disease. The phase 3 trial programmes with their bumpy SLE outcome measures awaits these agents. Emergent strategies for the treatment of systemic sclerosis was also discussed, including the repurposing of anti-fibrotic therapies from the idiopathic pulmonary fibrosis arena and also the use of rituximab, a drug with an impressive record in most autoantibody associated diseases with the possible exception of Sjögren's syndrome.

I sincerely hope that this brief distillate of the foregoing commentaries in recent developments in rheumatology highlights from EULAR will whet your appetite for a very enjoyable read. We hope that this document will keep your curiosity for the rheumatic diseases alive and well until we see you in the bustling educational environment of EULAR in Madrid in 2019 for the next instalment.

Best regards,
Prof. Dennis McGonagle

Biography

Dennis McGonagle, FRCPI, PhD, is an Academic Rheumatologist at the University of Leeds and section head of Experimental Rheumatology. He graduated in Medicine from the University College Dublin in 1990 and undertook postgraduate training in Dublin and Leeds where he completed his PhD. He has developed the modern enthesitis model for spondyloarthropathies and psoriatic arthritis including the cytokine mediated enthesis originating theory of disease (Lancet 1998). He also described the synovio-entheseal complex, nail anchorage to the skeleton, developed an integrated biomechanical and immunology model for PsA, and a mechanistic disease classification of immune diseases (PLoS Med 2006). His group also discovered synovial fluid mesenchymal stem cells, which is being researched towards osteoarthritis therapy development. Prof. McGonagle has also served on the EULAR scientific committee and is a member of the Editorial Board of ARD.

Rheumatoid Arthritis

More than 20 years of follow-up showed that early rheumatoid arthritis (RA) treatment seems to normalise mortality rates; thus, emphasising the benefits of this strategy. Further evidence presented at EULAR 2018 also shows that switching to biological disease-modifying antirheumatic drugs (bDMARDs) is safe as well as efficacious and that there are no significant differences between tapering tumour necrosis factor (TNF) blockers vs conventional synthetic (cs) DMARDs. Difficult-to-treat RA has recently been characterised in a survey, creating an opportunity to develop more specific recommendations for this more refractory population. Also, the clinical effectiveness of sarilumab in RA patients regardless of primary or secondary TNF failure has been demonstrated. With regard to safety, the long-term safety profile of adalimumab across indications has been confirmed, and other research showed that patients with high biologic drug levels run a higher risk of infection.

Early, intensive rheumatoid arthritis treatment seems to normalise mortality rates

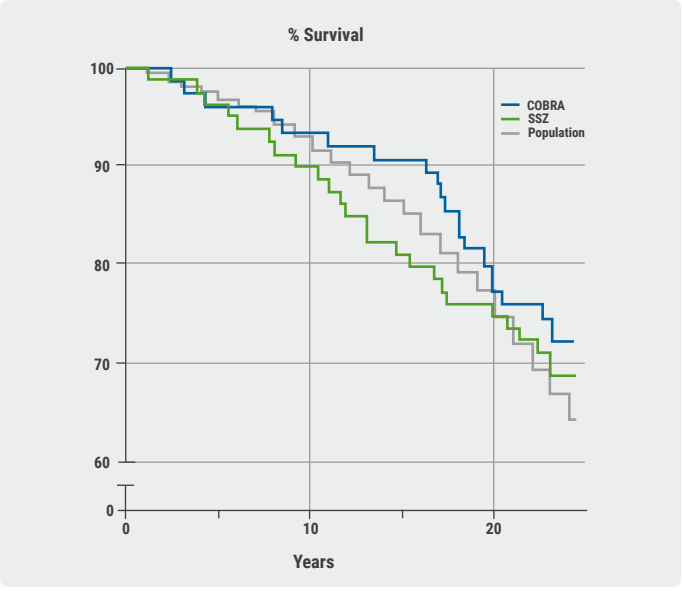
Data from the Dutch COBRA study show that RA mortality is normalised when compared to the general population after 23 years of follow-up. These findings confirm that early, intensive treatment of rheumatoid arthritis (RA) – which may include the use of glucocorticoids – offers long-term benefits and strongly suggests these benefits include reduced mortality towards controls. Mortality in patients with RA is known to be higher than what has been observed in the general population [1-3]. The adverse effects of the disease also take some time to show; they become apparent after more than a decade. Yet, it was unknown whether early, intensive treatment improved mortality rates. Research from the *COmbinatietherapie Bij Rheumatoïde Artritis* (COBRA) trial, a prospective cohort study of early RA, showed that early RA treatment provides long-term effectiveness without causing undue harm [4].

Patients with early RA (median disease duration 4 months) were treated with sulphalasazine monotherapy (n=79) or a combination of sulphalasazine, low-dose methotrexate, and initially high, step-down prednisolone (COBRA, n=76). In 2010, after 11 years of follow-up, the COBRA follow-up study showed numerically reduced mortality and a similar prevalence of comorbidity in patients with COBRA treatment compared to patients with initial sulphasalazine monotherapy. Also, lower progression of joint damage suggested long-term disease modification [5].

In the current analysis presented at EULAR 2018, researchers examined mortality in the COBRA trial cohort after 23 years. They compared this mortality to that of the general population in the Netherlands by using a reference sample of the general population matched for age and gender (data from Statistics Netherlands). The standardised mortality ratio (SMR) was used to compare the trial groups and the general population. Data for almost all COBRA patients (154/155) was available. The mean duration of follow-up in this cohort was 23 years (in patients alive, with a range between 22-24 years). In total, 44 (28%) of all patients had died (SMR = 0.80; 95% CI 0.59-1.06). This number consists of 20/75 of COBRA patients (27%; SMR = 0.75; 95% CI 0.47-1.14) and 24/79 of patients who used sulphasalazine (30%; SMR 0.85; 95% CI 0.56-1.25). This difference in mortality was not significant (P=0.61). Data from the reference sample of the general population (n=154) showed that 36% had died. The positive trend for combined treatment over sulphalasazine decreased over time (Figure 1) [1].

These results confirm long-term benefits of early, intensive treatment of RA that includes the use of glucocorticoids. Furthermore, this study is one of the first to show a normalisation of RA mortality compared to the general population after 23 years of follow-up [1].

Figure 1 Survival trend over time [1]



Switching to biosimilar bDMARDs is safe and efficacious

The use of biosimilars has truly taken off in the past few years and is expected to increase further. Results have shown that switching to biosimilar CT-P13 is not inferior to continued treatment with originator infliximab. These findings add to the increasing real-world evidence that switching from originator to biosimilar biological disease-modifying antirheumatic drugs (bDMARDs) is safe and efficacious.

Regulatory agencies in Europe and the United States have set up strict guidelines for the approval of biosimilars, which include extensive pre-clinical examinations. These guidelines also permit abbreviated clinical development paths for biosimilars than for an originator product. In general, biosimilars will be considered on the same level as originator products when treatments are started or changed for medical reasons by most rheumatologists. On the contrary, replacing an originator product by a biosimilar is carried out on non-medical grounds for (substantial) cost-savings only.

There is evidence from various studies on switching, most notably from the NOR-SWITCH trial. This randomised, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up was exclusively funded by the Norwegian government. It included 482 patients on stable treatment with the reference product infliximab across six different indications. In the full analysis set, 32% of patients had Crohn's disease (CD), 19% had ulcerative colitis (UC), 19% had spondyloarthritis (SpA), 16% had RA, 6% had psoriatic arthritis (PsA), and 7% had chronic plaque psoriasis (Ps). Patients were randomised to continued treatment with the reference product (n=241) or switch to CT-P13 (n=241) in which the dosing regimen was unchanged. Primary endpoint was occurrence of disease worsening, defined by the disease-specific composite measures, or clinically significant worsening leading to a major change in treatment.

Disease worsening occurred in 26% patients in the infliximab originator group and in 30% of patients in the CT-P13 group (per-protocol set; adjusted treatment difference -4.4%, 95% CI -12.7-3.9). The frequency of adverse events (AEs) was similar between groups, including serious AEs (10% for infliximab originator vs 9% for CT-P13). No differences were observed between the two groups in secondary endpoints, which included time to study drug discontinuation, remission rates, C-reactive protein levels, anti-drug antibody formation and drug trough levels. Thus, the NOR-SWITCH study demonstrated that switching to CT-P13 was not inferior to continued treatment with originator infliximab. These results support switching from originator product to CT-P13 for non-medical reasons [6]. Whereas the extension study has not yet been published, the results presented by Prof. Kvien (University of Oslo and Diakonhjemmet Hospital, Norway) confirm those from the main trial [7].

