Review

One year in review 2021: axial spondyloarthritis

C. Cardelli[1], S. Monti[2], R. Terenzi[3], L. Carli[1]

[1]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy;
[2]University of Pavia and IRCCS Policlinico San Matteo Foundation, Pavia, Italy;
[3]USL Toscana Centro, Florence, Italy.

Chiara Cardelli, MD
Sara. Monti, MD
Riccardo Terenzi, MD
Linda Carli, MD

Please address correspondence to:
Linda Carli,
Reumatologia, Dipartimento di Medicina Clinica e Sperimentale,
Università di Pisa,
Via Roma 67,
56126 Pisa, Italy.
E-mail: 81clinda@gmail.com

Received on September 30, 2021; accepted in revised form on October 20, 2021.

Clin Exp Rheumatol 2021; 39: 1272-1281.

Key words: axial spondyloarthritis, clinical picture, quality of life, imaging, therapy

Competing interests: none declared.

ABSTRACT

Axial spondyloarthritides (axSpA) are a group of systemic inflammatory rheumatic diseases with a broad spectrum of clinical manifestations and typical imaging features, rarely accompanied by laboratory abnormalities. They can be classified into a so-called non-radiographic form (nr-axSpA), unlike the radiographic one, because magnetic resonance imaging may show specific inflammatory lesions when conventional radiology is not able to highlight them. Inflammatory involvement of the axial skeleton tends to associate typically with new bone formation and peripheral joints may also be affected. Patients with axSpA are at higher risk of developing some typical extra-articular manifestations, particularly, acute anterior uveitis, psoriasis and inflammatory bowel disease. In this paper we review the literature on axSpA of 2019 and 2020 (Medline search of articles published from 1st January 2019 to 31st December 2020).

Introduction

Axial spondyloarthritides (axSpA) are a group of systemic inflammatory rheumatic diseases with a broad spectrum of clinical manifestations and typical imaging features, rarely accompanied by laboratory abnormalities. They can be classified into a so called non-radiographic form (nr-axSpA), different from the radiographic one (r-axSpA), because magnetic resonance imaging (MRI) may show specific inflammatory lesions that conventional radiology is not able to detect. R-axSpA are comparable to the classical ankylosing spondylitis (AS) that is genetically strongly associated with the major histocompatibility complex class 1 antigen HLA-B27. Inflammatory involvement of the axial skeleton tends to associate typically with new bone formation and peripheral joints may also be affected. Patients with axSpA may develop some typical extra-articular manifestations, particularly acute anterior uveitis (AAU), psoriasis (PsO) and inflammatory bowel disease (IBD). Moreover, axSpA represent a risk factor for the onset of comorbidities, above all, cardiovascular (CV) diseases, mood disorders, osteoporosis and malignancies. Such a complex clinical picture may easily compromise the quality of life (QoL) of patients. The therapeutical armamentarium of axSpA has been enriched in recent years, particularly due to advances in the knowledge of the immunological mechanisms at the basis of the disease, with the possibility of optimising the quality of care (QoC) of this group of patients and, consequently, their clinical outcomes (1-4). In this paper we review the literature on axSpA of 2019 and 2020 (Medline search of articles published from 1st January 2019 to 31st December 2020). Taking into account the historical period we are dealing with, we considered it appropriate to dedicate a particular section of this paper to the available literature data on COVID19 and axSpA.

Methods

Following our regular annual reviews on different aspects of rheumatology (5-12) we will here provide a critical digest of the recent literature on AxSpA of 2019 and 2020 (Medline search of articles published from 1st January 2019 to 31st December 2020).

Epidemiology

A number of different studies assessed the prevalence of SpA in the latest year underling the clinical and radiologic differences among entities of the group. A retrospective study from the Lazio region of Italy suggested that AS patients had longer disease history, were older and with a higher BMI than those with nr-axSpA, confirming that MRI features were different between the two conditions (13). A study carried out in Spain

in 2020 estimated an AS prevalence of 0.26% in the general population, which is comparable to other European countries (14). Moreover, the incidence of AS and SpA has been monitored in Denmark from 2000 to 2013, finding that patients diagnosed with both conditions increased in that period. However, the percentage of patients with SpA was significantly higher in the period from 2010 to 2013, suggesting an increased diagnostic awareness of the condition in the last few years (15).

Pathogenesis

Compared to the last *One year in review* (4), the most significant updates available on the pathogenesis of SpA could be the following.

As well known, the presence of HLA-B27 is the main genetic factor implicated in disease susceptibility. Consistent with this, in three different cohorts, a positive family history of SpA did not show an independent association with a diagnosis of axSpA, regardless of HLA-B27 status (16).

According to French DESIR cohort data, one locus of the IL23R gene, and specifically the single nucleotide polymorphism (SNP) rs1004819, appeared associated both with sacroiliac joints inflammation detected by MRI and with Spondyloarthritis Research Consortium of Canada scores in early onset SpA (17). The involvement of the complement system is supported by different plasmatic concentration of lectin pathway proteins in axSpA patients with respect to healthy controls (HCs). In particular, in a Danish cohort, H-ficolin, L-ficolin and collectin liver 1 levels were significantly higher in axSpA patients than in HCs, while collectin kidney 1 was significantly lower (18). Regarding environmental factors, smoking showed an association with the occurrence of uveitis in axSpA patients, according to a Portuguese cross-sectional study (19).

Clinical picture and biomarkers

Ax-SpA are a heterogeneous group of diseases in which both inflammatory involvement and consequently bone formation might regard not only spine, but also peripheral sites.

Taking into account the clinical impact of bone formation in SpA patients, the possibility to identify parameters associated to a higher risk of radiographic progression gained a central role in clinical research. Recently, Rademacher *et al*. found that altered baseline serum levels of leptin, HMW-APN and VEGF were related to a small but significant risk of a spine radiographic progression in AS patients, evaluated as a worsening on the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (20). Two different studies on AS patients showed a longer disease duration might represent a significant risk factor for the development of both syndesmophytes and peripheral arthritis (21, 22). Interestingly, a Chinese study underlined that an older age, HLA B27 positivity and a history of inflammatory bowel disease were related to a higher risk of developing uveitis in SpA patients (23).

In recent years, researchers have focused their attention on links between serum biomarkers (BM) and AS disease activity. In particular, they found the fibrinogen/albumin ratio (24) and altered values of the neutrophil-lymphocyte rate (25) and the platelet-lymphocyte rate (25, 26) could be considered as potential new BM of AS activity. Finally, a meta-analysis by Song *et al*. demonstrated that AS patients have higher red cell distribution widths and that it is positively associated with CRP levels (26).

Take home messages

- Altered baseline serum levels of leptin, HMW-APN and VEGF could be risk factors for radiographic progression in AS (20);
- Disease duration could be a risk factor for the development of syndesmophytes and for peripheral arthritis onset (21, 22);
- Some newly onset serological and haematological BM seem to be associated with disease activity in AS (24-26).

