Rheumatol Ther (2022) 9:705–719
https://doi.org/10.1007/s40744-022-00437-w

ORIGINAL RESEARCH

Responding to and Driving Change in Rheumatology: Report from the 12th International Immunology Summit 2021

Renaud Felten · Nicolas Rosine

Received: December 10, 2021 / Accepted: February 25, 2022 / Published online: March 12, 2022

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has accelerated changes to rheumatology daily clinical practice. The main goal of the 12th International Immunology Summit, held 25–26 June, 2021 (virtual meeting), was to provide direction for these active changes rather than undergoing change reactively in order to improve patient outcomes. This review describes and explores the concept of change in rheumatology clinical practice based on presentations from the Immunology Summit. Many of the changes to rheumatology practice brought about by the COVID-19 pandemic may be considered as having a positive impact on disease management and may help with the long-term development of more patient-focused treatment. Rheumatologists can contribute key knowledge regarding the use of immunosuppressive agents in the context of the pandemic, and according to the European League Against Rheumatism, they should be involved in any multidisciplinary COVID-19 guideline committees. New technologies, including telemedicine and artificial intelligence, represent an opportunity for physicians to individualise patient treatment and improve disease management. Despite major advances in the treatment of rheumatic diseases, the efficacy of available disease-modifying anti-rheumatic drugs (DMARDs) remains suboptimal and data regarding serological biomarkers are limited. Synovial tissue biomarkers, such as $CD68^{+}$ macrophages, have shown promise in elucidating pathogenesis and targeting treatment to the individual patient. In spondyloarthritis (SpA) or psoriatic arthritis (PsA), information regarding the effectiveness of the available agents with different mechanisms of action may be integrated to manage patients using a treat-to-target approach. Early diagnosis of SpA and PsA is important for optimisation of treatment response and long-term outcomes. Improving our understanding of disease pathogenesis and practice methods may help reduce diagnostic delays, thereby optimising disease outcomes in patients with rheumatic diseases.

R. Felten (✉)
Service de Rhumatologie and CNR RESO, Hôpitaux Universitaires de Strasbourg, 1, Avenue Molière, BP 83049, 67098 Strasbourg, France
e-mail: renaud.felten@chru-strasbourg.fr

N. Rosine
Service de Rhumatologie, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France

PLAIN LANGUAGE SUMMARY

The global COVID-19 pandemic has brought about several changes to the management of patients with rheumatic diseases, such as

rheumatoid arthritis, psoriatic arthritis or spondyloarthritis. Many of these changes are considered to have had a positive impact on rheumatology practice, including the potential use of virtual meetings rather than face-to-face consultations. Physicians are increasingly using new technologies to provide patients with individualised treatment. There is a need for more effective treatment options and strategies in patients with rheumatic diseases as well as ways of testing for biomarkers that may predict response to treatment. An improved understanding of the mechanisms underlying disease development may help rheumatologists to develop a new 'treat-to-target' approach that addresses the symptoms of the disease as well as their patients' preferences and quality of life. This may enable rheumatologists to improve their practice methods, thereby reducing diagnostic delays and optimising long-term outcomes in patients with rheumatic diseases.

Keywords: Ankylosing spondylitis; Biomarkers; COVID-19; Psoriatic arthritis; Rheumatology; Spondyloarthritis

Key Summary Points
Rheumatology daily practice has changed in response to the COVID-19 pandemic, with increased use of new technologies like telemedicine
These changes may allow physicians more opportunities to individualise patient treatment and improve outcomes
Synovial tissue biomarkers may help physicians to determine the patient's underlying pathogenesis and to adopt a 'treat-to-target' approach to patient management
Changes in rheumatology practice methods, combined with an improved understanding of disease pathogenesis, may lead to optimisation of disease outcomes in patients with rheumatic diseases

INTRODUCTION

The 12th International Immunology Summit, held virtually on 25 and 26 June 2021, and sponsored by UCB Pharma S.A., had an overarching theme of exploring the changes in the immunology healthcare landscape. The coronavirus disease 2019 (COVID-19) pandemic has challenged the medical profession, forcing the need to make changes in daily clinical practice. As a result of this unique healthcare scenario, two types of change have emerged: 'reactive change' and 'active change', with the latter referring to change that is intentionally introduced in response to the environment or clinical circumstances. The main learning objective of the summit was to provide direction for these changes rather than undergo them in order to improve patient outcomes. Although the human brain is 'wired' to be initially resistant to change, with effort and understanding, we can overcome this resistance so that change can be accepted as positive [1].

The aim of this review is to describe and explore the concept of change as applied to the clinical practice of rheumatology, based on the rheumatology-themed presentations given at the 2021 Immunology Summit. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors; therefore, ethical approval was not required.

CHANGES IN THE WAY RHEUMATOLOGISTS PRACTISE MEDICINE

Impact of COVID-19: The Reaction of the Immunology Community

The COVID-19 pandemic has changed the world, forcing rheumatologists to rethink the way they practise and work with patients and colleagues [2]. When social distancing measures are in place, rheumatologists need to work with their patients on a case-by-case basis to decide whether clinic visits are necessary.

Rheumatology associations, including the European League Against Rheumatism (EULAR), have released provisional recommendations for managing rheumatic diseases in the context of the pandemic [2]. Rheumatologists have become more reliant on e-health, meeting with colleagues and patients virtually rather than in person.

Some changes to rheumatology practice can be considered negative such as the reduction in almost all hospitals and outpatient clinics for all clinical activities, making it more difficult for both patients and physicians to follow the routine care or to perform a physical examination in patients with inflammatory arthritis [3]. However, many of these changes to rheumatology practice can be viewed as positive, with rheumatologists moving from old habits to choosing more effective, patient-focused methods. The pandemic has certainly redefined how we do things in our daily lives, and it is up to practitioners to define how these changes impact clinical practice.