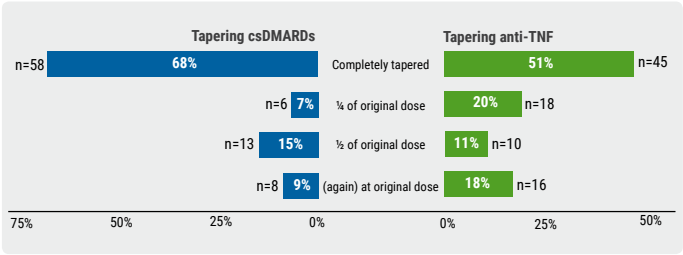
No significant differences when tapering TNF blockers versus csDMARDs

Tapering conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or anti-tumour necrosis factor (TNF) showed no significant differences in flare ratios, disease activity, functional ability, and quality of life (QoL) between both tapering strategies during the first 12 months of follow-up. Early detection of RA, early initiation of 'intensive' therapy, and a treat-to-target (T2T) approach have led to substantial improvements in clinical and radiographic outcomes in RA over the last two decades. This has resulted in 50% to 60% of early RA patients achieving sustained remission during the first year of follow-up. Although current guidelines recommend to consider tapering treatment, an optimal approach to gradually de-escalate csDMARDs or bDMARDs is still lacking substantial evidence.

Van Mulligen et al. aimed to evaluate the effectiveness of two tapering strategies: gradual tapering of csDMARDs and TNF therapy during one year of follow-up [8]. This study was set up as a multicentre, single-blinded, randomised, controlled trial. Eligible patients were adults with RA <10 years (2010 criteria) who were in sustained remission for at least 3 consecutive months (defined as a disease activity score (DAS) ≤2.4 and a swollen joint count (SJC) ≤1), which was achieved with csDMARDs plus a TNF blocker combination therapy. Patients were randomised into gradual tapering csDMARDs followed by the TNF blocker or vice versa. Medication was tapered in three steps over the course of 6 months. Gradual tapering was done by cutting the dosage into half, a quarter, and thereafter it was stopped. The primary outcome for the clinical effectiveness was disease flare defined as DAS44 >2.4 and/or SJC >1. Secondary outcomes were QoL and functional ability.

A total of 189 patients were randomly assigned to tapering csDMARDs (n=94) or tapering anti-TNF agents (n=95). The majority of patients were female (71% in the csDMARDs tapering group, and 61% in the anti-TNF tapering group) with mean age of approximately 56 years. No significant difference in flare ratio was found; the cumulative flare ratio in the csDMARD and anti-TNF tapering group was 35% and 45%, respectively, with the biggest difference in increased cumulative flair ratio between the groups in the last 3 months. A longer extension study is needed to see if these results are sustainable in the long term, as everyone might eventually flare. The tapering status at 12 months revealed that 68% of those tapering csDMARDs had completely

Figure 2 Tapering status at 12 months [8]



withdrawn their medication vs 51% for those tapering anti-TNF. Seven percent of patients tapering csDMARDs were at a quarter of the original dose (vs 20%), and 15% were at half of the original dose (vs 11%). Finally, 9% of csDMARDs tapering patients were (again) at the original dose vs 18% of those on anti-TNF (Figure 2).

Furthermore, no difference in DAS was observed between groups, or in patient-reported outcomes (PROs). Based on these outcomes, Dr Van Mulligen (Erasmus MC, the Netherlands) pleaded to taper medication in RA patients who are in sustained remission with a preference to taper anti-TNF over cSDMARDs, but also taking into account the risk of a disease flare and considering the wishes of the patient with regard to therapy [8].

Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey

Although the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommendations on RA predominantly focus on early phases of the disease and on pharmacological management, a sizeable portion of patients can be characterised as difficult-to-treat (estimated prevalence around 5-20%). In order to develop adequate guidelines and recommendations for this population, a difficult-to-treat RA classification needs to be defined.

Roodenrijs et al. set out to define characteristics of difficult-to-treat RA patients via an online survey among rheumatologists [9]. This questionnaire consisted of 9 questions regarding the background of the respondents, aspects to be included in the definition of difficult-to-treat RA, and missing items on its comprehensive management in the current EULAR management recommendations. Respondents answered questions on the necessity of incorporating the following items into the definition: disease activity level (e.g. the DAS assessing 28 joints [DAS28-ESR]), presence of fatigue, number of DMARDs that failed, and the inability to reduce oral glucocorticoid treatment. Optional open questions were used to identify additional features for the definition of difficult-to-treat RA and to collect items on its comprehensive management not covered by the current EULAR recommendations. A total of 390 rheumatologists from 31 countries, including a small number who were in training, completed the survey between July and December 2017. Half of respondents would include signs that are suggestive of active disease or a DAS28-ESR score >3.2 in the definition. Furthermore, 41% added fatigue. The most selected option for the number and category of DMARDs that had to have been used to be included in the definition was 1) failure to ≥2 conventional synthetic DMARDs, and 2) ≥2 bDMARDs or targeted sDMARDs with different mechanisms of action. Furthermore, 89% of respondents suggested including inability to taper oral glucocorticoids below 5 or 10 mg. The main finding of this survey was that difficult-to-treat RA is seen as a heterogeneous condition. This means that next to signs of active disease, failure to DMARDs and inability to taper glucocorticoids may be included in the definition. Researchers also noted that the large number of respondents, as well as responses with regard to items not covered by the current EULAR RA management recommendations, underscore the need for recommendations on comprehensive management of difficult-to-treat RA.

Link between obesity and rheumatoid arthritis not clear yet

A longstanding issue in risk assessment of RA is the role of obesity. Especially over the last decades, which have seen an increase in the prevalence of obesity worldwide, this question has become increasingly relevant. This is even more surprising as there could well be a link between obesity and RA, as adipose tissue harbours biologic mechanisms of inflammation which in its turn may be linked to chronic systemic inflammation. It has been shown that circulating adiponectin (a protein produced largely by adipocytes) levels are generally higher in RA patients than in the general population. It is also known that adiponectin levels drop as the weight of a subject increases, whilst they increase as a subject loses weight. There also seems to be an association between adipokines and cytokines (which are targeted in RA).

While there are several studies which have examined the potential influence of obesity on the development of RA, the results have been inconsistent. For instance, a review by Qin et al. showed that increased body mass index (BMI) can contribute to a higher risk for RA, but a Swedish study by Turesson et al. showed that there was not really such risk in obese subjects. In fact, the opposite was the case, where obesity may even have some protective effect [10,11].

Other studies, such as individual Nurses' Health Study, the Iowa Women's Health Study, and the British UK General Practice Research Database have found no or only modest association between obesity and the risk of RA. Two more studies showed that obesity was related to ACPA-negative RA with an inverse association between BMI and ACPA-positive RA for male subjects. Furthermore, abdominal obesity and BMI based obesity may carry different risks for RA. It can also be argued that RA associates with altered body composition and that the WHO definition of overweightness (BMI 25 - <30 kg/m2) and obesity (BMI ≥30 kg/m2) may not be adequate for RA patients. Specific attention may be needed for fat distribution in the body. Also, the role of adipokines in RA should be investigated further, as there is an association between obesity and chronic inflammation. Obese subjects also have higher levels of oestrogens and androgens; as sex hormones play a role in RA development and could be modified by obesity, this warrants further study as well.

In conclusion, there seems to be a slightly higher risk of RA in overweight and obese subjects, probably more pronounced in those who have seronegative RA. Inconsistent results have been seen for the contribution of gender and ACPA status on the background of a modest overall risk of RA in obesity. The reported negative association between ACPA+ RA status and obesity is intriguing. The evidence so far generates more questions than it answers, which prompts for ongoing research [12].

The association of biologic drug levels with infection risk

With the availability of TNF drugs, higher doses of anti-TNF agents have been reported to be associated with an increased serious infection risk [13]. Yet, no registries have systematically evaluated the effect of drug levels on infection risk. Jani et al. assessed the effect of biologic drug levels in RA patients on all infections and serious infections, defined as infections that require hospitalisation, intravenous antibiotics, or which lead to death [14].