Imaging

Conventional radiology

Conventional radiology was found to be a useful tool for the evaluation of Achilles tendon enthesitis, according to a study conducted by Kim *et al*.; in particular, they found bone erosions, retrocalcaneal recess obliteration and swollen posterior soft tissue were strongly associated with current painful posterior heels (27). In a Swiss cohort of patients with both nr-axSpA and r-axSpA, a 2-year study of radiographic progression showed structural damage, measured by mSASSS, was significantly lower in the first group (28). Interestingly, syndesmophytes development seemed to be usually preceded by sacroiliitis onset. Llop *et al*. evaluated the performance of an extended mSASSS, incorporating information also from anteroposterior lumbar radiographs; it seemed able to detect additional patients with radiographic progression over two years, not identified by conventional mSASSS score (29).

Computed tomography

Stal *et al*. evaluated the facet joint ankylosis detection and progression on whole spine low-dose computed tomography (ldCT) in r-axSpA, detecting that both facet joint ankylosis and its progression were more frequent in the thoracic spine (30). Very interestingly, the authors found that syndesmophythes were the lesions most responsible for the radiographic damage accrual.

According to another study, ldCT revealed radiographic changes in a significant proportion of nr-axSpA and was highly specific for axSpA; the authors also found that both MRI-structural lesions and MRI-bone marrow oedema were less specific for axSpA than ldCT, while MRI-bone marrow oedema was confirmed to be the most sensitive test for nr-axSpA (31).

Ultrasonography

Ultrasound (US) is known to have a central role in the evaluation of peripheral involvement in axSpA. US study of calcaneal and quadriceps entheses was found to be able to distinguish AS patients from healthy controls in a cross-sectional study, showing worse scores of the Madrid Sonographic Enthesitis Index with bone erosion of the calcaneal enthesis, bone erosion and thickening of the plantar fascia and the presence of calcification in the quadriceps enthesis (32).

The evaluation of the Achilles tendon showed similar findings in AS and nr-axSpA patients for entheseal calcification and bone profile scores, while tendon echotexture score in AS patients was higher than in the nr-axSpA group (33). Interestingly, this study demonstrated a positive correlation between power Doppler US and MASES scores in the AS group.

Another preliminary study showed no significant differences in terms of stiffness of the Achilles tendon in AS patients treated with TNF-α inhibitors (TNFi) for two years compared to controls; however, an increased thickness in the middle third of the tendon in the AS group was observed (34).

Arslan Alhussain *et al*. found PsA patients seemed to have a higher entheseal insertion US damage score than AS patients; although, no significant differences were described for US inflammation score between the two groups (35).

Wink *et al*. showed the US evaluation of the hip joints may identify inflammatory lesions in up to 17% of patients with an active AS, with no correlation to hip joints pain (36). Moreover, they found the US monitoring of TNFi therapy in this cohort could reveal an improvement of inflammatory hips involvement, with a decrease in the total amount of inflammatory lesions after six months of treatment. According to a study by Rosa *et al*., US could be a useful diagnostic tool to detect sacroiliitis in patients with inflammatory back pain (37).

Magnetic resonance imaging

A magnetic resonance imaging (MRI) study on axSpA patients found a correlation between MRI inflammatory lesions of facet and costovertebral joints and a restricted spinal mobility and functional impairment respectively evaluated with Bath Ankylosing Spondylitis Metrology Index (BASMI) and Bath Ankylosing Spondylitis Functional Index (BASFI) (38). Interestingly, therapy with TNFi may be able to improve the impairment assessed by BASMI and associated with MRI-detected lumbar spinal inflammation in AS (39).

Yang *et al*. found a positive correlation between the presence of bone marrow oedema in SI joints and pain VAS score, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), CRP, IL-1β, IL-17 and TNF-α levels in AS patients. In their cohort of patients, a quick decrease in sacroiliac oedema could predict a better treatment response to etanercept (ETN) (40).

Kang *et al*. analysed the association between trabecular bone score (TBS), measured at the lumbar spine and new bone formation in AS patients, finding a significant correlation between low TBS and new bone formation, regardless of the presence of fat metaplasia on MRI (41).

Furthermore, inflammation on spinal MRI, defined as the presence of bone marrow oedema, was negatively correlated with TBS, but not with bone mineral density (42). In this study conducted by Jung *et al*., the severity of MRI local bone inflammation was associated with poor bone quality and a high risk of fracture.

Baraliakos *et al*. studied fatty lesions on MRI by immunohistological analysis of vertebral body biopsies of AS patients compared to patients with degenerative disc disease (DDD): interestingly, they found adipocytes as the most frequently detected cells in AS and inflammatory mononuclear cells in DDD, with changes in cellular homeostasis towards diminution of osteoclasts and higher osteoblastic activity in the bone marrow of AS patients (43).

Advanced MRI imaging techniques could be useful in the assessment of disease activity and damage in axSpA patients. The MRI volumetric interpolated breath-hold examination showed a higher sensitivity than T1-weighted MRI in identifying erosive damage in the SI joints, especially in younger patients (44). According to a study by Shi *et al*., diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE-) MRI resulted useful tools to evaluate the degree of active changes in AS inflammation and treatment effects in patients with early AS (45).

Take home messages

- Conventional radiology can be useful not only to highlight structural damage accrual, but also to study the Achilles tendon and its enthesis (27-29);
- ld-CT is gaining a central role in the evaluation of not only chronic, but also active lesions in axSpA (30, 31);
- US confirms its ability to identify activity and damage signs on both tendons and enthesis in patients with SpA, also comparing groups of patients who differed for the diagnosis or for the therapy (32-35);
- US could be useful also in evaluating joint involvement in AS, even for detecting sacroiliitis (36, 37);
- MRI-detected spinal inflammation seems to correlate with BASMI and BASFI (38, 39);
- TBS seems to be negatively correlated with both new bone formations and bone marrow oedema detected with MRI studies, thus confirming a higher risk of osteoporosis and fractures in axSpA (41, 42);
- New MRI imaging techniques could give new insights into the pathogenesis of axSpA and could help to better assess disease activity (43-45).

Comorbidities

During the past months, a number of publications have focused on the impact of comorbidities in patients with SpA. The analysis of a large dataset of AS patients showed hypertension, diabetes, heart disease, depression and fibromyalgia were the most frequent comorbidities; interestingly an African-American origin seemed to be a risk factor for both a severe disease and the development of diabetes, depression and heart disease (46). Zhao *et al*. found AS and nr-axSpA have a similar burden and frequency of comorbidities, despite a significantly lower mean age of patients with nr-axSpA (47).