In addition to changing the way they practise medicine, immunologists have made vital contributions to the global response to the COVID-19 pandemic [4]. These contributions include providing advice and education to the general public, government officials and leaders as well as countering and responding to incorrect information, contributing to vaccine and treatment research and publications, increasing the speed at which information is published while maintaining thorough peer review and organising virtual training, conferences, mentoring and webinars. The above-mentioned provisional EULAR recommendations [2] are an example of how rheumatologists have contributed to the pandemic response. Recognising that there was an understandable lack of high-quality scientific knowledge available for the COVID-19 pandemic, but also that rheumatologists and their patients required guidance, EULAR convened an international task force of experts to formulate provisional guidance for the management of patients with rheumatic and musculoskeletal diseases during the pandemic [2]. In the context of COVID-19, immunosuppressive treatments have gained significant attention, both negative and positive, and rheumatologists can contribute in-depth knowledge about these agents. For this reason, EULAR recommends that rheumatologists should be involved in any multidisciplinary COVID-19 guideline committees. For patients who are diagnosed with COVID-19, it is also crucial that rheumatologists are involved in the decision to continue or alter immunosuppressive treatment. Treating physicians may be tempted to discontinue any agents that are thought to impair viral clearance; however, it is just as important to consider the risk of a rheumatic disease flare. In addition, there is evidence to suggest that some treatments for rheumatic diseases, such as tocilizumab, baracitinib and anakinra, are also effective in managing patients with COVID-19-related cytokine storm [5].

Impact of New Technologies: New Allies

Rapid advancements in digital technology are transforming the way medicine is practised, and the COVID-19 pandemic has resulted in the accelerated adoption of many of these technologies.

Telemedicine is a subgroup of digital medicine, which is itself a subgroup of e-health, and can be defined as ‘the use of digital technologies for the remote transmission of medical data’. Chan and colleagues conducted a 10-week study of rheumatology teleclinics (telephone and video) during the pandemic, in which 396 patients were reviewed, 78% via telephone and 22% via video clinics (88% of the appointments were follow-up visits) [6]. The authors of this study noted that rheumatology consultations were often not patient-initiated and often required in-depth review and planning for the management of complex conditions. A list of criteria was developed for determining whether a patient or clinical scenario was suitable for a teleclinic (Table 1). Guidance was also given for the necessary equipment and structure of a teleclinic. The authors reported that most important decisions were able to be made via teleclinic visits (Fig. 1). The authors found the major benefit to be in triaging and streaming patients into the most suitable service for their

Table 1 Inclusion and exclusion criteria for rheumatology teleclinics [5]

Inclusion criteria
Patients whose condition is clinically stable with low disease activity scores, who are making good progress and doing well on DMARDs or biologics
Patients who already have a wide appointment interval (e.g. 12 months) and in whom not much new has happened between appointments
Patients requiring discussion of test results and proposed treatments/drugs after initial appointment
Osteoporosis referrals where patients require interpretation of DEXA and advice about treatment
Alternate clinics for patients requiring monthly escalation for early inflammatory arthritis
Patients requesting to be seen earlier than their set appointment—this allows accurate assessment of the degree of urgency required
Patients on remote monitoring who are completing their outcome scores online and with low disease activity
Patients not suitable for patient-initiated follow-up, where a teleclinic will enable assessment of their condition
Exclusion criteria
Patients who decline to have teleconsultation
Patients not in a location where they can speak confidentially
New patients being referred with a new problem; they should have FTF appointments unless there is a good reason for a teleclinic (e.g. symptoms suggest that accurate advice can be given in a teleclinic)
Patients with new symptoms that need clinical examination for accurate evaluation
Patients with existing conditions that need clinical examination for meaningful assessment (e.g. swollen joint counts in patients with RA)
Situations where patient confidence requires FTF consultation even if appropriate decisions could be made in a teleclinic. Often such patients require the reassurance of a clinical examination
Children aged < 18 years, unless a parent or guardian is available, and vulnerable adults
Patients who are unable to use or access IT or phone
Patients with communication difficulties (e.g. speech/hearing impairments, poor English if independent interpreter service not accessible)
Patients with impaired cognition, unless a relative or friend is available to speak on patient's behalf with patient's adequate consent

Reproduced from Chan A, et al. Future Healthc J. 2021;8(1):e27–e31. © Royal College of Physicians 2021 with permission
DEXA dual-energy x-ray absorptiometry, *DMARDs* disease-modifying anti-rheumatic drugs, *FTF* face to face, *IT* information technology, *RA* rheumatoid arthritis

requirements. Because the inclusion criteria for teleclinics were based on patient type and clinical indication, rather than COVID-19 risk, the protocol developed should translate well to long-term, post-pandemic use [6].

The main disadvantage of teleclinics is the potential for breaching patient confidentiality, as the physician is unable to be certain that no one else is listening to the patient during their consultation [6]. Other disadvantages include a

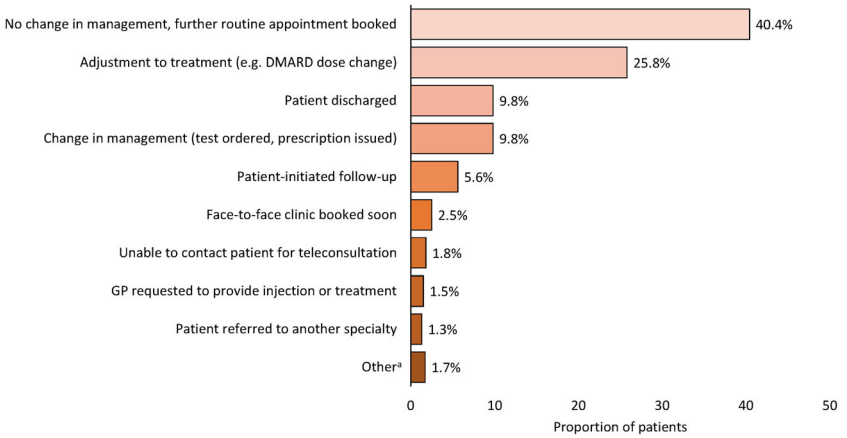


Fig. 1 Outcome of rheumatology teleclinics during the coronavirus disease 2019 (COVID-19) pandemic ($N = 396$) [5]. [a] 'Other' included: answering patient's question and offering a follow-up call in 1–2 weeks ($n = 3$, 0.8%); patient advised to see GP for issues unrelated to rheumatic disease ($n = 1$; 0.3%); patient referred to injection clinic ($n = 1$; 0.3%); patient asked to immediately go to an emergency department for evaluation ($n = 1$, 0.3%). *DMARD* disease-modifying anti-rheumatic drug, *GP* general practitioner

lack of access to suitable technology for some patients, the inability to physically examine patients or perform procedures and hearing or language barriers; however, the latter issues may be overcome with support of trusted translators, family members or friends, with the patient's consent [6].