A total of 703 patients recruited for the British Society for Rheumatology Biologics Register-RA (safety data) and the Biologics in RA Genetics & Genomics Syndicate (serological samples) were included. The cohort included 286 patients using etanercept, 179 adalimumab, 120 certolizumab, 104 tocilizumab, and 14 infliximab. The majority (74%) were women, the mean age was 58 years, and 89% was on a first biologic. Biologic drug levels were measured at 3, 6, and 12 months after biologic initiation and stratified as low/normal or high drug levels, as per thresholds defined using concentration-effect curves for each drug. The crude rate/1000 patient-years was 314 and 464 for all infections, and 54 and 76 for serious infections in the low/normal and high drug level groups, respectively. The adjusted hazard ratio for all infections within the first year differed significantly between the two groups; the high drug level group had a 50% higher risk of all infections (HR: 1.51; 95% CI 1.14, 2.01) [14].The most common types of all infections in the high drug level group were lower (34%) and upper (16%) respiratory tract infections, urinary tract infections (15%), and skin infections including shingles (8%). It was concluded that RA patients with high biologic drug levels have a higher risk of infection and that monitoring drug levels may be helpful in prediction of infection. For patients with high drug levels in disease remission, biologic dose tapering may lower infection risk [14].

Clinical effectiveness of sarilumab in rheumatoid arthritis patients with TNFi failure

Sarilumab, a human monoclonal antibody, binds membrane and soluble interleukin (IL)-6 and was recently approved for the treatment of moderate-to-severe RA. The TARGET (NCT10709758) trial showed that sarilumab 150 mg and 200 mg q2w plus cDMARDs was clinically efficacious in RA patients with an inadequate response or intolerance to TNF inhibitors (TNFi).15 In a post-hoc analysis of this trial, researchers assessed whether improvements in PROs differ between patients with primary or secondary TNFi failures prior to sarilumab treatment. Efficacy results of sarilumab after 24 weeks of treatment are outlined in Table 1.

In the TARGET study, 92.3% of patients failed prior TNFi, of which 38.6% had primary TNFi failure, and 53.7% had secondary TNFi failure. At week 24, numerical improvements were reported in all PROs for both the 150 and 200 mg sarilumab groups. Changes in all PROs were numerically similar in the primary and secondary TNFi failure patients with sarilumab 200 mg vs placebo at week 24. Furthermore, treatment-by-subgroup interaction testing did not show a statistically significant interaction of TNFi failure status and PRO outcome (all interaction P>0.05). Treatment-emergent AEs occurred in 59.7% of 150 mg sarilumab, 65.6% of 200 mg sarilumab, and 45.3% of placebo patients in the primary failure group. In the secondary failure group this was 73.6% of 150 mg sarilumab, 63.1% of 200 mg sarilumab, and 52.5% of placebo patients. Safety data were consistent with IL-6 receptor blockade with tocilizumab and the previously reported safety profile of sarilumab. Thus, sarilumab 150 mg and 200 mg q2w are clinically effective in treating TNFi failure in RA patients. Both led to improvements in PROs and changes in these PROs were similar regardless of whether patients had experienced primary or secondary TNFi failure [15].

Table 1 Least square mean changes at week 24 in PROs with sarilumab and placebo following TNFi failure [15]

PRO	1º failure		2º failure		Interaction P-value*
	Placebo (n=75)	Sarilumab 200 mg (n=64)	Placebo (n=99)	Sarilumab 200 mg (n=103)	
Patient global assessement	-22.56 (3.35)	-26.62 (3.43)	-18.91 (2.93)	-32.07 (2.67)	0.2943
Pain VAS	-21.25 (3.56)	-31.81 (3.57)	-21.90 (3.01)	-33.04 (2.70)	0.8399
HAQ-DI	-0.39 (0.08)	-0.52 (0.08)	-0.30 (3.07)	-0.59 (0.06)	0.1672
SF-36 PCS	4.03 (1.01)	8.78 (1.01)	4.61 (0.99)	7.95 (0.90)	0.7237
SF-36 MCS	4.78 (1.41)	5.28 (1.42)	4.84 (1.21)	6.81 (1.10)	0.8526
Physical functioning	5.98 (2.96)	18.05 (3.00)	10.40 (2.79)	14.77 (2.53)	0.2955
Role-physical	9.19 (3.03)	17.97 (3.00)	11.75 (2.76)	20.01 (2.49)	0.9874
Bodily pain	14.51 (2.99)	25.35 (2.93)	18.32 (2.63)	28.02 (2.36)	0.8947
General health	10.10 (2.29)	18.20 (2.26)	7.00 (2.17)	12.79 (1.96)	0.8196
Vitality	9.19 (2.58)	14.55 (2.58)	9.05 (2.30)	15.47 (2.12)	0.9265
Social functioning	12.93 (3.23)	17.09 (3.22)	12.76 (2.84)	18.86 (2.55)	0.8477
Role emotional	10.46 (3.34)	12.89 (3.29)	10.19 (3.04)	15.55 (2.72)	0.6854
Mental health	6.09 (2.49)	12.17 (2.49)	9.90 (2.13)	11.97 (1.93)	0.5772
FACIT-fatigue	7.19 (1.38)	7.32 (1.37)	6.50 (1.14)	10.95 (1.04)	0.1630
Morning stiffness VAS	-21.83 (3.58)	-32.11 (3.63)	-22.27 (3.28)	-35.22 (2.93)	0.8177
EQ-5D VAS	13.72 (3.32)	18.83 (3.28)	16.51 (2.83)	16.74 (2.45)	0.5919
EQ-5D single index utility	0.16 (0.04)	0.31 (0.04)	0.22 (0.03)	0.35 (0.03)	0.7003
RAID	-1.74 (0.31)	-2.49 (0.32)	-1.94 (0.28)	-2.81 (0.25)	0.9620

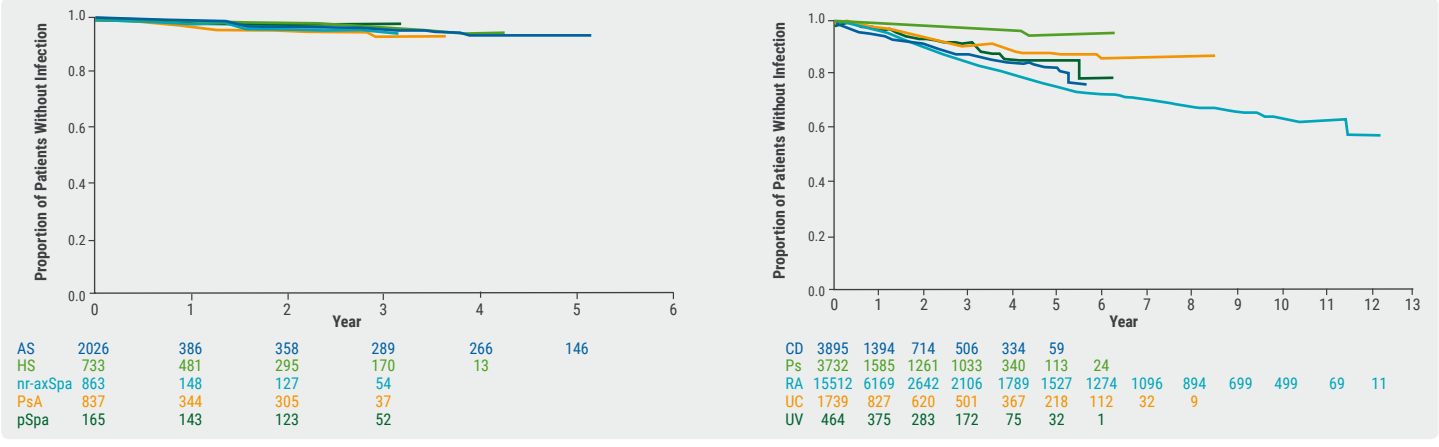
EQ-5D, EuroQol; FACIT, Functional Assessement of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire Disability Index; MCS, Mental Component Score; PCS, Physical Component Score; RAID, Rheumatoid Arthritis Impact of Disease; SF-36, short form 36; VAS, Visual Analog Scale

Confirmation of long-term safety profile adalimumab across indications

A recent analysis of data from 78 clinical trials of adalimumab, including 29,987 patients, demonstrated an overall safety profile consistent with previous findings and with the TNFi class in general. No new safety signals or tolerability issues with adalimumab treatment were identified and, for most indications, the mortality rate was below what would be expected in an age-adjusted and sex-adjusted population.