A number of studies assessed the frequency and risk factors for cardiovascular (CV) comorbidities. Recent evidence suggests that the risk for venous thromboembolism is increased in patients with AS, especially during the first year from diagnosis (48). Data from the ASAS-COMOSPA suggested the development of hypertension correlates with the disease duration, the presence of axial-only SpA, but not with the use of NSAIDs (49). In contrast,

another large study on patients with AS reported an association between the continuous use of NSAIDs and the occurrence of incident hypertension (50). The Spanish prospective CARMA project, including patients with inflammatory rheumatic diseases, reported that the cumulative incidence of the first CV event was highest in patients with AS, in particular, if male, older with a systolic hypertension and a longer disease duration (51). A 5-year follow-up study on AS patients identified elderly males with previous conductive disturbances, longer symptoms duration and concomitant medications suggestive of underlying CV disease (antiplatelets and beta-blockers) as those at higher risk of developing cardiac conduction disturbances (52). Another recent publication supporting similar findings reported AS, especially in younger males, as a novel risk factor for atrial fibrillation on a nationwide population-based study conducted in Korea (53). Moreover, left ventricular systolic myocardial function has been found to be significantly lower in AS patients than controls (54). Whether this leads to increased CV risk needs to be clarified by further studies.

Several studies have been published recently concerning the association between SpA and psychological issues, particularly depression (55, 56). Questionnaires performed on a sample of 680 patients demonstrated that approximately half of them were at risk of developing mental disorders (*e.g.* depression and anxiety) and the risk was strictly associated with the level of disease activity (57).

Another frequent comorbid condition in SpA is gastrointestinal complaints. While inflammatory bowel disease is a matter of particular concern in these patients, patients with SpA have been reported to often complain of gut symptoms meeting irritable bowel disease criteria (up to 30% of patients), particularly reported in female patients with a concomitant fibromyalgia (58).

The risk of cancer in patients with SpA is considered generally low, with a good safety profile of the treatment used for the management of the disease. The risk of highly prevalent cancers (colorectal or lung cancer) on a large cohort of patients with AS has been found to be lower than expected; nevertheless, the risk of melanoma, renal cell cancer, bladder, breast and prostate was increased (59). Another study conducted in Korea also reported male reproductive system cancers and pancreatic cancer to be more frequent in patients with SpA (60).

Another concern in the management of SpA, particularly related to the prolonged use of NSAIDs, is the development of end-stage-renal disease. Several studies have recently explored the risk of renal failure in patients with AS suggesting an overall low risk for these patients (61). Nonetheless, up to 25% of patients with SpA develop chronic kidney disease and a high level of vigilance is warranted (62).

Finally, a two-fold increased risk for the development of osteoporosis has been confirmed in a recent study (63), underlying the need for a holistic approach to the disease, which needs to take into consideration several comorbidities and complications of treatment.

Take home messages

- AS patients with African-American origins seemed at higher risk of severe disease and comorbidities such as diabetes, depression and heart disease (46);
- AS and nr-axSpA could have similar burden and frequency of comorbidities (47);
- The role of NSAIDs use in the onset of hypertension in axSpA patients is still on debate (49, 50);
- Both venous thromboembolism and cardiac conduction disturbances are CV comorbidities more frequent in axSpA patients than in general population (48, 52, 53);
- axSpA patients are at risk for neoplasia, with particular attention to melanoma, renal, bladder, breast, prostate and pancreatic cancer (59, 60);
- A high level of vigilance is warranted to monitor both renal function and bone mineral density in axSpA patients (61-63).

Quality of life

SpA are chronic conditions that usually significantly impact patients' QoL, also in the field of working ability. In Portuguese population, AS and PsA were found to be associated with poor QoL and a higher rate of disease-related early retirement, both in comparison with general population and patients with other rheumatic diseases (64). A case-control study showed higher scores of depression, fatigue and work instability in AS patients than in healthy controls; in particular, work instability scores were positively correlated with all clinical parameters except spinal mobility (65). In a cohort of Danish patients with RA, PsA and axSpA, fatigue was associated with QoL, work impairment, pain, sleep, depression and physical functioning, with no significant differences among the mean scores of fatigue in the three diagnostic groups (66).

Data from the British Biologics Register confirmed axSpA patients experienced some reduction in productivity at work and work absence; high disease activity (HDA), fatigue, a labour-intensive job and poorer physical function were all independently associated with a poor work outcome (67).

Short-term response to a first TNFi in AS patients was a predictor of long-term productivity and non-disability, according to the data from the Czech ATTRA AS biologic registry; the strongest predictor of work impairment was pain (68).

Radiographic parameters that seemed to mostly compromise QoL in Japanese AS patients regarded the involvement of the sagittal vertical axis, the sacral slope and the global kyphosis (69).

Urkmez *et al*. showed AS patients had a higher rate of sleep disorders and lower levels of physical activity than healthy controls; moreover, a low physical activity was also shown to significantly compromise sleep quality in this group of patients (70). Sang *et al*. confirmed this data, showing a standard exercise improved QoL in AS patients, thus highlighting the need to better educate them to this behaviour (71).

The results of the QUO-VADIS study proved clinical and health-related QoL improvement over 6-months in a real-life AS population newly treated with golimumab (GOL) or infliximab (IFX): higher baseline ASDAS, BASFI and CRP and a younger age were associated

with improvement in QoL and an overall stronger response to therapy (72).
Baseline data of the Italian QUASAR observational study showed that AS and nr-axSpA patients have similar QoL and disease burden and that bDMARDs and NSAIDs are associated with the best overall scores of disease activity, function and QoL (73).
Rohde *et al*. found no deterioration in health-related QoL in subjects with axSpA during 5 years of follow-up in the outpatient setting; in addition, an improvement in the physical dimension over the years in parallel with a reduction in disease activity was observed. The great majority of patients were treated with biologics over the follow-up period and baseline predictors of improvement in QoL, in agreement with previous reports, were found to be younger age, higher education, low BASDAI score, high BAS Patient Global Score, high CRP level and no use of biological therapy at baseline (74).
Data from the EMBARK study in patients with nr-axSpA treated with ETN showed that composite indices (ASDAS, BASDAI, ASAS) adequately reflect treatment-related changes experienced by patients (75).
A Portuguese cross-sectional study investigated educational needs in patients with AS and PsA, finding a higher level of educational needs in AS patients, female gender regardless of the diagnosis and in patients with a shorter disease duration (76). Social media data revealed that major concerns of AS patients are related to disease treatment, especially regarding biologic therapies and their short- and long-term side effects (77).
A long-term observational study from a tertiary centre in Greece showed as many as 10% of AS patients never achieve low disease activity (LDA), despite therapy with bDMARDs, thus highlighting the extent of the unmet needs in AS treatment (78).
An observational study by Hwang *et al*. confirmed the relevance of the Ankylosing Spondylitis Quality of Life (ASQoL) instrument for patients with nr-axSpA, supporting its use in this population (79).

