2018 ACR/ARHP Annual Meeting

American College of Rheumatology

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PEER-REVIEWED CONFERENCE REPORT

Late-Breaking Abstracts

The dual IL-17A and IL-17F inhibitor bimekizumab showed promising activity in psoriatic arthritis in a phase 2 study. In osteoarthritis, the peptide TPX-100 showed not only striking improvements in knee function but therapy also improved cartilage structure.

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What is New in Rheumatoid Arthritis?

Despite the general acceptance of the treat-to-target paradigm in RA, many patients do not switch therapy despite high disease activity. Incorporation of patient-reported outcome in management of RA could be one step forward in this respect.

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Improved Management in SLE

Systemic lupus erythematosus patients suffer less frequently from recurrent nephritis than two decades ago. Also, fewer pregnancy complications are seen today.

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MEDICOM MEDICAL PUBLISHERS

Editor Prof. Dennis McGonagle, University of Leeds, United Kingdom

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Letter from the Editor

Prof. Dennis McGonagle

Dear Reader,

The 2018 American College of Rheumatology Annual Meeting returned to the windy city of Chicago for the first time since 2011. Whilst a national meeting, the ACR/ARHP drew over 15,000 delegates from over 100 countries and had an extensive clinical and basic science curriculum to cater for all interests. The remarkable progress in the therapy of inflammatory arthritis continues apace. In RA, a move from biological therapy towards small molecules with the emergence of JAK was highlighted. The seronegative spondyloarthropathies witnessed the consolidation of IL-23/17 axis inhibition and emergence of JAK pathway inhibition but the failure of IL-23 pathway blockade in axial disease. The meeting also witnessed data on the potential re-emergence of pain pathway modulation and novel new therapies for osteoarthritis. Other Chicago experience highlights included the vibrant culinary experience in the evenings and the shuttle bus underground tunnel trip to the McCormick Convention Center, using the underground network that formed the set for a Batman movie.

Some of the highlights that will impact or potentially impact on clinical practice are highlighted in this report. We hope that you enjoy the brief meeting summary that we have distilled from only a small fraction of the excellent abstracts. We hope that you enjoy reading this report and we look forward to seeing you next year in Atlanta.

Sincerely,
Dennis

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.

Conflict of Interest Statement: Prof. McGonagle has undertaken research and/or educational programme activities with Pfizer, MSD, AbbVie, BMS, UCB, Novartis, Celgene, and J&J.

Late-Breaking Abstracts

The late-breaking abstract session attracted numerous attendants and provided a glimpse into the future of rheumatology. Below, a synopsis of recent developments in giant cell arteritis, psoriatic arthritis, fibromyalgia, rheumatoid arthritis, and osteoarthritis presented at the 2018 ACR/ARHP Annual Meeting.

Good diagnostic accuracy with PET/CT for giant cell arteritis

Combined PET/CT shows good diagnostic accuracy compared with a temporal artery biopsy (TAB) for diagnosing of suspected giant cell arteritis (GCA). A study of 64 patients with newly suspected GCA revealed a 98% negative predictive value of the PET/CT [1]. Traditionally, PET/CT has been used to image the aorta and primary branches. Newer generation scanners, however, can also detect inflammation in the smaller temporal, occipital, maxillary, and vertebral arteries. The accuracy of this newer generation of PET/CT to diagnose GCA was assessed in a study presented by Dr Anthony Sammel (Royal North Shore Hospital Sydney, Australia).

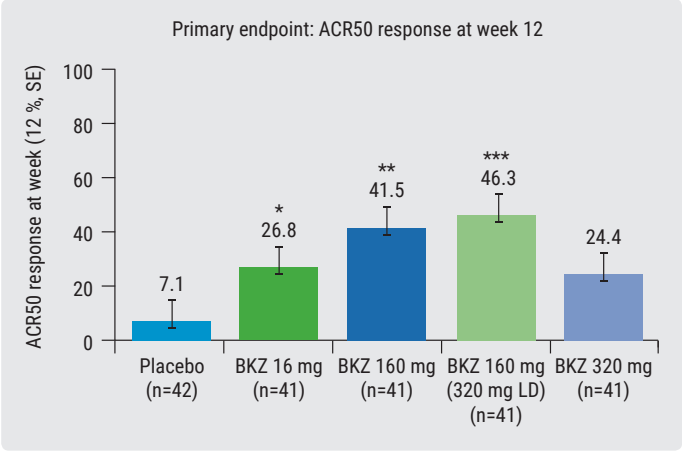
All participants underwent 18F-FDG-PET/CT from the vertex of the head to the diaphragm within 72 hours of starting corticosteroid therapy and prior to undergoing temporal artery biopsy (TAB). At 6 months, the diagnosis was made by consensus between the blinded treating clinician and external reviewers. Out of the 64 patients, 58 (91%) underwent TAB, and 12 of them (21%) had biopsies that were positive for GCA. In addition, 21 of the 64 patients (33 %) had a clinical diagnosis of GCA and 42 (66%) met the 1990 ACR criteria for GCA.Compared with TAB, global GCA assessment by PET/CT had a sensitivity of 92%, specificity of 85%, and positive predictive value of 61%. "Our findings, and particularly the high negative predictive value, suggest that PET/CT could be used as a first-line test to rule out suspected GCA, although the sample size in the study was modest," concluded Dr Sammel. "However, we do need to be mindful that it is not perfect," he said. Therefore, the threshold to do an additional TAB should be low in a patient with a negative scan. Of note, PET/CT also diagnosed alternative conditions in this study, including 7 acute infections. "Those patients could have been seriously harmed if they had followed the GCA therapy," said Dr Sammel.

Bimekizumab: a promising novel agent for the treatment of psoriatic arthritis

Results from the phase 2b, randomised, double-blind, placebo-controlled BE ACTIVE study showed promising response rates for the dual IL-17A and IL-17F inhibitor bimekizumab [2]. Response rates increased up to week 24 and were maintained to week 48 across musculoskeletal and skin manifestations in psoriatic arthritis (PsA). Despite the availability of new treatments, a substantial proportion of PsA patients fail to achieve adequate disease control. Thus, a medical need for novel treatment options that are active across the different disease manifestations still exists. Prof. Christopher Ritchlin (University of Rochester Medical Center, USA) believes that there is a substantial value in neutralising IL-17F in addition to IL-17A in the treatment of PsA. "Our clinical hypothesis is that neutralising IL-17F in addition to IL-17A results in a greater suppression of inflammation than inhibition of IL-17A alone," said Prof. Ritchlin. In vitro studies have demonstrated that IL-17F has a biologic effector function that can modulate inflammation.