According to Prof. Gerd Burmester (Charité University Hospital, Free University and Humboldt University of Berlin, Germany), aspects of efficacy of adalimumab are well known, but patients now want to be informed about the safety of the treatment, especially as it often involves long-term use. Adalimumab's long-term safety was previously reported in 23,458 patients representing up to 12 years of clinical trial exposure in RA, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), PsA, Ps, and CD. Mortality rates of patients under adalimumab were not increased compared with rates expected for the general population [16]. Infections represented the most frequently reported serious AEs across these indications. Burmester et al. reported an updated analysis examining the long-term safety of adalimumab in adult patients with RA, AS, non-radiographic axial SpA (nr-axSpA), peripheral SpA (pSpA), PsA, Ps, hidradenitis suppurativa (HS), CD, UC, and non-infectious uveitis (UV). Safety assessments included all (serious) AEs that occurred after the first adalimumab dose and up to 70 days after the last study dose. The majority of patients who were exposed to adalimumab were those in RA studies (n=15,512). The most frequently reported serious AE of interest was infection with the highest incidences in CD, RA, UV, and UC. The most commonly reported serious infections were pneumonia (0.6/100 patient-years) and notably cellulitis (0.2/patient-years). The risk of a serious infection event was generally stable over time and for all indications (Figure 3) [17].

Figure 3 Time to first serious infection by indication [17]



The assessment of malignancies showed that the overall rate of serious malignancies, excluding lymphoma, hepatosplenic T-cell lymphoma, leukaemia, non-melanoma skin cancer (NMSC), and melanoma was 0.6/100 patient-years. The highest rates of malignancies were seen among RA, UV, and UC studies suggesting the role of the underlying disease. For NMSC, the overall rate was 0.1/100 patient-years. The time to first malignancy, with the exclusion of the aforementioned exceptions, did not show any marked difference between indications. From the assessment of standardised mortality rates emerged that overall and for most of the adalimumab populations (i.e. AS, PsA, Ps, UC, CD, and RA), the observed number of deaths was below what would be expected in an age-adjusted and sex-adjusted population. For HS, nr-axSpA, pSpA, and UV studies, the small size of these trials precluded accurate assessment of the SMR, and the 95% CIs all included 1.0. Prof. Burmester concluded that the efficacy and safety data continue to support the well-established benefits of adalimumab for the approved indications [17].

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Ankylosing Spondylitis

Assessment of the clinical effect of vedolizumab on articular manifestations in patients with inflammatory bowel disease-associated spondyloarthritis brought to light that vedolizumab does not seem to show any efficacy in these patients. In fact, it might even induce exacerbation or new onset of spondyloarthritis. Other research presented at EULAR 2018 showed that combining nonsteroidal anti-inflammatory drugs (NSAIDs) plus TNFi has a synergistic effect in slowing radiographic progression in AS patients. The incidence of low bone mineral density – an often underdiagnosed and neglected aspect of axSpA, which is still a male-dominated disease, calls for more awareness among physicians to prevent fracture and comorbidities among patients.

Clinical effect of vedolizumab on articular manifestations spondyloarthritis associated with IBD

Paccou et al. evaluated baseline characteristics of CD and UC patients treated with vedolizumab, as well as assessing the effect of vedolizumab on joint manifestations in patients with inflammatory bowel disease (IBD)-associated SpA, and new onset of SpA under vedolizumab. This study was performed as a single-centre, retrospective, and observational study, conducted between July 2014 and July 2017. It involved reviewing the charts of all patients with IBD who had undergone treatment with vedolizumab for more than 3 months. A total of 171 patients diagnosed with IBD were treated with vedolizumab. It needs to be noted that 97.1% of patients had been previously treated with at least one TNFi. All patients included in this study completed the induction phase at last observation; the mean follow-up of the entire cohort was 14.3 months. Of the patient population, 8.2% (14 patients) had a history of IBD-associated SpA (according to ASAS criteria) at the time of initiation of vedolizumab. 5.8% (10 patients) were in clinical remission regarding SpA, while 2.4% (4 patients) had active SpA when they initiated vedolizumab. First, no clinical benefit on SpA following initiation of vedolizumab was found in those 4 patients with active SpA. Second, exacerbation of SpA in patients with clinical remission at initiation of vedolizumab was found in 6/10 patients whereas no effect was reported in the remaining 4/10 patients. All 14 patients with IBD-associated SpA were under TNFi just before starting vedolizumab. Finally, new onset of SpA induced by vedolizumab was reported in 1 patient (Table 2) [1].

Table 2 Characteristics of patients and the main results [1]

Variable	n=171
Age (years), mean ±SD	37.8 ±12.9
Female gender, n (%)	110 (64.3)
Body mass index (kg/m²), mean ±SD	23.7 (4.8)
Type of disease, n (%) • Crohn's disease (CD) • Ulcerative colitis (UC)	 104 (60.8) 67 (39.2)
Duration of disease (years), mean ±SD	10.5 (7.6)
Duration of follow-up under vedolizumab (months), mean ±SD	14.3 (12.0)
IBD-associated SpA, n (%) • No history • History (inactive at initiation of vedolizumab) • Active at initiation of vedolizumab	 157 (91.8) 10 (5.8) 4 (2.4)
Clinical benefit on SpA following initiation of vedolizumab (n=4) • No clinical benefit • Improvement	 4/4 (100) 0/4 (0)
Exacerbation of SpA in patients with clinical remission at initiation of vedolizumab (n=10) • Yes • No	 6 (60) 4 (40)
New onset of SpA induced by vedolizumab	1 (<1)

Dr Paccou (Amiens University Medical Center, France) concluded that this study of vedolizumab does not support its efficacy in patients with IBD-associated SpA. It might even induce exacerbation or new onset of SpA. However, inception cohort studies are needed to prospectively evaluate the effect of vedolizumab on joint manifestations.1 Overall, this study provides good translational therapeutic data supporting the concept that the pathomechanisms of joint manifestations in SpA and IBD differ, at least in a proportion of subjects.

Synergistic effect NSAIDs plus TNFi in slowing radiographic progression in ankylosing spondylitis patients

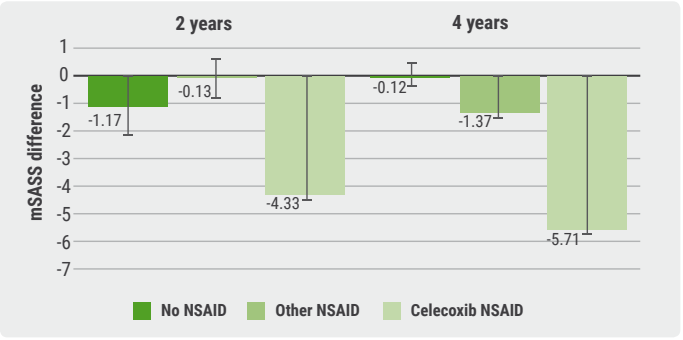
Dose-related use of NSAIDs together with TNFi in AS patients has a synergistic effect in slowing radiographic progression. The greatest effect is seen in those using both high-dose NSAIDs and TNFi. Of all NSAIDs, celecoxib appears to confer the greatest benefit in decreasing progression with effect at both 2 and 4 years. According to Dr Gensler (University of California San Francisco Medical Center, US), the potential of TNFi and/or NSAIDs to reduce radiographic progression in AS was uncertain.

Until now, causal effects of both exposures on radiographic progression have not been convincingly demonstrated. In addition, no study has evaluated whether effects are comparable among different NSAIDs in this setting. Therefore, Gensler et al. explored the causal effects of TNFi on radiographic progression in AS and determined whether the NSAID dose and type impact this relationship. A total of 519 adult patients from the Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) cohort who met the modified New York criteria were included with at least 4 years of clinical and radiographic follow-up. Clinical and medication data were collected every 6 months and radiographs were performed at baseline and every 2 years. Longitudinal targeted maximum likelihood estimation was used to estimate the causal effect of TNFi and NSAIDs (using the NSAID index) on radiographic progression as measured by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at 2 and 4 years, accounting for time-varying covariates. The researchers adjusted for sex, race/ethnicity, education, disease duration, enrolment year, number of years on TNFi, disease duration at time of TNFi start, NSAID use, TNFi use, days since last mSASSS measurement, Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP), smoking status, and missed visit status. The majority of patients was male (75%) and Caucasian (81%); the baseline mean age was 41.4 years and symptom duration was 16.8 years. Baseline mean mSASSS was 14.2. At baseline, 70% of patients used NSAIDs, TNFi were used by 46% of patients at baseline, and 15% used DMARDs. Patients using TNFi and high-dose NSAIDs showed less progression at 4 years, with the least progression observed at both 2 and 4 years in those using TNFi plus celecoxib (Figure 4) [2].

Celecoxib users had higher NSAID index in comparison to other NSAID users and after controlling for NSAID dosages, no change in mSASSS difference was seen. Dr Gensler added that it seemed that celecoxib use, and not the dose of celecoxib, confers benefit in the setting of TNFi.