Take home messages

- In the field of the QoL, an issue of increasing importance, is that of work ability; in particular, it seems to be associated with disease activity, fatigue and mood disorder, while TNFi therapy could improve it (64-68);
- Spinal involvement could significantly compromise QoL in AS patients (69);
- Physical activity significantly improves QoL in AS (70, 71);
- A therapy with bDMARDs seems to be associated with health-related QoL improvement (72-74);
- Vigilance regarding educational levels of AS patients should be made, in particular for female and for patients with a shorter disease duration; clinicians should pay particular attention to patients' concerns about medications, most of all bDMARDs (76-78).

Therapy

In the last two years a consistent number of studies explored new insights into the efficacy and safety profiles of SpA therapies, with most of contributions regarding TNFi and IL-17 inhibitors and particular attention to biosimilar drugs.

TNF-α blockers

A number of studies on AS patients confirmed that treatment with TNFi could significantly slow down the radiographic progression (80, 81), could improve the clinical picture and reduce bone loss (82), and seemed to associate with increased spinal mobility and chest expansion (83).
As a result of the BSRBR-AS prospective study, more than 50% of axSpA patients naïve to biologic therapy responded to their first TNFi by the first follow-up visit (84). The study shows comorbidities, poor mental health, as well as adverse socio-economic factors and fewer years in education were predictive of non-response.
Preliminary data by Kim *et al*. identified the SUVmax of the spine on whole-body 18F-NaF PET/CT as a potential reliable and non-invasive BM of TNFi efficacy, also showing better performances than quantitative pharmacokinetic parameters (85).
Serum certolizumab pegol (CZP) levels 20–40 mg/L were associated with treatment response up to three months in inflammatory joint diseases, especially for axSpA patients, as reported by the data from the NOR-DMARD study; higher serum levels did not show any additional benefits (86).
The GO-ALIVE study showed the efficacy of intravenous GOL 2 mg/kg in active AS patients, with a good safety profile (87).
Choi *et al*. observed analysed the 3-year cumulative occurrence rate of AAU in AS patients was higher in those treated with IFX, compared to the adalimumab (ADA)+GOL group (88); these data are confirmed in the GO-EASY study (89).
Another study by Lee *et al*. on the same topic showed a minor recurrence of AAU in AS patients treated with ADA, GOL and IFX than in patients treated with ETN (90).
Concerning biosimilar drugs, Ditto *et al*. evaluated the efficacy and safety of a single switch from ETN originator to ETN biosimilar in a little Italian cohort of PsA and AS patients, finding no significant differences in clinimetric parameters after the switch, with a minority of patients who stopped the treatment, mostly due to the lack of efficacy (91). Two different studies from Korea demonstrated the efficacy and safety of the IFX biosimilar CT-P13 in patients with AS, with similar drug survival and safety between naïve patients and those switched from reference IFX group (92, 93). ADA originator and its biosimilar candidate HS016 showed no significant differences in terms of ASAS20 response rates at 24 weeks, treatment-emergent adverse events (AEs), pharmacokinetic and immunogenicity parameters, on Chinese patients with active AS (94).
According to a Korean study, mild tapering of TNFi, but not heavy tapering, showed comparable efficacy with the standard-dose treatment to achieve ASDAS-inactive disease in axSpA patients (95).
Regarding the possibility of complete withdrawing treatment in patients in clinical remission, data from the REM-

INEA study showed that more than 60% of AS patients who presented persistent remission, experienced clinical relapse shortly after IFX withdrawal. After the reintroduction of the drug, only half of these patients achieved clinical remission as before treatment discontinuation (96).

IL-17 inhibitors

In late 2019, end-of-study results on efficacy and safety of SEC 150 mg in AS patients (MEASURE 1 extension trial) were released, showing improvements in efficacy outcomes were sustained over the 5 years of treatment period, confirming SEC as a good therapeutic option with a favourable safety profile (97).

The MEASURE 2 study, aimed at evaluating improvement in pain and fatigue in AS patients treated with SEC over 2 years, showed a rapid and sustained relief of these symptoms, regardless of baseline CRP levels and prior TNFi therapy (98).

Long-term surveillance data on the safety of SEC in PsA and AS confirmed the consistent safety profile of this biologic drug, with the most frequent AE represented by upper respiratory tract infections, a low percentage of serious AEs and discontinuation of treatment due to AEs (99). No cases of TBC or hepatitis B reactivation were reported in this work and the incidence of treatment-emergent anti-drug antibodies was low.

Both an Italian and an English study confirmed the efficacy and safety of SEC also in a real-life setting, with improvements of objective physical and serological measures, as well as for clinimetric indices and patient-reported outcomes (100, 101).

Moreover, SEC was the most cost-effectiveness biologic treatment option in AS patients according to a Canadian and a Finnish analysis (102, 103).

Finally, it could be interesting to cite the results of a pooled SEC safety analysis across 21 clinical trials from Schreiber *et al*., showing that the total amount of IBD events (both CD, UC and IBD unclassified) was low and did not seem to increase over time during the treatment (104).

Bimekizumab provided rapid and sustained improvement in outcome measures in active AS patients, according to a phase IIb, placebo-controlled, dose-ranging study, with a generally good safety profile (105).

In another RCT, ixekizumab appeared superior to placebo in patients with nr-axSpA, achieving both primary endpoints of ASAS40 response at weeks 16 and 52 (106). No new safety data were found, with a low frequency of serious AEs.

Subcutaneous netakimab, a humanised monoclonal antibody targeting IL-17A, represents a new potential treatment for patients with active AS. The results of a phase II trial confirmed superiority to placebo in terms of ASAS20 response, with no dose-dependent toxicity or serious AEs observed (107). The most rapidly effective dose with a favourable safety profile was 120 mg and a phase III clinical trial is actually ongoing to evaluate the efficacy of one year of treatment.

IL-12/23 inhibitors

Three placebo-controlled clinical trials have not demonstrated the efficacy of ustekinumab in the treatment of axSpA in terms of ASAS40 or ASAS20 response, with a safety profile consistent with that of previous study (108).

JAK inhibitors

SELECT-AXIS1, a phase II/III placebo-controlled clinical trial, showed efficacy and a good tolerability of upadacitinib 15 mg in active AS patients (109).

Opioids

A retrospective study on AS patients highlighted a common use of opioid drugs in the United States, regardless of the use of recommended therapies for the treatment of this condition, suggesting the need to improve patients' education in order to optimise clinical care (110).

Take home messages

- The role of TNFi in significantly reducing radiographic progression of axSpA patients has been confirmed (80-83);
- AAU recurrence in AS patients seems to be lower in those treated with ADA and GOL than IFX or, as expected, ETN (88-90);
- No significant differences in terms of efficacy and safety were found comparing ETN, IFX and ADA respectively to their biosimilar (91-94);
- To optimise TNFi therapy, mild tapering should be preferred to complete withdrawal (95, 96);
- SEC seems to represent a good therapeutic option with a favourable safety profile for axSpA patients; moreover, its cost-effectiveness profile is very favourable (97-104);
- Similarly, bimekizumab and ixekizumab are effective and safe treatments to control axSpA (105, 106);
- Netakimab, a humanised monoclonal antibody targeting IL-17A, could be another potentially valuable bDMARD to treat axSpA (107);
- Upadacitinib seems to be efficacious and safe in patients with active AS (109);
- US patients with axSpA should be educated to reduce their use of opioids, aiming at an optimisation of pain-relief therapy (110).