Patients with active PsA (206 in total) were randomised to receive 3 doses of bimekizumab (i.e. 16 mg, 160 mg, or 320 mg) with or without loading dose or placebo for a double-blind period of 12 weeks. From week 12, patients receiving placebo or the lowest bimekizumab dose were re-randomised to receive a higher dose; all other patients continued their previous dose. The study achieved its primary endpoint, an improvement of 50% according to criteria of the American College of Rheumatology (ACR50), at week 12. A clear dose-response relationship was observed. Of the PsA patients who received bimekizumab in a dose of 160 mg with a 360 mg loading dose, 46.3% experienced an ACR50 response vs 7.1% with placebo (Figure 1; $P<0.01$). These results were generally consistent regardless of prior exposure to an anti-TNF and were maintained to week 48 across doses. In addition, significantly more patients achieved an ACR20 response and an improvement of the Psoriasis Area and Severity Index (PASI) by 90 % (in patients that had skin lesions with a body surface area of ≥3%). ACR20/50/70, PASI75/90, minimal disease activity, and resolution of enthesitis response rates increased up to week 24 in those who continued their initial bimekizumab dose. Responses were maintained and similar

Figure 1 ACR50 response rates at week 12 (non-responder imputation) [2]



BKZ, bimekizumab; LD, loading dose. *P<0.05, **P<0.1, ***P<0.01

across the 3 dose groups at week 48. For the 320 mg dose, ACR20/50/70 response rates were 76%, 63%, and 39%, and PASI90 response rate was 85%. Serious adverse events were reported in 4.4% of patients at all doses at week 48. Nasopharyngitis was the most frequently reported adverse event (12.1%). Oral candidiasis was reported by 4.9% of patients and did not lead to discontinuations. "The results observed with bimekizumab are impressive, and this agent has the potential to offer a new therapeutic option in patients with psoriatic disease," concluded Prof. Ritchlin.

TENS improves pain and fatigue in patients with fibromyalgia

Compared with no treatment, transcutaneous electrical nerve stimulation (TENS) showed an effective symptom relief in women with fibromyalgia [3]. Patients with fibromyalgia suffer pain and fatigue, especially during physical activity. Thus, treatments designed to modulate central pain pathways to reduce activity-induced pain could improve function and quality of life in this population. "TENS activates endogenous central inhibitory pathways and decreases central excitability," said Prof. Leslie Crofford (Vanderbilt University Medical Center, USA). Therefore, she tested whether using TENS during physical activity can lessen disease impact, and improve activity-induced and resting pain, and fatigue.

Women aged 18 to 70 years with fibromyalgia were randomised to receive active TENS (n=103), placebo TENS (n=99), or no treatment at all (n=99). Primary study endpoint was the mean reduction in activity-induced pain after 1 month, assessed in the brief pain inventory in a numeric rating scale (NRS) of 1-10. Active TENS was applied on the upper and lower back at mixed frequency, with an intensity of 200 µsec pulse duration, which is a high yet still comfortable intensity. Placebo TENS comprised an electrical current delivered for 45s with a ramp to 0 in the last 15s. All study participants were instructed to use TENS at home for at least 2 hours per day, during activity pain and fatigue during activity (assessed with the 6-minute walking test) and at rest were reported before and during TENS at baseline and 1 month after use.

After 1 month, women in the TENS group had a significant mean reduction in activity-induced pain of 1.82. Those in the placebo group had a reduction of 0.85 and women who received no treatment had a reduction of 0.56. "Most women who received active TENS reported global improvement in their condition," reported Prof. Crofford. Women in the TENS group also had a significant mean reduction of 1.53 in activity-induced fatigue, assessed in the multidimensional assessment of fatigue, also in a NRS of 1-10. The placebo group only showed a 0.08 reduction, and the no treatment group had no reduction (both differences P<0.01). Participants who received active TENS had significant improvements in resting pain, activity-induced pain, and fatigue compared with placebo and no treatment (P<0.05 for all). Disease impact improved in 70% of those in the active TENS group compared with 31% in the placebo TENS group, and 9% in the no TENS group (P<0.001). "As a safe, inexpensive, home-based treatment, TENS may be included as part of the management strategy for women with fibromyalgia," concluded Prof. Crofford.

Glucocorticoid tapering possible in most RA patients with low disease activity on tocilizumab

Patients with rheumatoid arthritis (RA) achieving at least low disease activity (LDA) while receiving tocilizumab and long-term glucocorticoids 5 mg/day should be considered for tapering of their glucocorticoid dose, ideally targeting discontinuation. This was the primary result of the Steroid EliMination In RA (SEMIRA) study that compared glucocorticoid tapering vs continuation for maintaining disease control in RA with chronic glucocorticoid exposure in patients receiving tocilizumab [4]. Tapering strategies have been explored for various disease-modifying antirheumatic drugs (DMARDs) in RA patients in at least LDA. However, data concerning schedule and impact of glucocorticoid taper were lacking. "We would like to avoid long-term treatments with glucocorticoids to minimise risks," said Prof. Gerd-Rüdiger Burmester (Charité University Medicine Berlin, Germany) as he explained the objective of the SEMIRA study.

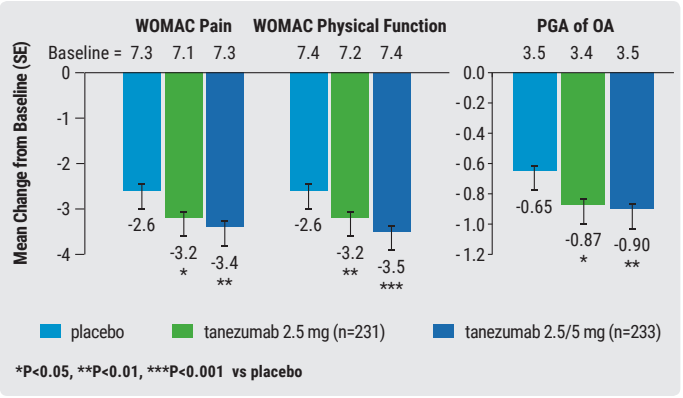
Before randomisation, enrolled patients had to receive tocilizumab +/– conventional synthetic DMARDs and glucocorticoids (prednisone-equivalent dose 5-15 mg/d) for ≥24 weeks. At randomisation, patients had to be in at least stable LDA and stable concomitant therapy (prednisone 5 mg/day) and tocilizumab ± DMARDs for ≥4 weeks. Patients were randomised either to continue blinded 5mg daily of prednisone (n=128) for 24 weeks or to undergo blinded glucocorticoid taper (n=131), starting at 4 mg/day with 1-mg reduction every 4 weeks to 0 mg/day at weeks 16-24. The primary outcome was a mean change in disease activity score (DAS)28-erythrocyte sedimentation rate (ESR) at week 24.

Continued glucocorticoids provided statistically significantly superior DAS28-ESR control to tapering glucocorticoids in RA patients treated with tocilizumab in LDA or remission. However, the difference was small: the between-arm difference was 0.6 DAS28-ESR units (95% confidence interval: 0.346, 0.879) favouring the continued glucocorticoid arm (P<0.001). Almost two thirds of patients who tapered, discontinued glucocorticoids without flare and maintained LDA. The authors conclude that all points achieving LDA or remission with tocilizumab who are receiving long-term low-dose glucocorticoids should be considered for glucocorticoid tapering. Safety was similar whether glucocorticoids were continued or tapered.

Blocking a nerve growth factor improves pain in osteoarthritis

Subcutaneous tanezumab, an antibody that blocks nerve growth factor, provides significant pain relief and improved function, compared with placebo, in patients with hip or knee osteoarthritis (OA). This was the main result of a study presented by Prof. Thomas Schnitzer (Northwestern University Feinberg School of Medicine, USA) [5]. The randomised, double-blind, placebo-controlled, multicentre study included OA patients who did not respond to or could not tolerate standard pain treatments. All patients had WOMAC pain and WOMAC function scores of ≥5, and a Patient Global Assessment of OA score of "fair", "poor", or "very poor". In addition, there was a documented history of inadequate pain relief or intolerance to standard treatments for OA pain. They were randomised to receive placebo (n=232) or tanezumab in 2 regimes for 16 weeks. One tanezumab group was treated with 2.5 mg for 16 weeks (n=231), the other group received 2.5 mg for 8 weeks followed by 5 mg for the remainder of the study (n=233). Primary efficacy outcomes were the mean change from baseline to week 16 in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, WOMAC Physical Function subscale, and PGA-OA.