It was concluded that in this study TNFi prevented radiographic progression in AS patients. This was especially evident when patients were also exposed to NSAIDs at a higher dose at 4 years and with a greater effect in the setting of celecoxib at 2 and 4 years. TNFi and NSAIDs may have a synergistic effect. However, Dr Gensler warned that despite the statistical approach taken in this trial, which addresses many of the biases in observational research, unmeasured confounders are still a possibility. It may be the case that

Figure 4 TNFi users on celecoxib have less mSASS progression at 2 and 4 years [2]



celecoxib users on TNFi rather have different patient characteristics, than there is a drug-specific effect of the combined use of celecoxib with TNFi [2].

Low bone mineral density is common in axial spondyloarthritis; more awareness required

Osteoporosis is typically related with inflammatory arthritis (IA). Although the impact of osteoporosis is well outlined in the general population and some IA, such as RA, it is often ignored in axSpA, which is a form of IA centred on sacroiliac joints and the spine. This can be explained by the fact that axSpA predominantly affects men, in whom osteoporosis is often not considered. As a result, osteoporosis prevalence figures are unclear, and a wide variation exists in the literature. Accurate epidemiology regarding bone mineral density (BMD) in axSpA is crucial to understanding the impact of low BMD in this cohort. Investigating the prevalence of low BMD in a well-characterised axSpA cohort and exploring relationships (e.g. demographic, disease-related, laboratory) between BMD and axSpA were therefore the objectives of a research by Fitzgerald et al [3].

A detailed assessment was performed on axSpA patients, including demographics, clinical characteristics, and laboratory investigations. A total of 104 patients with axSpA were consecutively recruited: 77.9% of them was male, 98.1% was Caucasian, the mean age was 51 years, and disease duration 26 years. The mean ASDAS-CRP was 2.3, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 3.9, Bath Ankylosing Spondylitis Metrology Index (BASMI) was 4.3, and Bath Ankylosing Spondylitis Functional Index (BASFI) was 3.8, reflecting mild to moderate disease burden. In 42.3% of subjects, a history of fracture was present, with only 3 fragility fractures reported. Osteopenia was observed in 42.3%, and 16.3% had osteoporosis. Low BMD was most prevalent at the spine, with 44% of the cohort affected followed by the femoral neck (30.1%). Low BMD at the radius was uncommon (seen in <10%). Only 6.4% of the cohort had a prior diagnosis of osteoporosis, and only 39.4% had a previous dual-energy X-ray absorptiometry. Three vertebral fractures were detected, and all patients were unaware of these fractures prior to the study. Factors that were significantly associated with bone loss at both the spine and the hip were female gender, higher BASFI, lower BMI, and lower urate levels. ASDAS-CRP and BASDAI had no impact on low BMD. Additionally, longer disease duration was associated with spine BMD loss. Non-obese patients were more likely to have low BMD at any site than obese patients (62.3% vs 40%, odds ratio 2.5, P=0.04). The use of biologics did not influence BMD. These findings led to the conclusion that low BMD is common in this axSpA cohort, with over 50% of patients affected. Most cases of low BMD were undiagnosed prior to this study and less than half of the cohort had ever had a dual-energy X-ray absorptiometry, which suggests a continued low awareness of the risk of osteoporosis in a still male-dominated disease [3].

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Psoriasis and Psoriatic Arthritis

Extensive data on apremilast was presented at EULAR 2018, focusing on long-term outcomes that demonstrated that this agent significantly improves PsA in patients who were treated over 5 years. Also, nearly all biological disease-modifying antirheumatic drugs (bDMARDs) – with the exception of ixekizumab every 4 weeks, golimumab, and apremilast – significantly improve Health Assessment Questionnaire Disability Index (HAQ-DI) scores from baseline vs placebo in PsA. Finally, the use of NSAIDs are prescribed to many patients with late onset PsA.

Apremilast significantly improves psoriatic arthritis in the long-term

Apremilast has demonstrated sustained and clinically meaningful improvements in signs and symptoms of PsA, as well as in physical function in patients who continued treatment over 5 years. Apremilast also demonstrated a favourable safety profile and was generally well tolerated at 5 years.

Apremilast is an oral phosphodiesterase 4 inhibitor that inhibits the PDE4 intracellular pathway of inflammatory mediators associated with the pathogenesis of PsA [1].

Long-term efficacy and safety of treatment with apremilast were evaluated for up to 5 years in patients with active PsA by using data from the phase 3 PALACE 1, 2, and 3 studies. Eligible patients had active PsA (duration >6 months, meeting CASPAR criteria, ≥3 SJC, and ≥3 TJC) despite prior conventional treatment with DMARDs and/or biologics. A total of 1,493 patients were randomised at baseline (1:1:1) to receive placebo, 30 mg apremilast BID, or 20 mg apremilast BID. Placebo subjects were re-randomised 1:1 to 30 mg apremilast BID or 20 mg BID at week 16 or week 24. All randomised subjects received ≥1 dose of study medication (placebo: n=496; 30 mg apremilast: n=497; 20 mg apremilast: n=500). Of the patients randomised to 30 mg apremilast at baseline, 66.6% continued 30 mg apremilast BID treatment until week 260.

The results showed that at week 260, modified ACR20, ACR50, and ACR70 responses were achieved by 67.2%, 44.4%, and 27.4% of these patients, respectively. Mean percent changes were -82.3% for SJC and -72.7% for TJC. For patients who had enthesitis or dactylitis at baseline, the number of patients who achieved a Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) of 0 or a dactylitis count of 0 increased over 52 weeks. At week 260, 60.4% of patients achieved a Clinical Disease Activity in Psoriatic Arthritis (cDAPSA) score ≤13 with continued 30 mg apremilast BID treatment [2]. Furthermore, mean improvement in the HAQ-DI of -0.33 at week 52 was maintained through week 260 (-0.42) in patients who received continuous 30 mg apremilast BID. In patients with baseline psoriasis body surface area (BSA) involvement ≥3% mean improvement in the Psoriasis Area and Surface Severity Index (PASI) score at week 52 (-3.54) was maintained throughout week 260 (-4.63) with continued 30 mg apremilast BID. At week 260, 65.8% and 43.6% of patients who received 30 mg apremilast BID achieved a PASI-50 or a PASI-75 response. Notably, all efficacy results were similar for subjects receiving 20 mg apremilast BID. Finally, most adverse events were mild to moderate in severity over weeks 0 to ≤52, and no new safety concerns or increases were observed with longer-term (up to 260 weeks) exposure to apremilast. Adverse events, occurring in ≥5% of apremilast-exposed patients during week 0 to ≤52, were diarrhoea, nausea, headache, upper respiratory tract infection, and nasopharyngitis [3].

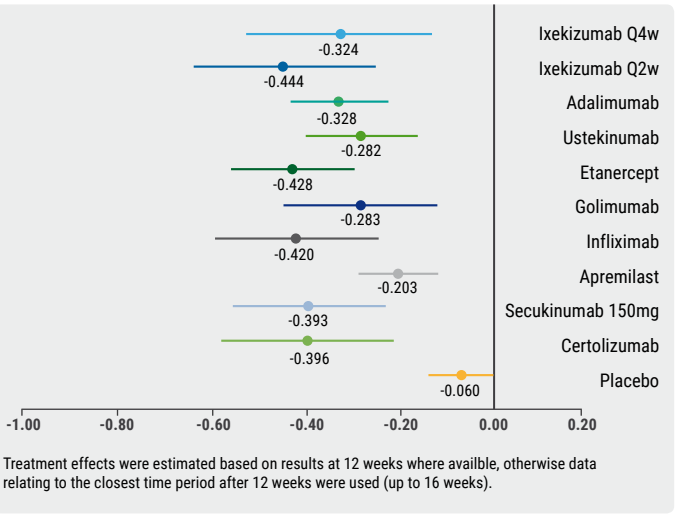
The role of bDMARDs in psoriatic arthritis

Infliximab, etanercept, adalimumab, ixekizumab every 2 weeks, ustekinumab, 150 mg secukinumab, and certolizumab pegol provided improvements in health assessment questionnaire-disability index (HAQ-DI) scores from baseline, which were significantly better than placebo in biologic-naïve patients with active PsA. Changes from baseline in HAQ-DI scores were more pronounced in Psoriatic Arthritis Response Criteria (PsARC) responders than in PsARC non-responders for each treatment.