Pregnancy

A Turkish group analysed pregnancy outcomes in women with AS and found increased rates of preterm delivery, intrauterine growth retardation and pre-eclampsia; interestingly, they observed patients taking medications for AS and those with a higher disease duration seemed to be at a higher risk of adverse pregnancy outcomes (111).

Considering the higher rate of caesarean sections in women with AS compared with healthy controls, in a study from Korea the authors analysed possible effects of pregnancy and delivery methods on AS treatment. They found that pregnancy did not seem to worsen AS evolution, and the overall change in prescription after delivery did not differ between vaginal delivery and caesarean section (112).

SpA and COVID-19

Since the onset of the COVID-19 pandemic, several studies have aimed to evaluate its impact on patients with

chronic conditions. COVID-19 cumulative incidence and case fatality rate did not seem to significantly differ between patients with inflammatory articular diseases and controls, although a cross-sectional study showed a higher incidence in PsA and SpA considering only cases confirmed by RT-PCR (113). On the other hand, SARS-CoV-2 infection seemed to be able to trigger the development of SpA according to some case reports, especially in HLA-B27+ subjects, even though the radiological evidence of erosions could suggest the pre-existence of an asymptomatic form with post-infection exacerbation (114, 115).

Although various surveys found agreement between patients and health-care professionals on the significant impact of COVID-19 pandemic, particularly with regard to access to care (116), depression and anxiety symptoms seemed to be comparable before and during the COVID-19 pandemic in axSpA (117). Significantly higher rates of drug non-compliance have been registered in the pandemic era as demonstrated by the Swiss Clinical Quality Management cohort, with a relative stability in the number of disease flares (118). Data from the DANBIO registry of patients with inflammatory arthritis confirmed these findings, with high patient satisfaction and stable PROs and remission rates despite a noticeable reduction in physical consultation (119).

References

1. GARCIA-MONTOYA L, GUL H, EMERY P: Recent advances in ankylosing spondylitis: understanding the disease and management. *F1000Res* 2018; 7: F1000 Faculty Rev-1512.
2. HWANG MC, RIDLEY L, REVEILLE JD: Ankylosing spondylitis risk factors: a systematic literature review. *Clin Rheumatol* 2021; 40: 3079-93.
3. STRAND V, SINGH JA: Patient burden of axial spondyloarthritis. *J Clin Rheumatol* 2017; 23: 383-91.
4. CARLI L, CALABRESI E, GOVERNATO G, BRAUN J: One year in review 2018: axial spondyloarthritis. *Clin Exp Rheumatol* 2019; 37: 889-98.
5. GIANNINI D, ANTONUCCI M, PETRELLI F, BILIA S, ALUNNO A, PUXEDDU I: One year in review 2020: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol* 2020; 38: 387-97.
6. SIGNORINI V, ELEFANTE E, ZUCCHI D, TRENTIN F, BORTOLUZZI A, TANI C: One year in review 2020: systemic lupus erythematosus. *Clin Exp Rheumatol* 2020; 38: 592-601.
7. FELICETTI M, TREPPO E, POSARELLI C *et al*.: One year in review 2020: vasculitis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S3-14.
8. HATEMI G, SEYAHI E, FRESKO I, TALARICO R, HAMURYUDAN V: One year in review 2020: Behçet's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S3-10.
9. ORLANDI M, LEPRI G, DAMIANI A *et al*.: One year in review 2020: systemic sclerosis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S3-17.
10. BOMBARDIERI M, ARGYROPOULOU OD, FERRO F *et al*.: One year in review 2020: pathogenesis of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S3-9.
11. ZANFRAMUNDO G, TRIPOLI A, COMETI L *et al*.: One year in review 2020: idiopathic inflammatory myopathies. *Clin Exp Rheumatol* 2021; 39: 1-12.
12. CALABRESI E, MONTI S, TERENZI R, ZANFRAMUNDO G, PERNIOLA S, CARLI L: One year in review 2019: psoriatic arthritis. *Clin Exp Rheumatol* 2020; 38: 1046-55.
13. CHIMENTI MS, CONIGLIARO P, NAVARINI L *et al*.: Demographic and clinical differences between ankylosing spondylitis and non-radiographic axial spondyloarthritis: results from a multicentre retrospective study in the Lazio region of Italy. *Clin Exp Rheumatol* 2020; 38: 88-93.
14. QUILIS N, SIVERA F, SEOANE-MATO D *et al*.: Prevalence of ankylosing spondylitis in Spain: EPISER2016 Study. *Scand J Rheumatol* 2020; 49: 210-13.
15. NYGAARD A. LJUNGDALH PS, IACHINA M, NIKOLOV TN, SCHIØTTZ-CHRISTENSEN B: Incidence of ankylosing spondylitis and spondyloarthritis in 2000-2013: a nationwide Danish cohort study. *Scand J Rheumatol* 2020; 49: 21-7.
16. VAN LUNTEREN M, VAN DER HEIJDE D, SEPRIANO A *et al*.: Is a positive family history of spondyloarthritis relevant for diagnosing axial spondyloarthritis once HLA-B27 status is known? *Rheumatology* (Oxford) 2019; 58: 1649-54.
17. RUYSSEN-WITRAND A, LUXEMBOURGER C, CANTAGREL A *et al*.: Association between IL23R and ERAP1 polymorphisms and sacroiliac or spinal MRI inflammation in spondyloarthritis: DESIR cohort data. *Arthritis Res Ther* 2019; 21: 22.
18. TROLDBORG A, THIEL S, MISTEGAARD CE *et al*.: Plasma levels of H- and L-ficolin are increased in axial spondyloarthritis: improvement of disease identification. *Clin Exp Immunol* 2020; 199: 79-87.
19. COSTA E, ALMEIDA D, CERQUEIRA M, COSTA JR, RIBEIRO AR, SOUSA-NEVES J: Smoking as associated factor for spondyloarthritis related uveitis: results from a single centre cross-sectional study. *Acta Reumatol Port* 2020; 45: 265-9.
20. RADEMACHER J, TIETZ LM, LE L *et al*.: Added value of biomarkers compared with clinical parameters for the prediction of radiographic spinal progression in axial spondyloarthritis. *Rheumatology* (Oxford) 2019; 58: 1556-64.
21. LIU GP, QIAN BP, QIU Y, HUANG JC, QIAO M, WANG B: Is any correlation present between the severity of syndesmophytes and spinopelvic and clinical parameters in advanced ankylosing spondylitis? *World Neurosurg* 2020; 137: e618-e625.
22. POLO Y LA BORDA, SZCZYPIORSKA M, BARTOLOMÉ N *et al*.: Clinical and genetic characteristics of ankylosing spondylitis patients with peripheral arthritis at disease onset. *Clin Exp Rheumatol* 2019; 37: 215-21.
23. WONG OM, TSANG HHL, CHAN SCW *et al*.: Clinical associations of uveitis in axial spondyloarthritis group and ankylosing spondylitis group: do they represent the same disease? *J Clin Rheumatol* 2020; 26: 1-6.
24. LIU M, HUANG Y, HUANG Z *et al*.: The role of fibrinogen to albumin ratio in ankylosing spondylitis: Correlation with disease activity. *Clin Chim Acta* 2020; 505: 136-40.
25. ENGINAR AU, KACAR C: Neutrophil-lymphocyte and platelet-lymphocyte rate and their seasonal differences in ankylosing spondylitis and rheumatoid arthritis patients using anti-TNF medication. *Bratisl Lek Listy* 2019; 120: 586-92.
26. SONG GG, LEE YH: Red cell distribution width, platelet-to-lymphocyte ratio, and mean platelet volume in ankylosing spondylitis and their correlations with inflammation: A meta-analysis. *Mod Rheumatol* 2020; 30: 894-9.
27. KIM TH, LEE JK, SUNG HK, KIM BH, SONG YS, SUNG IH: Radiologic features in symptomatic/asymptomatic heels of patients with ankylosing spondylitis. *Int J Rheum Dis* 2019; 22: 222–7.
28. HEBEISEN M, MICHEROLI R, SCHERER A *et al*.: Spinal radiographic progression in axial spondyloarthritis and the impact of classification as nonradiographic versus radiographic disease: Data from the Swiss Clinical Quality Management cohort. *PLoS One* 2020; 15: e0230268.
29. LLOP M, RIOS RODRIGUEZ V, REDEKER I *et al*.: Incorporation of the anteroposterior lumbar radiographs in the modified Stoke Ankylosing Spondylitis Spine Score improves detection of radiographic spinal progression in axial spondyloarthritis. *Arthritis Res Ther* 2019; 21: 126.
30. STAL R, VAN GAALEN F, SEPRIANO A *et al*.: Facet joint ankylosis in r-axSpA: detection and 2-year progression on whole spine low-dose CT and comparison with syndesmophyte progression. *Rheumatology* (Oxford) 2020; 59: 3776–83.
31. YE L, LIU Y, XIAO Q *et al*.: MRI compared with low-dose CT scanning in the diagnosis of axial spondyloarthritis. *Clin Rheumatol* 2020; 39: 1295-303.
32. ISHIDA SN, FURTADO RNV, ROSENFELD A, PROGLHOF JEP, ESTRELA GBQ, NATOUR J: Ultrasound of entheses in ankylosing spondylitis patients: The importance of the calcaneal and quadriceps entheses for differentiating patients from healthy individuals. *Clinics* (Sao Paulo) 2019; 74: e727.
33. VAHIDFAR S, SUNAR İ, ATAMAN Ş, YILMAZ G, AZARABADI JM, BÖLÜKBAŞI A: Ultra-