Figure 2 Both tanezumab treatment groups met the co-primary endpoint of the study [5]



PGA, patient global assessment; OA, osteoarthritis.

At week 16, both tanezumab dosing regimens met the study co-primary endpoints (Figure 2). The result in pain scores (11-point numerical rating scale) was -2.6 for the placebo group, -3.2 for the tanezumab 2.5 mg group (P=0.0129), and -3.4 for the tanezumab 2.5/5 mg group (P=0.0023). "Increasing the dose to 5 mg at week 8 was associated with modest additional benefit vs continuation on tanezumab 2.5 mg," noted Prof. Schnitzer. The mean change from baseline in WOMAC physical function scores was -2.6, -3.2, and -3.5, respectively (P=0.0065 and P=0.0002 for tanezumab 2.5 and 2.5/5 mg groups vs placebo, respectively). Tanezumab also significantly improved patient´s global assessment of OA. The most common adverse events were nasopharyngitis, pain in extremity, and paraesthesia. However, the incidence of serious adverse events or withdrawals due to adverse events was similar between treatment groups. Adjudicated rapidly progressive OA occurred in 1.3% of tanezumab-treated patients, and was not observed in the placebo group. "This study demonstrates that subcutaneous tanezumab may be an effective option for patients who have demonstrated intolerance or incomplete response to standard treatments for OA," concluded Prof. Schnitzler.

TPX-100: improves function response in osteoarthritis and increases cartilage thickness

In an analysis regarding the use of intra-articular TPX-100 in osteoarthritis (OA), it was demonstrated for the first time that clinically meaningful functional benefit is associated with MRI-confirmed knee cartilage thickness increases [6]. Previously, TPX-100, a peptide derived from matrix extracellular phosphoglycoprotein, has been shown to induce articular cartilage regeneration after cartilage injury in animal models. In addition, in a previously-reported phase 2 trial, therapy with TPX-100 led to statistically significant

and clinically meaningful improvements in knee function at 6 and 12 months compared with placebo-exposed knees in OA patients [7].

At the 2018 ACR/ARHP Annual Meeting, a post-hoc clinical responder analysis was presented, using pre-specified criteria for functional improvement. Since nearly 75% of subjects had bilateral tibiofemoral OA in addition to patellofemoral OA, changes in tibiofemoral cartilage thickness/volume were analysed in responders vs non-responders. In the previous study, a response was defined as an improvement in the Knee Osteoarthritis Outcome Scores of Daily Living (KOOS ADL) of ≥8 points from Baseline. A total of 118 patients with MRI-confirmed bilateral patellofemoral OA were enrolled. One knee was treated with 4 weekly TPX-100 injections, while the contralateral knee received identical placebo injections. KOOS ADL and WOMAC scores were evaluated for each knee. Baseline, 6-month and 12-month MRIs were read centrally, blind to treatment assignment.

Of the TPX-100-treated knees, 66% met pre-defined responder criteria, with significantly more TPX-100-treated knees than placebo-exposed knees showing functional improvement at 6 or 12 months or both (P≤0.02). "It is one thing to show a statistically significant change, but it is another thing to show a clinically meaningful change, and we saw this in the group that received the injections," said Dr Dawn McGuire (Chief Medical Officer of Ortho Trophix Inc, USA). TPX-100 responder knees also showed significant increases in tibiofemoral cartilage thickness compared with baseline (increases at 6 and/or 12 months 0.099 mm; P≤0.003). Many clinical trials of disease-modifying OA drug show a discordance between structural change and measures of patient benefit. As the authors hypothesised, in contrast, the present analysis showed that striking improvements in knee function in over half of TPX-100 treated knees are related to improvements in cartilage structure as measured by MRI. Additional larger studies are needed to confirm that cartilage regeneration robustly occurs and that it is consistently linked to pain reduction.

References:

1. Sammel A et al. Abstract L15, ACR/ARHP Annual Meeting, 19-24 October 2018, Chicago, USA.
2. Ritchlin R et al. Abstract L17, ACR/ARHP Annual Meeting, 19-24 October 2018, Chicago, USA.
3. Crofford L et al. Abstract L19, ACR/ARHP Annual Meeting, 19-24 October 2018, Chicago, USA.
4. Burmester GR et al. Abstract L18, ACR/ARHP Annual Meeting, 19-24 October 2018, Chicago, USA.
5. Schnitzer Th et al. Abstract L20, ACR/ARHP Annual Meeting, 19-24 October 2018, Chicago, USA.
6. McGuire D et al. Abstract L16, ACR/ARHP Annual Meeting, 19-24 October 2018, Chicago, USA.
7. McGuire D et al. Abstract 13L, ACR/ARHP Annual Meeting, 4-8 November 2017, San Diego, USA.

What is New in Rheumatoid Arthritis?

Besides numerous presentations on treatment strategies, the 2018 ACR/AHRP meeting also presented novel tests and data on comorbidities in rheumatoid arthritis. Adherence to a treat-to-target strategy is widely accepted but still not embedded in daily practice.

Many rheumatoid arthritis patients do not switch treatment – despite high disease activity

Adherence to a treat-to-target (T2T) strategy is a recommended paradigm for rheumatoid arthritis (RA). Both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommend routine measurement of RA disease activity and the adjustment of drug therapy in patients to attain low disease activity (LDA) or remission. However, studies have shown that there are many barriers to the implementation of this principle [1]. New data presented during the 2018 ACR/ARHP meeting emphasised the importance of this new treatment principle, but also the many impediments in applying T2T in daily practice. An analysis of the ACR´s national, qualified, clinical data registry, Rheumatology Informatics System for Effectiveness (RISE) showed that nearly half of adult RA patients did not change their current treatment to reach LDA [2].

"The main impetus for the study was to understand whether rheumatologists who routinely say that they follow T2T guidelines and strive for LDA and remission for most or all of their RA patients, are indeed doing so," said Prof. Jeffrey

Curtis (University of Alabama at Birmingham, USA). There is a concern for so-called clinical inertia: that although patients are not doing well, treatment is not changed in an attempt to improve disease control. To identify whether rheumatologists are following the T2T principle, researchers identified 50,996 patients who met the study's inclusion criteria: adult RA patients with one or more rheumatologist visits and available disease activity measures. The researchers assessed which disease activity measurements were used by the rheumatologist, and identified the subgroup of patients with moderate or high disease activity. They evaluated treatment and disease activity changes at follow-up visits occurring up to 12 months later. Results were stratified based on which disease activity measurement tool was used. Most patients were evaluated with the disease activity index Routine Assessment of Patient Index Data 3 (RAPID3) (79%), followed by the Clinical Disease Activity Index (CDAI) (34%).

Despite facing moderate or high disease activity, 36.8 to 58.4% of patients evaluated with the RAPID3 did not change RA treatments. Those on combination therapy with methotrexate and a biologic were the least likely to change treatments. Of the 2,433 patients with persistent moderate or high disease activity measured by CDAI at 2 or more consecutive visits, the proportion of treatment switching was similarly low (39.6% to 63.4%). When patients did change treatments, disease activity improved as expected. "These findings shine a spotlight on the relatively high proportion of patients who fail to change RA therapies despite not achieving the T2T goals of low disease activity or remission," said Prof. Curtis. The authors suggest that multi-touch, multi-modal interventions are needed to encourage clinicians and patients to strive to improve RA disease control. More effective intervention is needed to encourage treatment change, which might improve patient outcomes.