Artificial intelligence (AI), including machine learning, is another new technology that is being developed and increasingly used in several fields of medicine, including rheumatology. Machine learning is the process of using algorithms that build mathematical functions or models that map input data (e.g. images or numerical data) to patient outcomes [7]. There are several challenges in rheumatology that could potentially be addressed through the use of AI [8]. For example, assessment of disease activity in rheumatoid arthritis (RA) usually relies on non-specific blood tests and subjective measures, such as patient self-reporting, whereas AI could be used to identify specific and sensitive disease biomarkers that provide objective measures of change and earlier prediction of disease flairs and treatment non-compliance [8]. Machine learning methods using electronic health record data have been used to accurately identify patients with RA [9] and predict complex disease outcomes [10]. Deep learning algorithms using convoluted neural networks have been developed to perform automated image interpretation [11], selection of informative ultrasound images in patients with RA [12] and detection of radiographic sacroiliitis in patients with axial spondyloarthritis (SpA) [13]. As research into AI use in rheumatology is expanding, the EULAR have provided several 'points to consider' when collecting, analysing and utilising large datasets for rheumatic and musculoskeletal disorders [14]. These 'points to consider' include the use of global, comprehensive and harmonised standards and open data platforms, interdisciplinary collaboration and training and consideration for how these large datasets and AI can be implemented in clinical practice [14]. In the near future, it is expected that AI will change how rheumatologists manage their patients in clinical practice, enabling them to predict treatment response, acquire improved image diagnostics and achieve faster recognition of disease pathology from patient history, laboratory test results and imaging data.

PATHOGENESIS AND TREATMENT OF RHEUMATIC IMMUNE-MEDIATED INFLAMMATORY DISEASES

The Role of Biomarkers and Histopathology in Rheumatoid Arthritis

Although major advances have been made in the treatment of patients with rheumatic diseases, the strategy for choice of treatment still generally relies on a 'trial and error' approach because of a lack of predictive biomarkers [15]. This approach is in contrast to other fields of medicine, such as oncology; an oncologist would not start treatment without first obtaining a tissue-based diagnosis and using predictive biomarkers to choose the most suitable therapy for an individual patient. Thus, there is an unmet need for reliable biomarkers to help predict response to rheumatology treatment. Extensive research has investigated possible serological biomarkers; however, the results have been disappointing so far. Anti-citrullinated peptide antibodies in RA remain the exception although the expert community is not unanimous on the value to be placed on them.

Faced with the impasse in serum biomarker identification, Orr and colleagues have developed an approach based on analysis of synovial tissue [16]. This approach provides an improved method for characterising localised inflammation, which may better reflect the mechanisms underlying the inflammatory process. In patients with RA, the preferred biopsy site is the knee due to its size and ease of accessibility. Many rheumatologists have concerns about the safety or necessity of the synovial biopsy approach [15]; however, mini-arthroscopy is a minimally invasive technique that can be used on an outpatient basis and may lead to improved treatment outcomes in some patients. In addition to staining for cellular markers and cytokines, next-generation techniques (e.g. next-generation sequencing) can be performed on synovial biopsy samples [17].

In addition to improving our understanding of the pathogenesis of rheumatic diseases, synovial tissue analysis may allow for the identification of early changes in biomarkers that potentially predict subsequent response to treatment. This may provide physicians with the ability to determine whether a particular agent is appropriate for an individual patient in the early stages of treatment. In one of the earlier synovial tissue analysis trials in patients with RA, Gerlag and colleagues found a marked reduction in the number of infiltrating macrophages, including $CD68^+$ and $CD163^+$ stained cells, in synovial tissue after 2 weeks of a clinically effective oral prednisolone regimen, whereas an increase in these cells was observed with placebo [18]. This group has performed similar analyses with several other DMARDs and found that reduction in $CD68^+$ macrophages as early as week 2 was correlated with clinical efficacy at week 12 (measured by change in 28-joint Disease Activity Score [DAS28]) [19]. This type of biomarker testing could save valuable time for physicians and patients, as they will not need to wait for a treatment response that may never happen.

Small, focused, mechanism-of-action studies can be conducted to compare different treatment options. These studies are typically relatively short in duration and involve collection of as many biological samples as possible, including synovial tissue, blood samples and biopsies of lymph nodes and bone marrow. Imaging and clinical data are also collected. Combining these findings can inform researchers about the common or unique pathways involved in inflammatory diseases as well as help to identify novel targets and predict response to treatment.

An example of such a study was a 24-week trial that investigated the effects of interleukin (IL)-12p40/IL-23p40 blockade with ustekinumab in 11 patients with psoriatic arthritis (PsA) [17]. Synovial tissue samples were taken by needle arthroscopy at baseline and weeks 12 and 24 and analysed via quantitative polymerase chain reaction (qPCR), RNA sequencing and immunohistochemistry. RNA sequencing results showed clear differences between patients with response to treatment (defined as

a 20% improvement in American College of Rheumatology criteria [ACR20]) and non-responders. Responders had an increased number of differentially expressed genes (DEGs; either down- or up-regulated) after 12 weeks of ustekinumab, whereas non-responders had a low number of DEGs. Surprisingly, ustekinumab appeared to have a very low impact on the IL-23/IL-17 pathway but was associated with modulation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and Wnt signalling pathways as well as potentially the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) pathway [17].