sonographic evaluation of Achilles tendon: Is there any difference between ankylosing spondylitis, non-radiographic axial spondyloarthropathy and controls? *Int J Rheum Dis* 2020; 23: 511-9.
34. ZARDI EM, PIPITA ME, GIORGI C, AFELTRA A, MAFFULLI N, FRANCESCHI F: Strain ultrasound elastography in the Achilles tendon of ankylosing spondylitis patients treated with anti-TNF-α: a preliminary study. *In Vivo* 2019; 33: 1635-40.
35. ARSLAN ALHUSSAIN F, KASAPOGLU GUNAL E, KURUM E *et al*.: Greater magnitude of entheseal microdamage and repair in psoriatic arthritis compared with ankylosing spondylitis on ultrasound. *Rheumatology* (Oxford) 2019; 58: 299-303.
36. WINK F, ARENDS S, MAAS F *et al*.: High prevalence of hip involvement and decrease in inflammatory ultrasound lesions during tumour necrosis factor-α blocking therapy in ankylosing spondylitis. *Rheumatology* (Oxford) 2019; 58: 1040-6.
37. ROSA JE, RUTA S, BRAVO M *et al*.: Value of color doppler ultrasound assessment of sacroiliac joints in patients with inflammatory low back pain. *J Rheumatol* 2019; 46: 694-700.
38. CHUI ETF, TSANG HHL, LEE KH, LAU CS, WONG CH, CHUNG HY: MRI inflammation of facet and costovertebral joints is associated with restricted spinal mobility and worsened functional status. *Rheumatology* (Oxford) 2020; 59: 2591-602.
39. BARALIAKOS X, HERMANN K-GA, XU S, HSIA EC, BRAUN J: Spinal mobility in the cervical and lumbar spine correlates with magnetic resonance imaging findings for inflammatory and structural changes in patients with active ankylosing spondylitis. *Clin Exp Rheumatol* 2020; 38: 467-71.
40. YANG R, LIU H, FAN M: A quick decrease of bone marrow edema in sacroiliac joint could be served as a novel marker for dose tapering of etanercept in ankylosing spondylitis patients. *Medicine* (Baltimore) 2019; 98: e14620.
41. KANG KY, JUNG J-Y, LEE SK *et al*.: Trabecular bone score value is associated with new bone formation independently of fat metaplasia on spinal magnetic resonance imaging in patients with ankylosing spondylitis. *Scand J Rheumatol* 2020; 49: 292-300.
42. JUNG JY, HAN SH, HONG YS, PARK S-H, JU JH, KANG KY: Inflammation on spinal magnetic resonance imaging is associated with poor bone quality in patients with ankylosing spondylitis. *Mod Rheumatol* 2019; 29: 829-35.
43. BARALIAKOS X, BOEHM H, BAHRAMI R *et al*.: What constitutes the fat signal detected by MRI in the spine of patients with ankylosing spondylitis? A prospective study based on biopsies obtained during planned spinal osteotomy to correct hyperkyphosis or spinal stenosis. *Ann Rheum Dis* 2019; 78: 1220-5.
44. BARALIAKOS X, HOFFMANN F, DENG X, WANG Y-Y, HUANG F, BRAUN J: Detection of erosions in sacroiliac joints of patients with axial spondyloarthritis using the magnetic resonance imaging volumetric interpolated breath-hold examination. *J Rheumatol* 2019; 46: 1445-9.
45. SHI Z, HAN J, QIN J, ZHANG Y: Clinical application of diffusion-weighted imaging and dynamic contrast-enhanced MRI in assessing the clinical curative effect of early ankylosing spondylitis. *Medicine* (Baltimore) 2019; 98: e15227.
46. SINGH DK, MAGREY MN: Racial differences in clinical features and comorbidities in ankylosing spondylitis in the United States. *J Rheumatol* 2020; 47: 835-8.
47. ZHAO SS, ERMANN J, XU C *et al*.: Comparison of comorbidities and treatment between ankylosing spondylitis and non-radiographic axial spondyloarthritis in the United States. *Rheumatology* (Oxford) 2019; 58: 2025-30.
48. AVIÑA-ZUBIETA JA, CHAN J, DE VERA M, SAYRE EC, CHOI H, ESDAILE J: Risk of venous thromboembolism in ankylosing spondylitis: a general population-based study. *Ann Rheum Dis* 2019; 78: 480-5.
49. DERAKHSHAN MH, GOODSON NJ, PACKHAM JC *et al*.: Increased risk of hypertension associated with spondyloarthritis disease duration: results from the ASAS-COMOSPA study. *J Rheumatol* 2019; 46: 701-9.
50. LIEW JW, WARD MM, REVEILLE JD *et al*.: Nonsteroidal antiinflammatory drug use and association with incident hypertension in ankylosing spondylitis. *Arthritis Care Res* 2020; 72: 1645-52.
51. MARTÍN-MARTÍNEZ MA, CASTAÑEDA S, GONZÁLEZ-JUANATEY C *et al*.: Incidence of first cardiovascular event in Spanish patients with inflammatory rheumatic diseases: prospective data from the CARMA project. *Clin Exp Rheumatol* 2019; 37: 731-9.