Improved T2T adherence with patient-reported outcome measures

Incorporating patient-reported outcome measures for disease activity assessment into routine care can improve adherence to a T2T strategy. This was the outcome of a single-centre study with 2,549 patients presented during the ACR/ARHP meeting [3]. After 1 year, patients assigned to the intervention programme had a 15% improvement in their T2T implementation score compared with patients on standard treatment [4]. According to Dr Cianna Leatherwood (Kaiser Permanente Oakland Medical Center, USA), this is a clinically relevant difference. The interventions included having patients complete the RAPID3 survey via an online patient portal or an iPad each time they visited a rheumatologist, and attending patient group discussions prior and during the year. The RAPID3 scores were also available to the physicians during the visits.

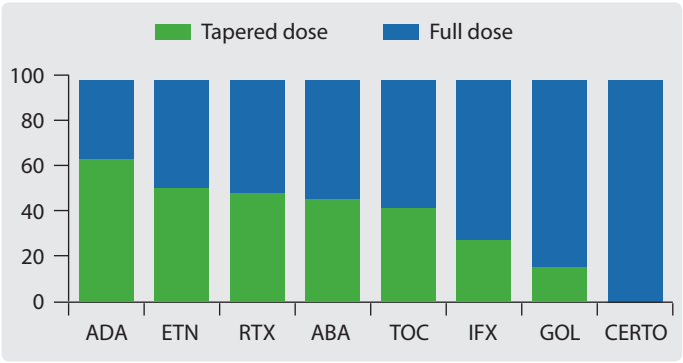
Rheumatologists in the intervention groups had monthly 'learning collaborative sessions' to discuss and develop T2T practices. In addition, they received frequent email reminders about adopting a T2T approach. Patients in the intervention groups received phone calls following a medication change to measure treatment satisfaction according to a standardised questionnaire. The control arm of the study included 11 rheumatologists who routinely cared for their patients. "One of the strongest characteristics of our study is that it is based on a real-life clinic model, and reflects our experience in an everyday setting," said Dr Leatherwood. "We hope that our experience can exemplify that it is possible to pursue routine implementation of patient-reported outcome measures into daily clinical practice". She is confident that other health systems could adapt and use the treatment model she used in this trial, and tailor it to their local conditions to improve the T2T paradigm.

Tapering of biologics is possible in many rheumatoid arthritis patients with moderate disease activity

A Belgian retrospective trial reached the conclusion that most RA patients with moderate disease activity are able to taper bDMARDs. [5]. "Tapering of biologics is essential in daily care," said Dr Patrick Durez (Université Catholique de Louvain, Belgium). The trial therefore evaluated the proportion of patients for whom biologics can be tapered in daily clinical practice, as well as the characteristics of tapering patients, and biologics that are more readily adaptable to dose tapering.

The study included data from 332 eligible RA patients from a UC Louvain cohort, who were treated with a biologic for at least 1 year and who were in sustained LDA or remission. A tapered biologic regimen was given to 140 patients (42.1%); the dose reduction was proposed by the senior physician when sustained LDA or remission was achieved. 192 patients received a full dose. RA patients that were treated with a tapered biologic regime had statistically significant less rheumatoid factor (83.3 vs 72.9%), Health Assessment Questionnaire (HAQ) (1.3 vs 1.5), a shorter disease duration at the introduction of the biologic (9.7 vs 12.1 years), and

Figure 3 Percentage of rheumatoid arthritis patients treated with a full or tapered dose according to treatment with different biologics [5]
As adalimumab has been on the market the longest and is frequently prescribed, more patients are tapered compared with other agents.



ADA, adalimumab; ETN, etanercept; RT, rituximab; ABA, abatacept; TOC, tocilizumab; IFX, infliximab; GOL, golimumab; CERTO, certolizumab

a higher concomitant use of methotrexate (86.7 vs 73.8%). No significant differences were found between the group for gender, anti-citrullinated protein (ACPA)-antibodies, erosions, the number of previous biologics, baseline disease activity as assessed by the DAS28-C-reactive protein (DAS28-CRP) and glucocorticoid use. Current measures of disease activity (DAS28-CRP) scores were lower in the tapered-dose group (2.26 vs 2.64, P=0.001). Only 15 patients had a flare during the follow-up. Anti-tumour necrosis factor (TNF) agents were the most commonly prescribed biologics, and the most frequently tapered biologics were adalimumab, etanercept, and rituximab (Figure 3). As expected, tapering was associated with a significant reduction in annual cost of treatment.

The authors concluded that tapering of biologics in RA patients with LDA or remission is an achievable goal in a large percentage of RA patients. However, more prospective data are needed to confirm these preliminary results.

Screening rheumatoid arthritis patients for preclinical interstitial lung disease

RA is associated with significant extra-articular manifestations in a large proportion of patients. Interstitial lung disease (ILD), a progressive fibrotic disease of the lung parenchyma, is the most common lung disease in RA patients, contributing significantly to increased morbidity and mortality. According to a genetic trial, a gene variant that is also responsible for idiopathic pulmonary fibrosis (IPF) without RA contributes significantly to the risk of developing ILD in RA [6]. RA-associated ILD and IPF share some phenotypic similarities. This was the rationale to study whether MUC5B promoter variant rs35705950, the strongest genetic risk factor for IPF, is also common or contributes to the risk of ILD in RA patients [6]. The study was published simultaneously to its presentation during the ACR/ARHP Annual Meeting [7].

A possible association was assessed in a 7-country genetic case-control study of 620 patients with RA-associated ILD, 614 with RA but no ILD, and 5,448 unaffected controls. The presence of the MUC5B promoter variant in patients with RA proved to be associated with substantially higher risk of RA-ILD than the previously recognised risk factors for RA-ILD, which included smoking and the human leukocyte antigen locus for RA. RA patients that had the MUC5B promoter variant had an adjusted 6.1-fold increased risk of ILD, with the typical interstitial pattern in high-resolution computer tomography also encountered in IPF patients, namely honeycombing and reticular abnormalities compared with RA patients without this variant. The risk of other types of ILD in RA was not affected by the presence or absence of the MUC5B variant.

This association has an important clinical consequence: similarly to IPF, ILD in RA patients is often diagnosed too late because of a lack of early symptoms. As Dr Pierre-Antoine Juge (Bichat Hospital, France) pointed out, detection of the MUC5B promoter variant could be used to screen patients with RA for preclinical ILD. In addition, anti-fibrotic drugs effective in IPF could also be tested in ILD in RA patients. Clinically significant ILD is present in about 10% of all RA patients, and the number of occult ILD cases in RA patients is probably higher. The authors emphasise that other IPF-related common variants may also participate in RA-ILD genetic susceptibility.

Positive anti-citrullinated protein antibodies in RA associated with increased response to abatacept

Multiple therapeutic options with different mechanistic actions are available to treat patients with RA, but the choice of therapy for an individual patient is not always clear. A study therefore set out to analyse treatment response of TNF inhibitors and abatacept dependent on the individual status of ACPA [8]. Data was derived from two registries: the BRASS registry included 797 RA-patients treated with TNF inhibitors, and the ACTION registry with 2,350 patients under abatacept. Patients treated with TNF inhibitors were evaluated by a rheumatologist once a year, patients treated with abatacept were evaluated quarterly. In the abatacept

cohort, average values for age and BMI were 57.8 and 27.3, while 67% had a positive ACPA status (ACPA+). Data of the TNF inhibitor subjects was 54.9, 26.8, and 70% for age, BMI, and ACPA+, respectively. Of note, all ACPA+ patients had a significantly longer average disease duration: 11 years with abatacept and 15.5 years with TNF blockers.