The R4-RA trial was the first biopsy-driven, randomised controlled trial in RA, in which the effect of rituximab was compared with that of tocilizumab over 48 weeks in 164 patients with an inadequate response to anti-tumour necrosis factor (TNF) treatment [20]. At baseline, patients were classified as either 'B-cell rich' or 'B-cell poor' based on synovial biopsy histology. To increase the accuracy of this stratification, patients were reclassified into the same categories based on the B-cell molecular signature following RNA sequencing of baseline synovial tissue. In B-cell rich patients, there was no significant difference between rituximab and tocilizumab in the proportion of patients with treatment response at week 16 (defined as a 50% improvement from baseline in Clinical Disease Activity [CDAI50%]). In patients stratified as B-cell rich by histology, the response rate was 39% with rituximab and 52% with tocilizumab ($P = 0.33$); respective values when stratified by RNA sequencing were 50% and 48% ($P = 0.89$). There was also no significant between-treatment difference in response rate in B-cell poor patients when stratified by histology (45% with rituximab vs. 56% with tocilizumab; $P = 0.31$); however, when stratified as B-cell poor by RNA sequencing, the response rate was significantly higher with tocilizumab versus rituximab (63% vs. 36%; $P = 0.035$) [20]. These results indicate the potential value of molecular-based stratification for guiding treatment choice in patients with RA, but also that RNA sequencing-based stratification of synovial tissue may better predict clinical response compared with histology-based classification.

Although synovial tissue analysis appears to be an extremely useful tool, the ideal scenario would be the availability of a non-invasive technique for visualising immunopathological features to guide treatment selection. Currently, several methods for distinguishing different types of synovial inflammation are under investigation such as histological assessment of infiltrative cellular populations or RNA sequencing [20].

Thus, it seems important that rheumatologists start to change their approach to managing patients by embracing emerging molecular biology and imaging approaches that allow patients to be classified by the presence of biomarkers before initiating treatment. The available data suggest that an integrated approach, using multiple testing types, may help to guide treatment choices, predict treatment response and possibly identify novel targets.

Advances in the Understanding of the Pathogenesis of Spondyloarthritis

There is known to be a strong link between SpA and gastrointestinal inflammation, as shown by the high proportion of SpA patients with inflammatory bowel disease (IBD; approximately 10%) or microscopic gastrointestinal inflammation (approximately 50%) [21]. The two hypotheses for this link include the 'causal' hypothesis, which suggests that gastrointestinal inflammation causes joint inflammation, and the 'correlative' or 'comorbid' hypothesis, in which the two types of inflammation co-exist (caused by similar immunological mechanisms) [21, 22]. The causal hypothesis does not explain how patients without gastrointestinal inflammation develop joint inflammation; however, it is possible that these patients have had transient, undetected gastrointestinal inflammation in the past [21].

Amongst immune-mediated inflammatory diseases (IMIDs), SpA is one of the most genetically driven. Genome-wide association studies have shown a large overlap between SpA and IBD at the genetic level, although there are also a number of loci linked to one disease and not

the other [21]. Type 3 cytokines, which are important for gastrointestinal barrier homeostasis, are dysregulated in patients with SpA, which leads to dysbiosis of the gut microbiome (Fig. 2) [21]. A study using murine models of collagen-induced arthritis showed preferential migration of T cells from the small intestine to synovial tissue during the early stages of arthritis formation, indicating that disruption of the gastrointestinal barrier function occurs prior to the development of inflammation, potentially making it the point where arthritis transitions from being an autoimmune to an inflammatory condition [23].

IL-17 plays an important role in both gastrointestinal and joint tissues; however, these effects appear to be tissue specific [21]. This is highlighted by the fact that IL-17 inhibitors are effective in patients with SpA, but are ineffective or possibly even deleterious for those with IBD. Current treatment options for patients with SpA are suboptimal, which highlights the need for further research, but also the importance of tailoring treatment to individual patients.