52. BENGTSSON K, KLINGBERG E, DEMINGER A *et al*.: Cardiac conduction disturbances in patients with ankylosing spondylitis: results from a 5-year follow-up cohort study. *RMD Open* 2019; 5: e001053.
53. MOON I, CHOI E-K, JUNG J-H *et al*.: Ankylosing spondylitis: A novel risk factor for atrial fibrillation - A nationwide population-based study. *Int J Cardiol* 2019; 275: 77-82.
54. MIDTBØ H, SEMB AG, MATRE K, ROLLEFSTAD S, BERG IJ, GERDTS E: Left ventricular systolic myocardial function in ankylosing spondylitis. *Arthritis Care Res* 2019; 71: 1276-83.
55. PARK J-S, JANG H-D, HONG J-Y *et al*.: Impact of ankylosing spondylitis on depression: a nationwide cohort study. *Sci Rep* 2019; 9: 6736.
56. WEBERS C, VANHOOF L, LEUE C, BOONEN A, KÖHLER S: Depression in ankylosing spondylitis and the role of disease-related and contextual factors: a cross-sectional study. *Arthritis Res Ther* 2019; 21: 215.
57. GARRIDO-CUMBRERA M, DELGADO-DOMÍNGUEZ CJ, GÁLVEZ-RUIZ D *et al*.; ATLAS WORKING GROUP: The effect of axial spondyloarthritis on mental health: results from the Atlas. *J Rheumatol* 2019; 46: 1284-9.
58. WALLMAN JK, MOGARD E, MARSAL J *et al*.: Irritable bowel syndrome symptoms in axial spondyloarthritis more common than among healthy controls: is it an overlooked comorbidity? *Ann Rheum Dis* 2020; 79: 159-61.
59. WARD MM, ALEHASHEMI S: Risks of solid cancers in elderly persons with osteoarthritis or ankylosing spondylitis. *Rheumatology* (Oxford) 2020; 59: 3817-25.
60. NAM B, KIM H, JANG EJ, CHO S-K, SUNG Y-K, KIM T-H: Malignancy risk in Korean male patients with ankylosing spondylitis. *Rheumatol Int* 2019; 39: 1741-8.
61. CHEN H-H, LIN C-H, LAI K-L *et al*.: Relative risk of end-stage renal disease requiring dialysis in treated ankylosing spondylitis patients compared with individuals without ankylosing spondylitis: A nationwide, population-based, matched-cohort study. *PloS One* 2020; 15: e0231458.
62. WU Y, GUO Y, WANG N, XUE Q: Influence of therapeutic drugs on different manifestations of renal involvement in 907 Chinese patients with ankylosing spondylitis. *Clin Nephrol* 2020; 93: 283-93.
63. HU L-Y, LU T, CHEN P-M, SHEN C-C, HUNG Y-M, HSU C-L: Should clinicians pay more attention to the potential underdiagnosis of osteoporosis in patients with ankylosing spondylitis? A national population-based study in Taiwan. *PloS One* 2019; 14: e0211835.
64. RODRIGUES J, RODRIGUES AM, DIAS SS, SOUSA RD, BRANCO JC, CANHÃO H: Psoriatic arthritis and ankylosing spondylitis impact on health-related quality of life and working life: a comparative population-based study. *Acta Reumatol Port* 2019; 44: 254-65.
65. ULUS Y, AKYOL Y, BILGICI A, KURU O: Association of work instability with fatigue and emotional status in patients with ankylosing spondylitis: comparison with healthy controls. *Clin Rheumatol* 2019; 38: 1017-24.
66. ESBENSEN BA, STALLKNECHT SE, MADSEN ME, HAGELUND L, PILGAARD T: Correlations of fatigue in Danish patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. *PLoS One* 2020; 15. e0237117.
67. MACFARLANE GJ, SHIM J, JONES GT, WALKER-BONE K, PATHAN E, DEAN LE: Identifying persons with axial spondyloarthritis at risk of poor work outcome: results from the British Society for Rheumatology Biologics Register. *J Rheumatol* 2019; 46: 145-52.
68. TUŽIL J, MLČOCH T, JIRČÍKOVÁ J *et al*.: Short-term response in new users of anti-TNF predicts long-term productivity and non-disability: analysis of Czech ATTRA ankylosing spondylitis biologic registry. *Expert Opin Biol Ther* 2020; 20: 183-92.
69. SATO T, YONEZAWA I, INOUE H *et al*.: Relationship between characteristics of spinopelvic alignment and quality of life in Japanese patients with ankylosing spondylitis: a cross-sectional study. *BMC Musculoskelet Disord* 2020; 21: 41.
70. URKMEZ B, KESKIN Y: Relationship between sleep quality and physical activity level in patients with ankylosing spondylitis. *Mod Rheumatol* 2020; 30: 1053-9.
71. SANG Y, DONG C, FU T *et al*.: Associated factors with adherence to standard exercise therapy and health-related quality of life in Chinese patients with ankylosing spondylitis. *Mod Rheumatol* 2020; 30: 149-54.
72. VAN DEN BOSCH F, FLIPO RM, BRAUN J, VASTESAEGER N, KACHROO S, GOVONI M: Clinical and quality of life improvements