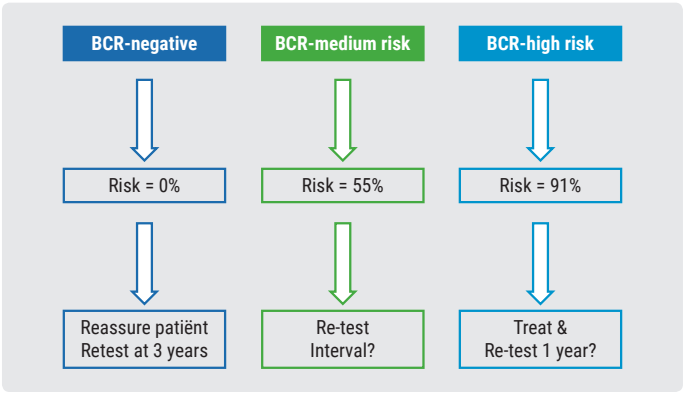
Changes in disease activity assessment of ACPA+ vs ACPA- patients treated with abatacept were significantly greater in Clinical Disease Activity Index (-15.6 vs -13.6), Simple Disease Activity Index (SDAI; -15.9 vs -14.7; P= 0.016), and swollen joint count (-4.2 vs -3.8; P=0.013). Differences in the TNF inhibitor cohort were not as pronounced. The study demonstrates that ACPA status has an important impact on treatment response depending on the mode of action of the drug of choice. In accordance to former data from registries, abatacept seems to be more effective in ACPA+ patients [9]. This could be of future help when it comes to choosing the adequate medication in RA.

Rheumatoid arthritis prevention: blood test predicts onset in at-risk individuals

Many patients with RA experience a preliminary phase marked by joint pain, the presence of RA-specific autoantibodies, IgM rheumatoid factor, and/or ACPA; although they do not suffer from synovial inflammation. According to a study presented at the ACR/ARHP meeting, a positive B-cell clonality test in a peripheral blood sample is able to predict imminent onset of RA with a high degree of accuracy in at-risk individuals [11].

Prof. Niek De Vries (University of Amsterdam, the Netherlands) and his co-authors developed a method of B-cell receptor (BCR) analysis using polymerase chain reaction (PCR) and next-generation sequencing techniques. When a clone comprises more than 0.5% of the total BCR population, it can be considered an expanded or dominant clone. In previously published trials, the researchers found that a BCR test was considered positive when a patient in pre-RA phase had 5 or more dominant clones in a peripheral blood sample. A positive BCR test in the pre-RA stage accurately predicted onset of overt RA within the next few years [12,13]. Interestingly, at the time of RA onset, the BCR clones disappeared from peripheral blood and reappeared in the synovium.

Figure 4 Patients with a BCR-negative test do not have a risk to develop RA, whereas preventive therapy might be indicated in BCR-high risk individuals [11]



At the 2018 ACR/ARHP Annual Meeting, Prof. De Vries presented the results of another BCR test validation study in 129 Dutch patients in pre-RA-phase. The objective of this study was to learn how predictive the BCR test is compared with clinical predictors such as the Risk Rule Model, and to assess whether a higher number of dominant clones predicts RA onset even more accurately than the 5-or-more clone threshold the investigators had been using previously. A total of 75% of patients with a positive BCR test went on to develop RA within the next 3 years, and none of the patients with a negative BCR test result. This indicates a test sensitivity of 100%, a specificity of 87%, a positive predictive value of 71%, and a negative predictive value of 100%. A positive BCR blood test was associated with a 120-fold increased relative risk of an RA diagnosis (95%-CI: 7.5 – 1917; P<0.0001) within 3 years. A high degree of BCR test positivity was associated with an even higher likelihood to develop RA: 91% of patients with 9 or more expanded clones in the BCR test developed RA within 3 years compared with 55% of those with 5 to 8 clones. "Based on our test, we can distinguish 3 groups: BCR-negative, BCR-medium risk, and BCR-high risk, who, in our view, might be candidates for treatment," said Prof. De Vries (Figure 4). Further studies have to evaluate the risk/benefit ratio of a preventive treatment.

Better flu protection with high-dose vaccine in rheumatoid arthritis patients

Vaccine-induced antibody responses and flu protection in people with RA have shown to be suboptimal. A study demonstrated that a high-dose influenza vaccination substantially improves immune responses against influenza in adults with seropositive RA [14]. RA patients have a 2.75-fold increased risk of influenza compared with healthy patients in the same age group, so annual flu vaccination is of key importance. Yet, vaccine-induced antibody responses and protection in RA are low. Prof. Inés Colmegna (McGill University, Canada) and her team compared a high-dose trivalent inactivated influenza vaccine with a standard-dose quadrivalent inactivated influenza vaccine in RA patients.

Antibody responses to both vaccines were assessed in a total of 279 adult seropositive RA patients.

Vaccination responses were relatively low in the RA patients. However, responses were consistently higher in the 139 RA patients who were treated with the high-dose vaccine (containing 60 µg of hemagglutinin per strain compared with 15 µg of hemagglutinin in the standard-dose vaccine). In logistic regression models, only vaccine dose and patient age were predictors of vaccine seroresponse. The high-dose vaccine was associated with a superior seroconversion rate in all 3 inactivated influenza viruses: RA patients that were treated with the high-dose vaccine were 2.8 times more likely to H3N2 seroconvert, 2 times more likely to B/Brisbane seroconvert, and 2.3 times more likely to H1N1 seroconvert compared with patients that were treated with the standard vaccine. The high-dose vaccine was as safe as the standard vaccine. "Influenza vaccines are safe, effective, and associated with significant reductions in the number of physician visits, hospitalisations for pneumonia or influenza, and deaths among high-risk adults," concluded Prof. Colmegna. She therefore advocates the use of high-dose vaccines in RA patients.

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Osteoarthritis: Focus on a Conservative Approach

Two trials presented during the ACR/ARHP Annual Meeting demonstrated that patients with osteoarthritis often benefit from a non-invasive approach, and that a regular brisk walk, even when painful, can delay the need of joint replacement surgery.

Both physical therapy and surgery provide long-term pain relief after meniscal tear

In patients with meniscal tears and osteoarthritic changes, arthroscopic partial meniscectomy is not superior to physical therapy. Both approaches lead to substantial pain relief over 5 years. This was shown by a long-term study of researchers from the Brigham and Women's Hospital and Harvard Medical School in Boston (USA)[1]. In this multicentre, randomised trial, researchers enrolled patients with knee pain, meniscal tear, and osteoarthritis (OA) changes on X-ray or MRI, and compared outcomes after 5 years among patients randomised to physical therapy or to physical therapy with an additional arthroscopic partial meniscectomy. The primary endpoint of the trial was pain, assessed with the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain scale, with scores ranging from 0-100, with 100 being the worst pain. The secondary outcome was total knee replacement.

From the 351 study participants, 164 received meniscectomy immediately, 68 were first randomised to physical therapy and then received meniscectomy, and 109 participants received physical therapy. Ten participants were excluded. Between 9 and 12 follow-up questionnaires were completed by 66% of the participants, with similar completion rates across all treatment groups. All three treatment groups saw a similar improvement in pain: Baseline KOOS pain scores were 40-50 and improved to 20-25 by 6 months. After this time, there were only minor changes until month 60. Over the follow-up period, 25 patients in the study had a total knee replacement.