Apart from a decreased quality of life, PsA is also characterised by a substantial economic burden [4,5]. Biologic treatments for PsA are increasingly scrutinised in health technology assessments, and the most commonly used economic model framework for assessing biologics in PsA is the York Assessment Group model developed as part of a National Institute for Health and Care Excellence (NICE) appraisal (the so-called 'York model') [6]. In this model, improvement in HAQ-DI reflects physical function, and is linked to initial treatment response measured by joint improvement assessed by PsARC.

Ruyssen-Witrand et al. assessed the effectiveness of bDMARDs on HAQ-DI among active biologic-naïve PsA patients through Bayesian network meta-analyses to understand the relationship between HAQ-DI and PsARC response. Data was identified through a systematic literature review and Bayesian network meta-analyses were conducted in line with NICE Guidelines to assess the mean HAQ-DI scores change from baseline for ixekizumab, adalimumab, ustekinumab, etanercept, golimumab, infliximab, apremilast, secukinumab, certolizumab pegol, and placebo in the biologic-naïve overall population, as well as in PsARC responders and non-responders [7]. Results were expressed as absolute mean change from baseline and associated standard deviations, and 95% CI. Treatment effects were estimated based on results at 12 weeks where available; otherwise data relating to the closest time period after 12 weeks were used (up to 16 weeks). A total of 14 randomised clinical studies were identified for inclusion in the analyses evaluating effects on HAQ-DI scores, which included ixekizumab every 2 weeks (n=1) and every 4 weeks (n=1), etanercept (n=1), infliximab (n=2), ustekinumab (n=1), golimumab (n=1), apremilast (n=3), secukinumab (n=1), and adalimumab (n=3). For apremilast, certolizumab pegol, and secukinumab, data were not available specifically from biologic-naïve and data were used from the full study population (i.e. biologic-naïve and biologic-experienced). It was shown that in the overall population, the improvement in HAQ-DI scores from baseline was greatest for ixekizumab every 2 weeks, etanercept, infliximab, certolizumab pegol, and secukinumab (Figure 5) [8].

Figure 5 Absolute HAQ-DI change from baseline to week 128



Treatment effects were estimated based on results at 12 weeks where availble, otherwise data relating to the closest time period after 12 weeks were used (up to 16 weeks).

Among PsARC responders, the greatest improvement from baseline in HAQ-DI scores was observed for infliximab, etanercept, secukinumab and ixekizumab [8].

NSAIDs widely used in first years in patients with late-onset psoriatic arthritis

Gili et al. initiated a prospective observational study which aimed to describe treatment prescribing patterns in PsA over the first 2 years of follow-up. They also evaluated if the treatment patterns in PsA are in any way conditioned by the age of onset of the disease. A total of 46 patients with at least 2 years of follow-up within the PsArT (Psoriatic arthritis Age-related Treatment patterns) study were included in the study. These were patients who were diagnosed with early (symptom duration <52 weeks) PsA. Twenty-four of them were female, mean age was 49 with range 16-90 years, and mean disease duration was 20 weeks (range 1-52). This group was divided into Adult-Onset (AOPsA) (age <60 years) and Late-Onset (LOPsA) (onset age ≥60 years) PsA according to the age at the onset of musculoskeletal manifestations. Data were collected at the time of enrollment (baseline), at 12 months, and at 24 months.

It was found that those patients who had LOPsA (n=15) when compared to AOPsA patients (n=31), had a significant shorter disease duration (17 vs 21 weeks, p<0.05) as well as showing more frequently increased levels of erythrocyte sedimentation rate (ESR; 75% vs 43%, p<0.05) and CRP (87% vs 52%, p <0.01). Moreover, LOPsA patients developed more frequently inflammatory extremity swelling with pitting oedema over the dorsum of hands and/or of feet (56% vs 13%, p<0.01). No other significant differences between both groups were seen.

For instance, sensitivity of the CASPAR criteria was similar in AOPsA (78%) and LOPsA (75%) patients.

With regard to medication used during the first year, 80.4% of patients received NSAIDs, 32.6% received oral corticosteroids, 13.0% received local corticosteroids, 19.5% received sDMARDs, and 6.5% received bDMARDs (infliximab, adalimumab, golimumab, and etanercept). For the second year, these percentages were 73.9%, 30.4%, 30.4%, 50%, and 15.2%, respectively. The only statistical significant difference between both groups was the rate of patients using NSAIDs in the LOPsA group during the first year (100% vs 70.9%, p=0.02). No other significant differences in drug intake, therapy changes, discontinuation, or add-on therapy according to the age of PsA onset were observed. It was concluded that during the two years of follow up period, NSAIDs were used in a large number of LOPsA patients during the first year. However, the researchers pointed out that this study had only a low number of patients, thus no robust conclusion could be drawn. New studies into this matter with larger numbers of patients would be very helpful to elucidate these findings further and to clarify if and what the influence is of the age of onset with regard to treatment patterns [9].

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Osteoporosis and Osteoarthritis

Patients with axSpA often suffer from osteoporosis and vertebral fractures; it has now been shown that these are both associated with disease activity, vitamin D insufficiency, and radiographic damage. Preclinical research showed that glucosepane which is very strongly increased in the severe form of osteoarthritis, is a potential biomarker for diagnosis and progression of osteoarthritis. Finally, more research found that the role of miRNA-146A is an important one in bone metabolism and osteoporosis, as it seems to control bone turnover and may be used as a therapeutic target in the treatment of osteoporosis.

Osteoporosis and vertebral fractures associated with disease activity/radiographic damage in axial spondyloarthritis

It is widely known that osteoporosis and vertebral fractures are common comorbidities of axSpA, as well as the fact that they have deleterious effects on patients' physical function. It was recently shown by Romera-Lopez et al. that in those patients, low femoral neck bone mineral density (BMD) is associated with disease activity and vitamin D insufficiency and vertebral fractures are associated with CRP and low hip bone mass density. This relationship between disease activity and radiographic damage and BMD, 25 (OH) vitamin D levels and vertebral fractures in patients with axSpA was evaluated in a cross-sectional study, involving 206 patients. The majority was male (144 men/62 women), and 86% had AS, 14% nr-axSpA, and associated peripheral involvement was seen in 42%. Mean age was 52 years and mean BASDAI was 3.6, mean ASDAS-CRP 2.2, mean ASDAS-ESR 2.5, mean CRP 4.97 mg/L, mean ESR 18 mm. With regard to physical function, mean BASFI was 3.3; radiographic progression: mean mSASSS total was 20.46, lumbar 10.41, and cervical 10.05. It emerged that 85.7% of patients had insufficient levels of 25 (OH) vitamin D (mean 19.83 ng/mL). Low lumbar spine BMD was seen in 25.7% (z-score) and 28.9% (t-score), and low femoral neck BMD occurred in 45.2% (z) and 28.9% (t) of the patients. The prevalence of osteoporosis in lumbar spine was 3.2% (z)/6.9% (t) and in femoral neck 9.1% (z)/13.4% (t). Morphometric vertebral fractures were identified in 34% of the patients. Bivariate analysis demonstrated that ESR, ASDAS-ESR, age, male sex, low 25 (OH) vitamin D levels, and the mSASSS were associated with low femoral neck BMD. Multivariate models confirmed the association between disease activity (assessed by ASDAS-ESR OR 3.32; 95% CI 2.35-4.55; p=0.016), 25(OH) vitamin D (OR 0.95; 95% CI 0.86-0.98; p=0.029) and low femoral neck BMD (z-score). An association was confirmed between CRP (OR 2.34; 95% CI 1.10-4.98; p=0.027), radiographic damage (lumbar mSASSS OR 1.06; 95% CI 1.03-1.10; p=0.001), high lumbar spine BMD (OR 296; 95% CI 5.07-12258; p=0.006), and low femoral neck BMD (OR 0.11; 95% CI 0.03-0.12; p=0.000) and the presence of vertebral fractures (Table 3)[1]. It should be noted that the association with high lumbar spine BMD might be related to the presence of radiographic damage, or to effects of new bone formation in the lumbar spine.