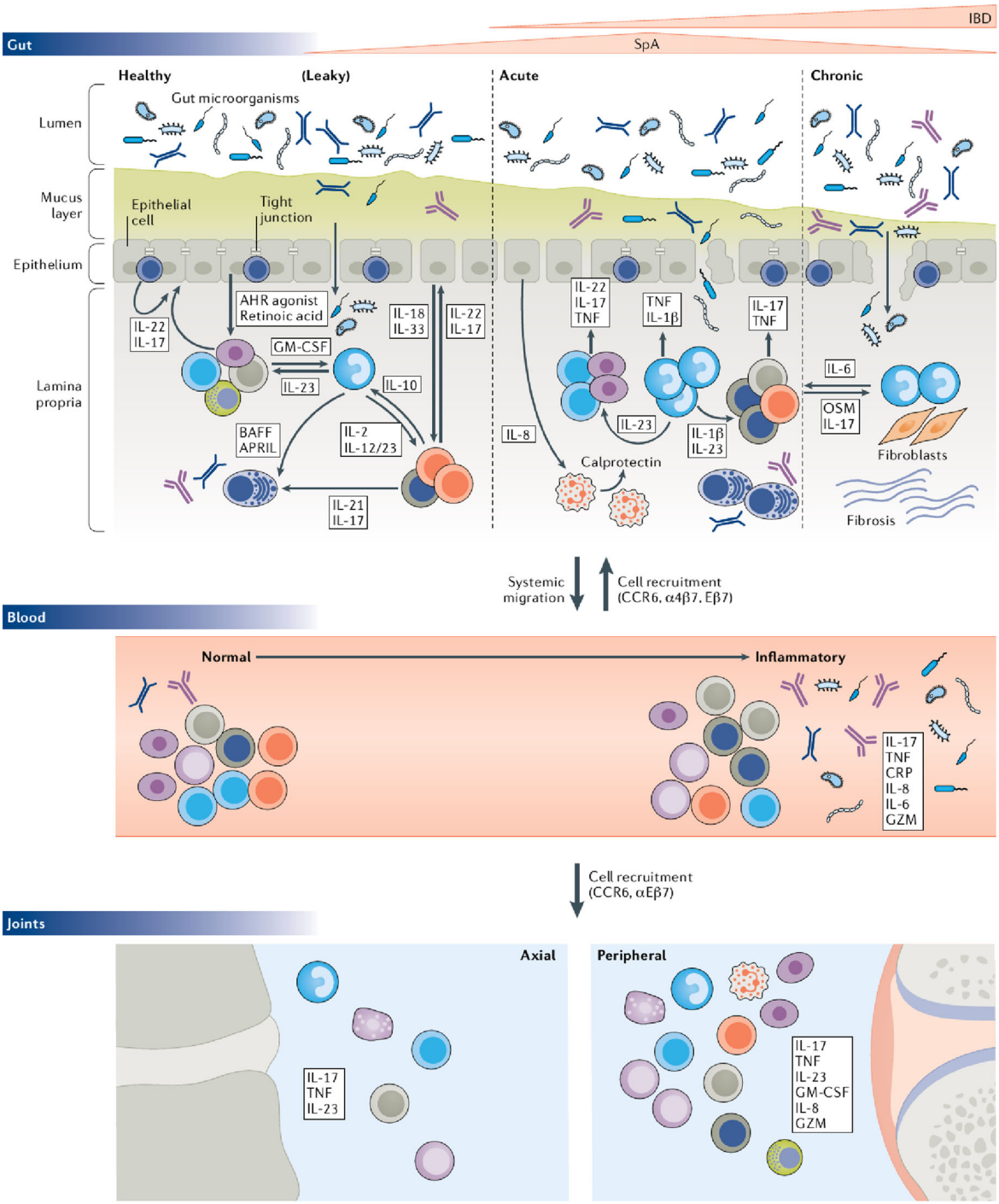
Fig. 2 Changes in the gastrointestinal-joint axis during inflammation in spondyloarthritis (SpA) [20]. In healthy gastrointestinal tissue (top left), innate and adaptive type 3 immune cells and intraepithelial lymphocytes maintain epithelial barrier homeostasis. In SpA (top centre left), gastrointestinal barrier 'leakiness' increases, and dysbiosis and subclinical inflammation occur. In early inflammatory bowel disease (IBD) and in most SpA cases (top centre right), subclinical acute inflammation is present, characterised by a loss of barrier function, increased recruitment of immune cells, enhanced type 3 immunity and increased antibody production. In IBD, and some cases of SpA (top right), chronic inflammation is present, and loss of epithelial integrity, transmural inflammation, tissue remodelling and fibrosis occur. In the blood (centre), changes to type 3 immune cells, cytokines and other soluble factors are detected. Immune cells and cytokines are detectable in bone and entheseal tissue in peripheral and axial joints (bottom) and in the synovial fluid of peripheral joints. *AHR* aryl hydrocarbon receptor, *APRIL* a proliferation-inducing ligand, *BAFF* B cell activating factor, *CCR6* CC chemokine receptor type 6, *CRP* C-reactive protein, *Ig* immunoglobulin, *IL* interleukin, *ILC3* type 3 innate lymphoid cell, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *GZM* granzyme M, *MAIT* mucosal associated invariant T, *NKT* natural killer T cell, *OSM* oncostatin M, T_H17 *cell* T helper 17 cell, T_{reg} *cell* regulatory T cell, *TNF* tumour necrosis factor. Reproduced with permission from Gracey E, et al. Nat Rev Rheumatol. 2020;6(8): 415–433. © Springer Nature 2020

Improving Outcomes: The 'Treat-To-Target' Approach in SpA and PsA

SpA and PsA are both complex diseases that can be difficult to treat. For patients with radiographical axial SpA or ankylosing spondylitis (AS), non-head-to-head clinical trials show that agents with varying mechanisms of action, including TNF inhibitors [24–27], IL-17A inhibitors [28, 29] and Janus kinase (JAK) inhibitors [30, 31], have broadly similar efficacy, with treatment response rates of 41–69% after 12–-16 weeks of treatment (based on a 20% improvement in Assessment Of Spondyloarthritis International Society [ASAS20] response criteria) (Fig. 3). This suggests that a large proportion of patients are non-responders, which represents an unmet need in this indication. Furthermore, agents with different mechanisms of action have differing effects on the extra-musculoskeletal manifestations of SpA. For IBD manifestations, effective agents include TNF inhibitors (except for etanercept) and the JAK inhibitor tofacitinib, while IL-17 inhibitors are ineffective, and the effects of some of the newer agents are not yet known.

For patients with psoriasis, TNF inhibitors and JAK inhibitors are effective, and IL-17 and IL-23 inhibitors are highly effective. Similarly, in patients with PsA, head-to-head trials have shown that the IL-17A inhibitors ixekizumab [32] and secukinumab [33] are significantly more effective at treating cutaneous psoriasis than the TNF inhibitor adalimumab, with similar results regarding articular manifestations. TNF inhibitors (except for etanercept) are effective for uveitis, but there are few data available for the other classes of agents.