Of those who received a meniscectomy (immediately or after physical therapy), 10% had a total knee replacement compared with 2% who received physical therapy and no surgery. "For clinicians, these results suggest that patients with meniscal tear and osteoarthritic changes can be reassured that they are likely to experience improvement with either surgery or physical therapy," said Prof. Jeffrey Katz (Harvard Medical School, USA). "For researchers, the increased rate of knee replacements noticed in the meniscectomy group requires more detailed studies."

Get osteoarthritis patients moving

Another trial presented during the meeting showed that OA patients have a distinct benefit from vigorous walking – even if it is painful [2]. Existing literature shows contradicting evidence whether walking more and at a high intensity is associated with structural worsening and total knee arthroplasty (TKA) in OA patients. One reason for inconsistent findings might be that walking can occur at different intensities. Hence, researchers at the University of Delaware conducted a study to examine the extent to which walking intensity is associated with the risk of TKA over 5 years.

The study used data from the Osteoarthritis Initiative and included participants who did not have TKA at or before a 48-month follow-up visit. Time spent walking at different intensities was quantified by step cadence recorded by an accelerometer. They defined less than one step/minute as non-walking, 1-49 steps/minute as very light walking, 50-100 steps/minute as light walking, and more than 100 steps/minute as moderate-to-vigorous walking. In addition, the researchers examined the effects of replacing time spent not walking with walking at either very light, light, or moderate-to-vigorous intensities with TKA risk over 5 years.

Over 5 years, 108 of 1,854 participants received a TKA. Those participants who replaced 5 minutes per day of non-walking time with 5 minutes per day of walking at moderate-to-vigorous intensity reduced their risk of TKA by 16%. Very light and light intensity walking had no effect. Similar results were found for patients with either radiographic or symptomatic knee OA. "Our findings suggest that even small changes in walking behaviour may delay the need for TKA in people with or at high risk of knee OA. Clinicians should consider encouraging these patients to go for a brisk walk for 5 to 10 continuous minutes each and every day," said Dr Hiral Master (University of Delaware, USA).

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Cytokine Blockade: Highly Efficacious in Psoriatic Arthritis

New data on IL-17 blockers in psoriatic arthritis demonstrates the long-term efficacy of these agents. Selective blockade of IL-22 is another effective treatment mode.

During the 2018 ACR/ARHP Annual Meeting, new long-term data from the FUTURE 1 trial confirms that the IL-17 blocker secukinumab provides sustained improvements in the signs and symptoms of psoriatic arthritis (PsA) up to 5 years [1]. A total of 460 patients entered a 3-year extension period following the initial 2-year study FUTURE 1. Over 80% of these patients completed the 5 years of the study. Patients could have the dose escalated from 150 to 300 mg and from 75 to 150/300 mg from week 156, based on the physician´s judgement. At the end of the observation period, 83% and 94% of PsA patients achieved total resolution of enthesitis and dactylitis, respectively [1]. Efficacy improved proportionately with dose escalation of secukinumab to 150 or 300 mg during the study. Clinical responses, e.g. ACR20 response, the primary endpoint of the MEASURE1 trial, were sustained or further improved through 5 years of treatment. The safety profile was consistent with that found in previous evaluations, with no new safety signals.

IL-23 blockade effective in dactylitis

In a phase 2 study, the selective IL-23 blocker guselkumab has shown to be effective in patients with active PsA [2]. In an analysis presented during the meeting, the effect of guselkumab on dactylitis in a subset of patients with dactylitis at baseline was evaluated [3]. At baseline, 81 of 149 patients presented with dactylitis. Patients treated with guselkumab during the 24 week double-blind treatment period had significantly greater reduction in dactylitis score at weeks 16 and 24 compared with placebo (Figure 5). In patients that continued guselkumab at week 24, this improvement in dactylitis persisted. The improvement in dactylitis was greater in ACR20/ACR50 responders vs non-responders in patients treated with guselkumab. As Prof. Dafna Gladman (University of Toronto, Canada) pointed out, this trial shows that guselkumab is efficacious in resolving symptoms of dactylitis, an effect that is correlated with improvement in joint symptoms.

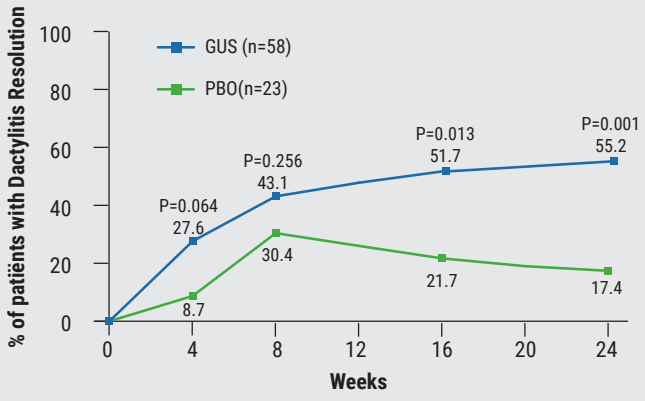
Etanercept beats methotrexate in psoriatic arthritis

For the first time, methotrexate and etanercept were tested for patients with PsA in a head-to-head comparison of monotherapy and a combination; both etanercept monotherapy and etanercept plus methotrexate showed a distinct superiority compared with methotrexate [4]. The international, phase 3, randomised, controlled trial examined ACR20 response at week 24 as primary endpoint and also watched for minimal disease activity and progressive joint damage. Included were 851 patients with active PsA according to the CASPAR criteria randomised into 3 groups. None of them had a prior treatment with biologics or methotrexate. Group 1 received a weekly dose of 50 mg etanercept plus 20 mg methotrexate (n=283), group 2 etanercept 50 mg plus placebo (n= 284) and group 3 methotrexate 20 mg plus placebo (284). Baseline characteristics were well balanced in all study arms.

The ACR20 response was more pronounced in patients treated with etanercept monotherapy or with the combination of etanercept and methotrexate (60.9% and 65.0% vs 50.7% with the methotrexate monotherapy, respectively). Minimal disease activity response at week 24 was significantly greater in the etanercept monotherapy and combination groups compared with the methotrexate monotherapy group (35.9% and 35.7% vs 22.9%, respectively). At week 48, the etanercept monotherapy group and combination group both showed less radiographic progression than the methotrexate monotherapy arm (mean change in modified total Sharp/van der Heijde score from baseline –0.04 and –0.01 vs 0.08). Overall, there were only minor differences between the etanercept monotherapy and the combination therapy group. Treatment was well tolerated with similar adverse event rates in the 3 study arms. Only nausea occurred more often with methotrexate. The most common serious adverse events were infections and infestations (1.1% of patients in the methotrexate monotherapy arm vs 2.8% of patients in the etanercept monotherapy arm, and 2.5% of patients in the combination arm).

As the authors pointed out, despite the fact that methotrexate is widely used in PsA, little clinical evidence exists to guide its use. In particular its benefit in addition to a TNF blocker remained unclear. The current findings demonstrate that adding methotrexate does not appear to increase the efficacy of etanercept monotherapy for most outcomes except an improvement in skin symptoms (i.e. improvement in psoriasis-affected body surface area and percentage of patients reaching clear or almost clear skin). These results support the use of etanercept as a monotherapy in PsA patients without skin manifestations.

Figure 5 Guselkumab leads to a fast and sustained improvement of dactylitis in patients with PsA [3]



P-values are based on Cochran-Mantel-Haenszel test.
Patients with dactylitis assessed based on imputed values with EE and missing data rules applied.