Table 3 Differences in parameters in axSpA patients with/without vertebral fractures [1]

	Patients without vertebral fractures	Patients with vertebral fractures	P-value
CRP (mg/L)	5.10±1.6	9.51±2.1	p=0.003
ESR (mm/h)	15.87±4.8	23.12±6.2	p=0.002
25 (OH) vitamin D (ng/mL)	20.80±4.6	18.04±3.7	p=0.049
Cervical mSASSS	8.02±2.5	13.11±4.8	p=0.002
Lumbar mSASSS	8.93±3.7	12.36±6.5	p=0.000
Total mSASSS	17.66±7.3	27.13±10.7	p=0.000
Lower spine BMD	1.090±0.09	1.191±0.13	p=0.002
Femoral neck BMD	0.912±0.11	0.773±0.18	p=0.000

Glucosepane is a new biomarker for the severity of osteoarthritis

Levels of amino acids and glycated, oxidised, or nitrated proteins in culture media of chondrocytes cultivated in multi-layers and in the blood of guinea pigs or osteoarthritis patients were studied by mass spectrometry. This study analysed 60 male, 3-week-old guinea pigs. At 4-weeks and subsequently 8-week intervals until week 36, 12 animals were sacrificed and evaluated for histological severity of knee osteoarthritis and cartilage vascularisation. Patients with early and advanced osteoarthritis and healthy subjects were recruited. Human chondrocytes cultured in multilayers were treated for 10 days with IL-1β. Amino acids and glycated, oxidised, and nitrated proteins were analysed in the serum of guinea pigs,

osteoarthritis patients and in the culture medium conditioned by chondrocytes by stable isotopic dilution analysis liquid chromatography-tandem mass spectrometry. The results showed that the severity of osteoarthritis increased progressively in guinea pigs with age. Glycated, oxidised, and nitrated amino acids were increased markedly at week 36. Glucosepane and dityrosine increased progressively from weeks 20 and 28, respectively. Glucosepane was correlated with the osteoarthritis histological severity ($r=0.58$, $p<0.0001$) and the Young's modulus ($r=0.52$-0.56, $p<0.0001$). Oxidation of free adducts was correlated with osteoarthritis severity ($p<0.0009$-0.0029) and hydroxyproline with cartilage thickness ($p<0.0003$-0.003). In the clinical study, plasma glucosepane was increased 38% in patients with early osteoarthritis ($p<0.05$) and 6-fold in patients with advanced osteoarthritis ($p<0.001$) compared to healthy subjects. IL-1β increased the release of glycated, oxidised, and nitrated products from chondrocytes *in vitro*. It was concluded that glycation, oxidation, and nitration of proteins are reactions related to the severity of osteoarthritis. The products of these reactions can be detected in blood by mass spectrometry and candidate as biomarkers of osteoarthritis. More specifically, glucosepane is an advanced glycation product strongly increased in the severe form of the disease and therefore considered as a potential biomarker for diagnosis and progression of osteoarthritis [2].

miRNA-146A plays key role in bone metabolism and osteoporosis

Micro RNAs (miRNAs) play a crucial role in various cellular functions of the human body. A good example of their importance is miR-146a, an important anti-inflammatory miRNA. This was found to negatively impact osteogenesis and bone regeneration *in vitro,* by controlling the differentiation of mesenchymal stem cells. The influence of miR-146a on bone stability as well as the development of osteoporosis and remodelling has not been fully delineated. Saferding et al. analysed the role of mIR-146a in bone metabolism by assessing systemic bone, tibiae, and femur of wildtype and miR-146a deficient mice (3 to 18 months of age) with histological and µCT analysis. Serum cytokine levels were analysed by ELISA, and miRNA expression levels in bone were analysed by qPCR. Ovariectomy induced bone loss was performed to induce osteoporosis. Significantly increased trabecular bone mass was seen in miR-146a deficient mice compared to wildtype animals, starting from 6 months of age, while cortical thickness of systemic bones was significantly reduced. Analysis of serum in aged miR-146a deficient animals showed elevated activity of bone-resorbing osteoclasts compared to wildtype animals. qPCR results showed elevated expression of signature molecules of osteoclasts as well as osteoblasts in aged miR-146a deficient mice, suggesting a regulatory role of miR-146a in both cell types. Histological analysis of long bones showed significant trabecular bone loss in ovariectomised wildtype mice. However, there was no trabecular bone loss in ovariectomised miR-146a deficient animals. It was concluded by the researchers that miR-146a controls bone turnover and miR-146a deficient mice build up bone over time. Furthermore, the loss of miR-146a protects bone loss induced by oestrogen deficiency, which suggests that miR-146a may be used as a potential therapeutic target in the treatment of osteoporosis [3].

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Systemic Sclerosis and Systemic Lupus Erythematosus

Various new therapy options are in development for systemic sclerosis (SSc), which may provide better outcomes for patients. One of these agents is rituximab; although further studies are needed to confirm the current findings. The same applies to baricitinib, which has been assessed as a potential therapy for systemic lupus erythematosus (SLE) patients and has an acceptable benefit/risk profile.

Novel systemic sclerosis drugs: an overview of what might be to come

A plethora of therapies have been tested in SSc, and many eventually failed. Currently, multiple therapies are being tested that modify the immune and vascular system as pathogenetic nodes underlying the pathogenesis of SSc. Among these is abatacept, targeting T-cell activation. Although the completed clinical trial data is still embargoed at the time of writing, there was a significant difference between placebo and abatacept in terms of percentage improvement in skin scores. Another new agent is belimumab, a B-cell inhibitor. Data show that it needs to be used very early on in the disease, but the results so far are encouraging. Lenabasum, an oral endocannabinoid-mimetic medicine designed to target chronic inflammation and fibrosis simultaneously, has been studied in a small study (n=25) vs placebo. Patients who had completed 52 weeks of lenabasum treatment in the extension trial showed an improvement by 56% on their ACR CRISS (American College of Rheumatology's diffuse cutaneous systemic sclerosis) score. Skin thickness improved by 8.6 points (measured by modified Rodnan Skin Score [mRSS]). Safety and tolerability has been considered to be acceptable with no severe or serious AEs [1]. A Phase 3 trial (RESOLVE-1) using lenabasum, is currently underway in Europe [2]. Pirfenidone, a small molecule inhibitor of several pathways, including transforming growth factor beta, fibroblast growth factor, and platelet-derived growth factor is approved for idiopathic pulmonary fibrosis (IPF) and may be another option for SSc; a systematic literature review of five randomised controlled trials showed it decreased all-cause mortality vs placebo. Furthermore, main AEs during pirfenidon seem to be gastrointestinal by nature [3]. Encouraging data are also seen with nintedanib, approved for IPF, and therefore may also promising for SSc [4]. Nintedanib is a tyrosine kinase inhibitor which specifically aims at platelet-derived growth factor receptors, fibroblast growth factor receptors, and vascular endothelial growth factor receptors [5]. However, the available data on IPF require caution since they differ from SSc (e.g. more male patients) and warrants further study. Tocilizumab, an IL-6 receptor inhibitor, has shown interesting results in a Phase 2 trial in SSc patients in comparison to placebo. Although tocilizumab was not associated with a significant reduction in skin thickening, the difference was greater in those receiving tocilizumab than those on placebo. Furthermore, some evidence of diminished forced vital capacity was observed [6]. Phase 3 data are needed to support these findings with regard to efficacy and safety of tocilizumab. A very different approach is the use of adipose derived mesenchymal cells and mesenchymal products such as exosomes and microparticles that are studied in early clinical studies in SSc. Overall, this is an exciting and encouraging time for novel therapies to treat SSc, one of the most detrimental systemic rheumatic disease [7].

Promising results rituximab in systemic sclerosis

The largest study of use in routine care of rituximab in patients with SSc showed significant changes on skin fibrosis but not on lung fibrosis. The safety profile was considered good and future studies are warranted into the possible role of rituximab in this patient population. According to Prof. Allanore, (University of Paris Descartes University, France), a few small-sized observational studies have suggested that rituximab is a promising treatment in patients suffering from SSc. The study aimed to evaluate the outcomes of SSc patients receiving in routine care rituximab. This was done as a retrospective longitudinal multicentre observational study in which eligible SSc patients were treated with rituximab upon the decision of their physician within the framework of European Scleroderma Trials and Research group (EUSTAR). This is an international scleroderma research network that aims to foster the awareness, understanding, and research on systemic sclerosis and its management throughout Europe and the rest of the world.