The information regarding individual agents may be integrated to manage patients with rheumatic disease by using a treat-to-target approach. In the 48-week, open-label,


Gut
IBD
SpA
Healthy
(Leaky)
Acute
Chronic
Gut microorganisms
Lumen
Mucus layer
Epithelial cell
Tight junction
Epithelium
Lamina propria
AHR agonist
Retinoic acid
IL-22
IL-17
GM-CSF
IL-23
IL-10
IL-18
IL-33
IL-22
IL-17
BAFF
APRIL
IL-2
IL-12/23
IL-21
IL-17
IL-22
IL-17
TNF
IL-1β
IL-17
TNF
IL-8
IL-23
IL-1β
IL-23
Calprotectin
IL-6
OSM
IL-17
Fibroblasts
Fibrosis
Systemic migration
Cell recruitment (CCR6, α4β7, Eβ7)
Blood
Normal
Inflammatory
IL-17
TNF
CRP
IL-8
IL-6
GZM
Cell recruitment (CCR6, αEβ7)
Joints
Axial
IL-17
TNF
IL-23
Peripheral
IL-17
TNF
IL-23
GM-CSF
IL-8
GZM

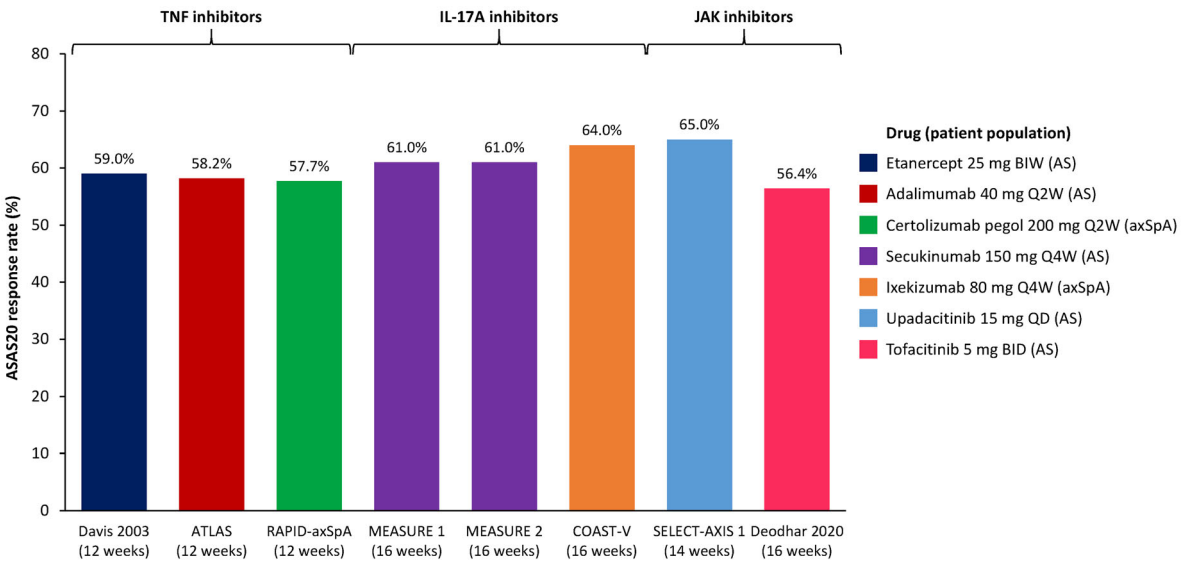


Fig. 3 Treatment response rates based on a 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) response criteria with tumour necrosis factor (TNF) inhibitors [23, 25, 26], interleukin (IL)-17A inhibitors [27, 28] and Janus kinase (JAK) inhibitors [29, 30] in clinical trials of patients with axial spondyloarthritis (axSpA), including patients with ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA). *BID* twice daily, *BIW* twice a week, *Q2W* once every 2 weeks, *Q4W* once every 4 weeks, *QD* once daily

randomised TIght COntrol of Psoriatic Arthritis (TICOPA) trial, the effect of standard care (with review every 12 weeks) was compared with that of tight control (review every 4 weeks, with treatment escalation if targets were not met) in patients with early PsA (N = 206) [34]. A significantly higher proportion of patients achieved the primary endpoint of ACR20 in the tight control group than in the standard care group as well as the secondary endpoints of ACR50, ACR70 and 75% improvement in Psoriasis Area and Severity Index (PASI75). However, the incidence of serious adverse events was higher in the tight control group, and the cost of treatment was higher [34].

In the open-label, randomised, 1-year Tight Control in Spondyloarthritis (TICOSPA) trial in patients with axial SpA (N = 160), the treat-to-target approach was not significantly better than standard care for the primary endpoint of a $\geq$ 30% improvement in the ASAS-Health Index (ASAS-HI; 47.3% vs. 36.1%, P = 0.07) [35]. However, several secondary endpoints were significantly better with the treat-to-target approach versus standard care, including Ankylosing Spondylitis Disease Activity Score (ASDAS) low disease activity, ASDAS clinically important improvement, ASAS40, ASAS20 and 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50). Furthermore, the treat-to-target approach had a similar safety profile but was more cost-effective compared with standard care [35].

When applying the treat-to-target approach to clinical practice, rheumatologists are required to address multiple issues, including axial, peripheral and extra-musculoskeletal manifestations, patient-reported outcomes and patient preferences. Physicians must consider all of these factors and apply treat-to-target principles. However, this should not be interpreted as a recommendation for a dogmatic approach, such as assigning a patient a 'score' and blindly treating them according to this score. It is also important to measure outcomes in order to optimise patient management. Additionally, patient and physician treatment targets do not always overlap, so this must be taken into account. It is hoped that the treat-to-target approach may help untangle the

complexity of these diseases; excellent physician-patient communication is essential for the successful implementation of this approach.

One of the best examples of the challenges associated with the treat-to-target approach is the management of female patients who wish to become pregnant, as many of the available antirheumatic medications are contraindicated in pregnancy and breastfeeding [36]. In current practice, it is no longer acceptable for pregnancy to limit patient care, particularly regarding biological therapy. In this case, the key to effective patient management is a planned pregnancy with supervision from a multidisciplinary team. This highlights how personalised medicine should begin by taking gender into account.