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Systemic Lupus Erythematosus: Less Complications due to Better Management

Socially and economically disadvantaged patients with systemic lupus erythematosus (SLE) benefit from treatment by a rheumatologist when early specialist access is facilitated. Thanks to modern, more tolerable immunosuppression regimens, complications like recurrent nephritis occur less often than two decades ago. The validation of a definition of low disease activity in SLE opens the door for a treat-to-target (T2T) principle in this disease.

Difficult-to-treat patients with SLE have a decreased risk of hospitalisation and a shorter length of stay in hospital, when their access to rheumatologic care is improved [1]. This was shown by a study presented by Dr Allen Anandarajah (University of Rochester Medical Center, USA). Previously, the researchers demonstrated that a small group of high-risk, high-cost patients accounts for the majority of hospitalisations among all lupus patients. In the current trial, the researchers tried to determine the impact of interventions to improve access to rheumatology care for these high-risk, high-cost SLE patients.

All study participants were high-risk patients, defined as lupus patients who required 3 or more hospital admissions over a 3-year period between 2013 and 2016. In July 2018, to improve access to rheumatology care, the University of Rochester Medical Center launched the IQ-LUPUS project (Improve Quality in Low-income, Underserved, Poor, Underprivileged SLE patients). The programme offers direct access to a nurse care coordinator and a social worker. To date, 54 patients are enrolled in IQ-LUPUS. In 2017, 16 high-risk, high-cost patients had 52 hospital admissions and a total length of stay of 231 days. In 2018, after the start of the programme, there were 17 high-risk, high-cost patients with only 36 hospital admissions and a total length of stay of 159 days. "Early results of IQ-LUPUS suggest that improved access to rheumatology care through innovative care coordination and special clinics can decrease hospitalisations and length of hospital stay for these high-risk, vulnerable patients," concluded Dr Anandarajah.

Less recurrent lupus nephritis thanks to more tolerable immunosuppressants

Lupus nephritis is a severe complication for patients with SLE with end-stage renal disease who undergo kidney transplant. Past studies have shown variable recurrence rates for these patients depending on patient characteristics, as well as immunosuppressive regimens. Currently, the standard post-transplant regimen consists of prednisone, mycophenolate mofetil, and tacrolimus compared with the previous standard regimen of prednisone, azathioprine, and cyclosporine. An analysis of lupus patients treated in a transplant centre set out to answer whether this could affect the outcome of patients [2]. Included in the analysis were 38 patients treated with kidney transplant due to end-stage renal disease from lupus nephritis between 2006 and 2017. Patient electronic medical records were reviewed retrospectively. Recorded were patient demographic information and transplant and dialysis-related information, including kidney biopsy, graft loss, and overall survival. The authors then examined the association between recurrent lupus nephritis, survival, and graft loss.

A total of 11% of patients had a biopsy-proven lupus nephritis recurrence. Ten patients (26%) had graft loss or death during the median follow-up time of 1,230 days. Patients with recurrent lupus nephritis showed a trend for increased risk of graft loss or death compared with recipients without recurrence. "In our practice, we are seeing less recurrence, and patients are doing better compared with what has been reported in the literature," concluded Prof. Debendra Pattanaik (University of Tennessee Health Science in Memphis, USA) during the presentation. "Graft loss secondary to recurrence of lupus should therefore be less of a concern when nephrologists and rheumatologists are considering renal transplant for their patients." As Prof. Pattanaik pointed out, the inclusion of mycophenolate mofetil into the standard post-transplant regimen might explain the findings, because this agent has also been used for treatment of proliferative lupus nephritis.

Fewer pregnancy complications

For women with SLE, pregnancy has long been considered high-risk and associated with both medical and obstetric complications. According to a retrospective analysis presented during the ACR/ARHP meeting, maternal and foetal mortality, along with important clinical outcomes, have improved in pregnancies of women with SLE during the last two decades [3].

Researchers used a National Inpatient Sample database from 1998-2014. They identified diagnoses and procedures using ICD-9 codes. The study included 87,065 pregnant women with SLE and 70,162,163 pregnant women without SLE who had been hospitalised in the USA during this 17-year time span. Although the SLE patients were older, had a higher maternal mortality, and higher intrauterine foetal death compared with those without SLE, maternal mortality as well as intrauterine foetal death fell over time. This decline was greater in patients with SLE than those without. "It is very encouraging to see steady improvement in maternal mortality and intrauterine foetal death, and to see that the improvements in fact outpaced improvements for non-SLE pregnancies," concluded Dr Bella Mehta (Hospital for Special Surgery, USA).

Low disease definition in systemic lupus erythematosus gets a late validation

A definition of low disease activity in SLE published 5 years ago [4] was validated by a prospective multicentre study presented during the ACR/ARHP meeting [5]. The definition was developed by the Asia Pacific Lupus Collaboration (APLC, Table 1). The organisation prospectively collected data from 1,735 SLE patients at 13 centres in 8 countries during May 2013-December 2016, with a median follow-up of 2.2 years, totalling 12,534 visits (with a mean interval of 0.34 ± 0.17 years).

Lupus low disease activity state (LLDAS) was achieved in 54.6% of observed visits; 78% of the patients achieved the LLDAS at least once in the follow-up period. Two-thirds of the patients had at least one sustained period of LLDAS of at least 3 months, and, overall, the enrolled patients spent 69% of the time in LLDAS. In the validation analysis presented by Dr Vera Golder (Monash University, Australia), the correlation was assessed between the amount of time that patients spent in the defined LLDAS and their subsequent clinical outcomes. When patients achieved LLDAS, their rate of subsequent flare or damage accrual was substantially reduced. Patients in LLDAS for at least half the time had a 51% relative reduced risk rate of subsequent flare and a 47% reduced rate of subsequent damage accrual (both differences P<0.01). Patients with a LLDAS of 3-6 months had a 57% reduced rate of damage accrual. The more time patients spent in continuous LLDAS, the lower was the rate of subsequent damage accrual. Patients with LLDAS sustained for more than 9 months and as long as 12 months had an 86% reduction in subsequent damage accrual. "Periods of sustained LLDAS that extended longer than a year continued to maintain a nearly 90% reduced rate of damage accrual," said Dr Golder. According to the authors, this LLDAS definition should now be tested in treat-to-target intervention studies.

Table 1 Lupus patients need to achieve the following criteria to be considered in a lupus low disease activity state (LLDAS) [3]

A SLEDAI score of 4 or less with no major organ involvement
A physician's global assessment of the patient of 1 or less on a 0-3 scale
No new disease activity
Maintenance on a prednisolone dosage of 7.5 mg/day or less
Maintenance on a standard immunosuppressive regimen

IL-12/23 blockade may be useful in lupus

The anti-IL12/23 monoclonal antibody ustekinumab is currently approved for the treatment of psoriasis, psoriatic arthritis, and Crohn´s disease. In a phase 2, clinical trial presented during the meeting, the efficacy and safety of this biologic was also tested in patients with SLE [6]. Patients with active SLE were randomised to receive ustekinumab or placebo on top of stable standard-of-care therapy for 24 weeks, followed by continued treatment with ustekinumab for all patients. The primary outcome of the trial was the proportion of patients achieving SLE response index (SRI)-4 response after 24 weeks of treatment.