It has a multicentre online database that allows following prospectively more than 15,000 patients with scleroderma in more than 200 international centres [8]. Epidemiological and clinical characteristics, the indication for initiating the treatment, as well as parameters at baseline and at the last visit under treatment were determined. These parameters included mRSS, joint, lung and gastrointestinal involvements, treatment, laboratory tests, and safety events. A total of 254 patients were included. Of these, 65% had diffuse cutaneous SSc, 54% was positive for anti-topoisomerase, and 71% had lung fibrosis. The indication for the treatment with rituximab was lung involvement in 56% of cases, followed by articular (42%) and skin involvements (30%). Mean follow-up was 2.5 years. A decrease was seen in patients with skin fibrosis and baseline mRSS ≥10 from 21.7 at baseline to 13.6 at the last visit ($p<0.0001$). In patients with lung fibrosis, forced vital capacity at baseline was 74.4 and at last visit 76.1; for diffusing capacity or transfer factor of the lung for carbon monoxide, this was 52.7 at baseline and 53.0 at the last visit. In the whole population, 45 patients were able to stop the use of steroids and mean dose decreased from 10 mg to 7 mg in the other. AEs were seen during the follow-up in 31% of patients of which 14% (n=35) had serious AEs. Of the patients experiencing serious AEs, 9/35 had infections, 9/35 patients had cardiovascular events, 6/35 died (of which 2 deaths were possibly related to rituximab), 5/35 developed cancer, 4/35 had allergic reactions, 1/35 had agranulocytosis, and 1/35 had SRC. A total of 9.4% of patients discontinued the treatment. Researchers pointed out that these results need to be confirmed by future randomised controlled studies [9].

New systemic lupus erythematosus classification criteria

According to experts and physicians, the classification criteria for SLE were in need of an update and subsequent validation. The main goal was to simplify and validate the new criteria in a large international cohort. This proved to be a substantial task and was achieved by using a multinational committee which involved 23 expert centres, which added up to 100 patients each either with SLE and with non-SLE diagnoses. Three independent reviewers verified diagnosis for 1,193 SLE and 1,059 non-SLE patients. The derivation cohort contained 500 randomly selected SLE patients as well as non-SLE patients; the remaining patients then made up the validation cohort. A new set of weighted criteria were compared to non-SLE controls and it was decided that an SLE diagnosis had to have an Anti-Nuclear Antibody titre greater >1:80 and a classification threshold of 10, derived from adding up the values given to the separate items as outlined in Table 4. The highest number of points was given to nephritis on biopsy whilst oral ulcers had the least number of points (Table 4).

Table 4 Weighted criteria [10]

Renal	Class III/IV nephritis	**10**	Class II/V nephritis	**8**	Proteinuria ≥0.5 g/day	**4**
Specific antibodies	Anti-Sm **or** Anti-dsDNA	**6**				
Muco-cutaneous	Acute cutaneous LE	**6**	Subacute cutaneous LE **or** Discoid LE	**4**	Alopecia **or** oral ulcers	**2**
Serosa	Acute pericarditis	**6**	Effusion	**5**		
Musculo-skeletal	Arthritis	**6**				
CNS	Seizures	**5**	Psychosis	**3**	Delirium	**2**
Blood	Autoimmune hemolysis **or** thrombocytopenia	**4**	Leukopenia	**3**		
Complement	Low C3 and C4	**4**	Low C3 **or** C4	**3**		
Anti-phospholipid	Anti-Cardiolipin **or** anti-β2-GPI **or** lupus anticoagulant	**2**				
Constitutional	Fever	**2**				

The new criteria significantly increased the sensitivity to approx. 96%-98% which is an increase of 14% over the previous ACR 1998 SLE criteria and improved the specificity (which is now 93-96%) over the 2012 SLICC criteria by 6%. It was thus concluded that the new criteria, which were developed with EULAR/ACR support, achieved sensitivity which lies very close to that of the SLICC criteria, whilst the specificity of the ACR criteria was maintained [10].

Baricitinib may be potential therapy for systemic lupus erythematosus patients

Recent data has shown that once-daily oral baricitinib 4 mg for patients with SLE who receive standard background therapy is associated with significant clinical improvements on skin and joint manifestations compared to placebo. The results of a phase 2 study over 24 weeks showed a promising benefit/risk profile. Baricitinib is an oral selective inhibitor of Janus kinase (JAK)1 and JAK2. This agent has been approved for the treatment of RA in over 40 countries in the European Union, the United States and Japan and has prompted research in other fields such as SLE. Wallace et al. reported the results from a 24-week global, Phase 2, double-blind, placebo-controlled study of baricitinib in patients with SLE who received standard therapy. A total of 314 patients with positive antinuclear antibodies or anti-double stranded DNA, clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) ≥4, arthritis or rash were randomised 1:1:1 to placebo (n=105) or baricitinib (2 or 4 mg, n=105 and n=104, respectively) once daily. The primary endpoint of the study was resolution of SLEDAI-2K

for arthritis or rash at week 24. Of this population, 79% of patients on placebo, 82% on baricitinib 2 mg and 83% on baricitinib 4 mg completed 24 weeks of treatment. At week 24, a significantly greater proportion of patients who received baricitinib 4 mg achieved resolution of SLEDAI-2K arthritis or rash compared to placebo (67% vs 53%, p<0.05) and Systemic Lupus Erythematosus Responder Index 4 (SRI-4) response (64% vs 48%, p<0.05). At week 24, the proportion of patients achieving flare reduction (SELENA-SLEDAI Flare Index [SFI]), Lupus Low Disease Activity State (LLDAS), and TJC change from baseline were also significantly improved for baricitinib 4 mg compared to placebo. Researchers did not observe statistically significant differences between baricitinib 2 mg and placebo in any of the above endpoints. The occurrence of AEs leading to treatment discontinuation and serious AEs was higher for both baricitinib dose groups compared to placebo with both around 10% for baricitinib. No deaths, malignancies, major adverse cardiovascular events, cases of tuberculosis, or serious herpes zoster infections were reported, while there was one serious AE (deep vein thrombosis) reported in a Korean patient with known risk factors (positive anticardiolipin antibodies) in the baricitinib 4 mg group. It was concluded that the safety and tolerability profile of baricitinib remained satisfactory as no new events occurred. Wallace et al. concluded that these interesting findings support further study of baricitinib 4 mg as a potential therapy for patients with SLE [11].

Clinical benefit of ustekinumab for patients with systemic lupus erythematosus

Treatment with ustekinumab provides clinical benefits in patients with SLE; safety was as expected based on earlier extensive experience with the agent in psoriasis, PsA and CD. Based on these results, ustekinumab – targeting IL-12 and -23 – may have the potential to offer a new treatment option for patients with SLE. The study reported by van Vollenhoven et al. evaluated ustekinumab – a monoclonal antibody which blocks the shared p40 subunit of the cytokines IL-12 and IL-23 in patients with active SLE in a Phase 2, placebo-controlled study in 102 patients. They were randomised (3:2) to receive ustekinumab ~6 mg/kg or placebo at week 0, followed by ustekinumab s.c. 90 mg or placebo injections every 8 weeks beginning at week 8, and both added to standard care. Primary endpoint was the proportion of patients achieving SRI-4 response at week 24. Secondary endpoints were change from baseline in SLEDAI-2K, PhGA and the British Isles Lupus Assessment Group (BILAG)-based Composed Lupus Assessment (BICLA) response. Additional pre-specified endpoint analyses included no BILAG worsening (which was defined as no new BILAG A and ≤1 new BILAG B domain) and BILAG flare (≥1 new BILAG A or ≥2 new BILAG B domain score). The results show that ustekinumab exhibited a statistically significant improvement in SRI-4 response at week 24 compared to placebo (60% vs 31%, p=0.0046). Patients on ustekinumab had greater median change from baseline SLEDAI-2K and PhGA vs placebo (-4.4 vs -3.8 and -2.17 vs -1.93, respectively). No difference was observed in BICLA response at week 24. However, in the ustekinumab group vs placebo, more patients had no BILAG worsening (48.3% vs 26.25, p=0.028) and the risk of a new BILAG flare was significantly lower (HR 0.11; 95% CI 0.01-0.94; p=0.0078). Moreover, ustekinumab demonstrated improvement in musculoskeletal and mucocutaneous disease features vs placebo, with the mean change from baseline in active joint count at week 24 of -4.5 for ustekinumab and -2.8 for placebo (median value -4.0 and -3.0, respectively) (Table 5) [12].

Table 5 Change from baseline in active joint count at week 24 [12]

Imputed data	Ustekinumab	Placebo
Patients with ≥2 active joints at baseline	57	41
Difference from baseline in number of active joints at week 24 Mean (SD) -4.0 (-12; 4) // -3.0 (-17; 18)	**-4.5** (4.4)	**-2.8** (7.3)
P-value LS Means test		0.1032

Low C3 and elevated anti-double stranded DNA autoantibody levels, which are markers of increased disease activity, improved in ustekinumab patients over time when compared to placebo. CRP levels and antinuclear antibody titres were stable over time in both treatment groups. With regard to AEs through week 24, 78% of patients on ustekinumab vs 67% of placebo patients had ≥1 AE; 8.3% and9.5% respectively, had ≥1 serious AE. No deaths occurred during the study and it was concluded that the overall safety profile was comparable between ustekinumab and placebo [12].

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