THE IMPORTANCE OF EARLY DIAGNOSIS OF SPA AND PSA

Technological advances in imaging and diagnostics mean that it is generally possible to diagnose rheumatoid diseases relatively soon after the onset of symptoms; however, long diagnostic delays still occur, particularly for patients with axial SpA, and delayed diagnosis and longer disease duration can be associated with poorer disease outcomes [37]. In several trials, a longer duration of symptoms was associated with a poorer response to treatment [38–40]; for example, in two randomised placebo-controlled trials of TNF inhibitors in patients with active AS, the proportion of patients who achieved BASDAI 50 after 12 weeks was 73% in those with a disease duration of $\leq$ 10 years versus 58% with disease duration of 11–20 years and 31% with a disease duration of $>$ 20 years [40]. A systematic review of 21 studies found that delays in diagnosing axial SpA was associated with a worse clinical outcome (BASDAI, BAS Metrology Index and BAS Functional Index), a higher prevalence of depression and a greater economic burden [41–44]. Similarly, a study in patients with AS found that patients who were 'work disabled' had a significantly longer diagnostic delay than those who were not, and for every year of diagnostic delay the risk of being work disabled increased by 6.6% [45].

Studies have indicated that early diagnosis and initiation of treatment may lead to improved treatment response. In four large placebo-controlled trials of etanercept or sulfasalazine in patients with AS, the proportion of patients with partial remission (defined as ASAS20) at Week 12 was highest in patients with the shortest disease duration [46]. Among etanercept recipients, partial remission was achieved by 35% of those with baseline disease duration of $\leq$ 2 years, 30% with a disease duration of 2–5-years, 28% with a disease duration of 5–10 years and 23% with a $>$ 10-year disease duration [46]. Furthermore, in a 5-year study of adalimumab use in patients with active AS, achievement of early remission (i.e. ASAS partial remission or ASDAS inactive disease after 12 weeks of treatment) was the strongest predictor of long-term sustained remission at 1 and 5 years [47].

Another advantage of early diagnosis is that prompt initiation of long-term anti-TNF treatment could inhibit radiographic spinal progression through reduction of disease activity in patients with radiographic axial SpA [48].

Early diagnosis of PsA is also important for long-term treatment outcomes. In a registry study of patients with early PsA, a shorter delay between symptom onset and diagnosis was one of the independent predictors of minimal disease activity after 5 years of follow-up [49]. Similarly, in studies of PsA patients with a $>$ 10-year disease duration, patients with a diagnostic delay of $>$ 6 months [50] or $>$ 1 year [51] had a poorer functional outcome, according to Health Assessment Questionnaire scores, than patients with a shorter diagnostic delay. An improved understanding of rheumatic disease pathogenesis and more patient-focused practice methods, as well as development of multidisciplinary strategies, may help to shorten the time to diagnosis in these patients.

CONCLUSIONS

Rheumatologists have made important changes to the way they manage patients, with the

COVID-19 pandemic accelerating the adoption of new practices and technology. Many of these changes can be seen as having a positive impact on disease management and will assist in the long-term development of more patient-focused practices.

Although major advances have been made in the treatment of rheumatic IMIDs, the efficacy of the available agents is still suboptimal, highlighting the need for a better understanding of the pathogenesis of these complex diseases. Research into serological biomarkers has yielded disappointing results; however, synovial tissue biomarkers have shown promise in both determining the underlying pathogenesis and targeting treatment to individual patients. Our improved understanding of the varying effectiveness of certain agents for different IMID symptoms may aid in the implementation of a treat-to-target approach, which has shown promise in patients with PsA and SpA. It is also hoped that improvements in disease understanding and practice methods may help to reduce diagnostic delays, thereby helping to optimise disease outcomes in these patients.

ACKNOWLEDGEMENTS

Funding. Support for third-party writing assistance for this manuscript was provided by UCB Pharma, France.

Medical Writing and Editorial Assistance. The authors thank Toni Dando and Sarah Greig, PhD, of Springer Healthcare Communications, who wrote the outline and first draft of the manuscript, respectively. This medical writing assistance was funded by UCB Pharma, France.

Authorship. The named authors of this article meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Renaud Felten and Nicolas Rosine were both involved in the selection of the content for coverage in this review for the plan of the paper and the revision of successive drafts. Both authors approved the final version for submission.

Prior Presentation. This article is based on rheumatology-themed presentations given by the author at the 12th International Immunology Summit, held virtually on 25 and 26 June 2021 and sponsored by UCB Pharma S.A. The content of the presentations and this article are based on work that has been previously published.