"This widely used outcome for SLE trials was achieved by significantly more patients on ustekinumab than on placebo (62% vs 33%)," said Prof. Ronald van Vollenhoven (Academic Medical Center; Amsterdam Rheumatology and Immunology Center, the Netherlands). This result was sustained at 1 year in the ustekinumab group (63%). "Other outcomes like the physician´s global assessment or the number of joints with pain also showed differences favouring ustekinumab," said Prof. Van Vollenhoven. Of the patients who switched from placebo to ustekinumab at week 24, 54.5% achieved an SRI-4 response at 1 year. "I think the results of this trial are very encouraging and suggest that ustekinumab could

be an effective treatment for SLE," concluded Prof. Van Vollenhoven.

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Best of the Posters

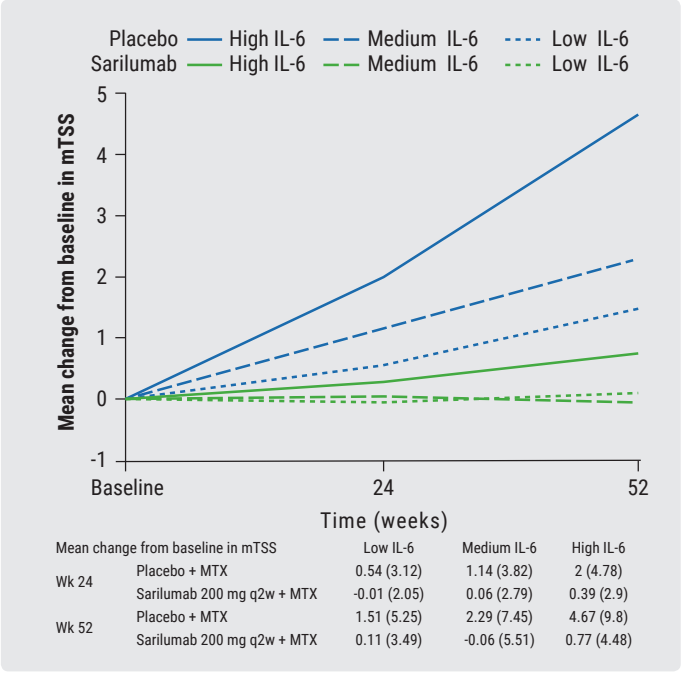
A post-hoc analysis of the MOBILITY and MONARCH identified IL-6 levels as a predictor for treatment response in rheumatoid arthritis, and IL-17 blocker ixekizumab has shown promising results in the treatment of axial spondyloarthritis compared with TNF-blockers. These results were presented during the late-breaking poster session at this year's ACR/ARHP meeting.

Sarilumab: increased response in rheumatoid arthritis patients with high IL-6 levels

The treatment possibilities for patients with rheumatoid arthritis (RA) are numerous. Thus, indicators that could predict treatment response in RA are increasingly important. The latest post-hoc analysis of the MOBILITY and MONARCH trials set out to show whether patients with high IL-6 serum concentration benefit more from the IL-6 inhibitor sarilumab. The analysis examined the association between IL-6 levels and the extent of response to RA treatment with sarilumab as monotherapy or combined with methotrexate in comparison to adalimumab or placebo [1]. In the MOBILITY trial, 1,193 RA patients were randomised to receive either 150 mg or 200 mg of sarilumab plus methotrexate every second week or placebo plus methotrexate at equal intervals. In the MONARCH trial, 300 patients were treated with either sarilumab 200 mg or adalimumab 40 mg every 2 weeks. Initially, all participants had their IL-6 levels tested. Radiographic as well as clinical response was evaluated between and within the different treatment regimen based on their initial IL-6 tertile. Low tertile values equalled normal IL-6 values, whereas >85% of high tertile presented IL-6 levels of 3 times the upper normal limit.

With a combination therapy of sarilumab 200 mg plus methotrexate, the odds ratio for reaching an ACR70 response at week 52 was 7.3 in the high tertile and only 1.9 in the low IL-6 group. Comparing baseline characteristics, patients of the low tertile had a lower mean C-reactive protein (10.5 mg/L), less mean joint damage, assessed in total Sharp/van der Heijde score (TSS 40.8), and lower disease activity (CDAI 38.3) compared with the mean values of the patients in the high tertile (C-reactive protein 36.4 mg/L, modified TSS 56.7, CDAI 43.0; Figure 6). The higher the baseline IL-6 tertile, the greater was the clinical and radiographic efficacy of sarilumab plus methotrexate compared to placebo plus methotrexate. Interestingly, in the group treated with placebo

Figure 6 Mean change from baseline in modified TSS with sarilumab 200 mg Q2W with methotrexate compared with methotrexate and placebo in the MOBILITY study [1]



Mean change from baseline in mTSS		Low IL-6	Medium IL-6	High IL-6
Wk 24	Placebo + MTX	0.54 (3.12)	1.14 (3.82)	2 (4.78)
	Sarilumab 200 mg q2w + MTX	-0.01 (2.05)	0.06 (2.79)	0.39 (2.9)
Wk 52	Placebo + MTX	1.51 (5.25)	2.29 (7.45)	4.67 (9.8)
	Sarilumab 200 mg q2w + MTX	0.11 (3.49)	-0.06 (5.51)	0.77 (4.48)

mTSS, modified Total Sharp Score.

plus methotrexate, patients in the high tertile developed more joint damage than those in the low tertile. The assessment of efficacy in high tertile in MONARCH revealed ACR20/70 of 89%/30% for sarilumab vs 52%/4% for adalimumab. Respective results in the low tertile were 64%/18% vs 58%/18%. In summary, a greater treatment response to sarilumab is to be expected in the presence of higher IL-6 levels before treatment.

Ixekizumab effective in axial spondyloarthritis patients nonresponsive to TNF inhibitors

In case of insufficient response to nonsteroidal anti-inflammatory drugs, TNF inhibitors are the therapy of choice in axial spondyloarthritis (axSpA). However, for patients who are intolerant or inadequate responders to TNF inhibitors, IL-17 blockers seem a more effective alternative [2]. This was shown by the phase 3 COAST-W study, in which the safety and efficacy of the IL-17 blocker ixekizumab was investigated in axSpA patients who were either intolerant to TNF inhibitors or showed inadequate response to treatment. The 316 enrolled participants had a very active axSpA with a mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 7.4. They were randomised to either 80 mg ixekizumab every 2 (Q2W) or every 4 weeks (Q4W), with either 80 mg or 160 mg starting dose (assigned 1:1) or placebo. Of the participants, 65.1% had not responded adequately to one and 24.8% to two prior TNF inhibitors, and 10.2% were intolerant. Primary endpoint was defined as an Assessment of SpondyloArthritis International Society (ASAS) 40 response at week 16. Mean duration of the disease symptoms at baseline was 16.7 years.

In the final assessment at week 16, the percentage of patients achieving the primary endpoint was 30.6% in patients treated with ixekizumab Q2W, 25.4% in patients treated with ixekizumab Q4W, and 12.5% in placebo. Patients were found to perform significantly better if they had baseline higher disease activity, functional impairment, reduced quality of life, spinal MRI inflammation, and high sensitivity C-reactive protein elevation. Mild and moderate adverse events occurred consistently across the arms. Serious adverse events were found in 4.8% of the placebo group, 3.1% of patients receiving ixekizumab Q2W, and 3.5% of patients receiving ixekizumab Q4W. Prof. Atul Deodhar (Oregon Health & Sciences University, USA) and his fellow researchers concluded that therapy with ixekizumab induced significant ameliorations in axSpA-patients with prior TNF inhibitor intolerance or non-responders.

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