Disclosures. Renaud Felten and Nicolas Rosine have both received honoraria from UCB France, but have no other financial disclosures to declare.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors; therefore, ethical approval was not required.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. Berry W. Changing for a change. 2016. Psychology Today. https://www.psychologytoday.com/us/blog/the-second-noble-truth/201610/changing-change. Accessed 20 July 2021.
2. Landewé RB, Machado PM, Kroon F, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020;79:851–8.
3. Lubrano E, Scriffignano S, Perrotta FM. Rheumatology care in the face of COVID-19. Rheumatol Ther. 2020;7(3):425–8.
4. Osier F, Ting JPY, Fraser J, et al. The global response to the COVID-19 pandemic: how have immunology societies contributed? Nat Rev Immunol. 2020;20:594–602.
5. Elemam NM, Maghazachi AA, Hannawi S. COVID-19 infection and rheumatoid arthritis: mutual outburst cytokines and remedies. Curr Med Res Opin. 2021;37:929–38.
6. Chan A, Suarez A, Kitchen J, Bradlow A. Teleclinics in rheumatology introduced during the first lockdown phase of the COVID-19 pandemic of 2020. Fut Healthc J. 2021;8:e27–31.
7. Hügle M, Omoumi P, van Laar JM, Boedecker J, Hügle T. Applied machine learning and artificial intelligence in rheumatology. Rheumatol Adv Pract. 2020;4:5.
8. Kothari S, Gionfrida L, Bharath AA, Abraham S. Artificial intelligence (AI) and rheumatology: a potential partnership. Rheumatology. 2019;58:1894–5.
9. Maarseveen TD, Meinderink T, Reinders MJT, et al. Machine learning electronic health record identification of patients with rheumatoid arthritis: algorithm pipeline development and validation study. JMIR Med Inform. 2020;8:e23930.
10. Norgeot B, Glicksberg BS, Trupin L, et al. Assessment of a deep learning model based on electronic health record data to forecast clinical outcomes in patients with rheumatoid arthritis. JAMA Netw Open. 2019;2:e190606.
11. Stoel B. Use of artificial intelligence in imaging in rheumatology - current status and future perspectives. RMD Open. 2020;6:e001063.
12. Cipolletta E, Fiorentino MC, Moccia S, et al. Artificial intelligence for ultrasound informative image selection of metacarpal head cartilage. A pilot study. Front Med. 2021;8:589197.
13. Bressem KK, Vahldiek JL, Adams L, et al. Deep learning for detection of radiographic sacroiliitis: achieving expert-level performance. Arthritis Res Ther. 2021;23:106.
14. Gossec L, Kedra J, Servy H, et al. EULAR points to consider for the use of big data in rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2020;79:69–76.
15. Pitzalis C, Choy EHS, Buch MH. Transforming clinical trials in rheumatology: towards patient-centric precision medicine. Nat Rev Rheumatol. 2020;16:590–9.
16. Orr C, Vieira-Sousa E, Boyle DL, et al. Synovial tissue research: a state-of-the-art review. Nat Rev Rheumatol. 2017;13:463–75.
17. Fiechter RH, de Jong HM, van Mens LJJ, et al. IL-12p40/IL-23p40 blockade with ustekinumab decreases the synovial inflammatory infiltrate through modulation of multiple signaling pathways including MAPK-ERK and Wnt. Front Immunol. 2021;12:611656.
18. Gerlag DM, Haringman JJ, Smeets TJ, et al. Effects of oral prednisolone on biomarkers in synovial tissue and clinical improvement in rheumatoid arthritis. Arthritis Rheum. 2004;50:3783–91.
19. Wijbrandts CA, Vergunst CE, Haringman JJ, Gerlag DM, Smeets TJ, Tak PP. Absence of changes in the number of synovial sublining macrophages after ineffective treatment for rheumatoid arthritis: Implications for use of synovial sublining macrophages as a biomarker. Arthritis Rheum. 2007;56:3869–71.
20. Humby F, Durez P, Buch MH, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. Lancet. 2021;397:305–17.
21. Gracey E, Vereecke L, McGovern D, et al. Revisiting the gut-joint axis: links between gut inflammation and spondyloarthritis. Nat Rev Rheumatol. 2020;16:415–33.

22. Di Jiang C, Raine T. IBD considerations in spondyloarthritis. Ther Adv Musculoskelet Dis. 2020;12: 9410.

23. Tajik N, Frech M, Schulz O, et al. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. Nat Commun. 2020;11:1995.

24. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54:2136–46.

25. Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis. 2005;64:1557–62.

26. Davis JC Jr, Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003;48:3230–6.

27. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2014;73:39–47.

28. Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med. 2015;373:2534–48.

29. van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet. 2018;392:2441–51.

30. van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet. 2019;394:2108–17.

31. Deodhar A, Sliwinska-Stanczyk P, Xu H, et al. Tofacitinib for the treatment of adult patients with ankylosing spondylitis: primary analysis of a phase 3, randomized, double-blind, placebo-controlled study [abstract L11]. Arthritis Rheumatol. 2020;72: 2.

32. Mease PJ, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis. 2020;79:123–31.

33. McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet. 2020;395:1496–505.

34. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015;386: 2489–98.

35. Molto A, López-Medina C, Van den Bosch FE, et al. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. Ann Rheum Dis. 2021;80:1436–44.

36. Talabi MB, Himes KP, Clowse MEB. Optimizing reproductive health management in lupus and Sjogren's syndrome. Curr Opin Rheumatol. 2021;33(6):570–8.

37. Poddubnyy D, Sieper J. Diagnostic delay in axial spondyloarthritis—a past or current problem? Curr Opin Rheumatol. 2021;33:307–12.

38. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013;72:815–22.

39. Rudwaleit M, Gensler LS, Deodhar A, et al. Earlier treatment of non-radiographic axial spondyloarthritis with certolizumab pegol results in improved clinical outcomes [abstract FRI0408]. Ann Rheum Dis. 2019;78:891.

40. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis. 2004;63: 665–70.

41. Abdelrahman FI, Mortada M. Impact of application of asas criteria for axial spondyloarthritis on the diagnostic delay in Egyptian patients [abstract AB0858]. Ann Rheum Dis. 2018;77:1556.

42. Aggarwal R, Malaviya AN. Diagnosis delay in patients with ankylosing spondylitis: factors and outcomes–an Indian perspective. Clin Rheumatol. 2009;28:327–31.

43. Fitzgerald G, Gallagher P, O'Sullivan C, et al. Delayed diagnosis of axial spondyloarthropathy is

associated with a higher prevalence of depression [abstract 112]. Rheumatology. 2017;56:93–4.

44. Hajialilo M, Ghorbanihaghjo A, Khabbazi A, Kolahi S, Rashtchizadeh N. Ankylosing spondylitis in Iran; late diagnosis and its causes. Iran Red Crescent Med J. 2014;16:e11798.

45. Gunasekera W, Shaddick G, Jobling A, Smith A, Sengupta R. Diagnostic delay worsens mobility and work disability in ankylosing spondylitis [abstract AB0735]. Ann Rheum Dis. 2014;73:1046.

46. Baraliakos X, Koenig AS, Jones H, Szumski A, Collier D, Bananis E. Predictors of clinical remission under anti-tumor necrosis factor treatment in patients with ankylosing spondylitis: pooled analysis from large randomized clinical trials. J Rheumatol. 2015;42:1418–26.

47. Sieper J, van der Heijde D, Dougados M, Brown LS, Lavie F, Pangan AL. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. Ann Rheum Dis. 2012;71:700–6.

48. Molnar C, Scherer A, Baraliakos X, et al. TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: results from the Swiss Clinical Quality Management cohort. Ann Rheum Dis. 2018;77:63–9.

49. Theander E, Husmark T, Alenius GM, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis. 2014;73:407–13.

50. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2015;74:1045–50.

51. Tillett W, Jadon D, Shaddick G, et al. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. Ann Rheum Dis. 2013;72:1358–61.