with golimumab or infliximab in a real-life ankylosing spondylitis population: the QUO-VADIS study. *Clin Exp Rheumatol* 2019; 37: 199-207.
73. D'ANGELO S, GILIO M, D'ATTINO RM *et al*.: Observational study on the QUality of life of Italian Axial SpondyloARthritis patients (QUASAR): baseline data. *Clin Exp Rheumatol* 2019; 37: 748-55.
74. ROHDE G, BERG KH, PRIPP AH, PRØVEN A, HAUGEBERG G: No deterioration in health-related quality of life in patients with axial spondyloarthritis followed for 5 years in ordinary outpatient clinics in the biological treatment era. *Qual Life Res* 2020; 29: 99-107.
75. DOUGADOS M, VAN DER HEIJDE D, TSAI WC *et al*.: Relationship between disease activity status or clinical response and patient-reported outcomes in patients with non-radiographic axial spondyloarthritis: 104-week results from the randomized controlled EMBARK study. *Health Qual Life Outcomes* 2020; 18: 4.
76. MARQUES ML, FERREIRA RJ, MACHADO PM, MARQUES A, DA SILVA JA, NDOSI M: Educational needs in people with ankylosing spondylitis and psoriatic arthritis: a cross-sectional study. *Clin Exp Rheumatol* 2020; 38: 282-8.
77. DZUBUR E, KHALIL C, ALMARIO CV *et al*.: Patient concerns and perceptions regarding biologic therapies in ankylosing spondylitis: insights from a large-scale survey of social media platforms. *Arthritis Care Res* (Hoboken) 2019; 71: 323-30.
78. PELECHAS E, KALTSONOUDIS E, VOULGARI PV, DROSOS AA: Unmet needs in the treatment of ankylosing spondylitis: a long-term observational study from a single university center. *Rheumatol Int* 2019; 39: 663-8.
79. HWANG MC, MARTIN M, HARRIS K, GEERDTS P, STARK JL, REVEILLE J: Content validity of the ASQoL for use in a non-radiographic axial spondyloarthritis population: a qualitative study. *Qual Life Res* 2020; 29: 3155-66.
80. KOO BS, OH JS, PARK SY *et al*.: Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence. *Ann Rheum Dis* 2020; 79: 1327-32.
81. RIOS RODRIGUEZ V, HERMANN KG, WEIß A *et al*.: Progression of structural damage in the sacroiliac joints in patients with early axial spondyloarthritis during long-term anti-tumor necrosis factor treatment: six-year results of continuous treatment with etanercept. *Arthritis Rheumatol* 2019; 71: 722-8.
82. GULYÁS K, HORVÁTH Á, VÉGH E *et al*.: Effects of 1-year anti-TNF-α therapies on bone mineral density and bone biomarkers in rheumatoid arthritis and ankylosing spondylitis. *Clin Rheumatol* 2020; 39: 167-75.
83. NAM EJ, LEE WK: Early achievement of ASDAS clinical response is associated with long-term improvements in metrological outcomes in patients with ankylosing spondylitis treated with TNF-α blockers. *Medicine* (Baltimore) 2020; 99: e22668.
84. MACFARLANE GJ, PATHAN E, JONES GT, DEAN LE: Predicting response to anti-TNF-α therapy among patients with axial spondyloarthritis (axSpA): results from BSRBR-AS. *Rheumatology* (Oxford) 2020; 59: 2481-90.
85. KIM K, SON SM, GOH TS *et al*.: prediction of response to tumor necrosis value-α blocker is suggested by ^{18}F-NaF SUV_{max} but not by quantitative pharmacokinetic analysis in patients with ankylosing spondylitis. *AJR Am J Roentgenol* 2020; 214: 1352-8.
86. GEHIN JE, GOLL GL, WARREN DJ *et al*.: Associations between certolizumab pegol serum levels, anti-drug antibodies and treatment response in patients with inflammatory joint diseases: data from the NOR-DMARD study. *Arthritis Res Ther* 2019; 21: 256.
87. REVEILLE JD, DEODHAR A, CALDRON PH *et al*.: Safety and efficacy of intravenous golimumab in adults with ankylosing spondylitis: results through 1 year of the GO-ALIVE study. *J Rheumatol* 2019; 46: 1277-83.
88. CHOI EY, LEE M, LEE CS: Uveitis occurrence in patients with ankylosing spondylitis according to the type of tumour necrosis factor inhibitor: a cohort study of 175 patients. *Clin Exp Rheumatol* 2020; 38: 1132-7.
89. VAN BENTUM RE, HESLINGA SC, NURMOHAMED MT *et al*.: Reduced occurrence rate of acute anterior uveitis in ankylosing spondylitis treated with golimumab - the GO-EASY study. *J Rheumatol* 2019; 46: 153-9.
90. LEE S, PARK YJ, LEE JY: The effect of tumor necrosis factor-alpha inhibitors on uveitis in patients with ankylosing spondylitis. *J Korean Med Sci* 2019; 34: e278.
91. DITTO MC, PARISI S, PRIORA M *et al*.: Efficacy and safety of a single switch from etanercept originator to etanercept biosimilar in a cohort of inflammatory arthritis. *Sci Rep* 2020; 10: 16178.
92. KIM TH, LEE SS, PARK W *et al*.: A 5-year retrospective analysis of drug survival, safety, and effectiveness of the infliximab biosimilar CT-P13 in patients with rheumatoid arthritis and ankylosing spondylitis. *Clin Drug Investig* 2020; 40: 541-53.
93. KIM HA, LEE E, LEE SK *et al*.: Retention rate and long-term safety of biosimilar CT-P13 in patients with ankylosing spondylitis: data from the Korean College of Rheumatology Biologics registry. *Clin Exp Rheumatol* 2020; 38: 267-74.
94. SU J, LI M, HE L *et al*.: Comparison of the efficacy and safety of adalimumab (Humira) and the adalimumab biosimilar candidate (HS016) in Chinese patients with active ankylosing spondylitis: a multicenter, randomized, double-blind, parallel, phase III clinical trial. B*ioDrugs* 2020; 34: 381-93.
95. PARK JW, KIM HA, SHIN K *et al*.: Effects of tapering tumor necrosis factor inhibitor on the achievement of inactive disease in patients with axial spondyloarthritis: a nationwide cohort study. *Arthritis Res Ther* 2019; 21: 163.
96. MORENO M, GRATACÓS J, TORRENTE-SEGARRA V *et al*.: Withdrawal of infliximab therapy in ankylosing spondylitis in persistent clinical remission, results from the REMINEA study. *Arthritis Res Ther* 2019; 21: 88.
97. BARALIAKOS X, BRAUN J, DEODHAR A *et al*.: Long-term efficacy and safety of secukinumab 150 mg in ankylosing spondylitis: 5-year results from the phase III MEASURE 1 extension study. *RMD Open* 2019; 5: e001005.
98. DEODHAR A, CONAGHAN PG, KVIEN TK *et al*.: Secukinumab provides rapid and persistent relief in pain and fatigue symptoms in patients with ankylosing spondylitis irrespective of baseline C-reactive protein levels or prior tumour necrosis factor inhibitor therapy: 2-year data from the MEASURE 2 study. *Clin Exp Rheumatol* 2019; 37: 260-9.
99. DEODHAR A, MEASE PJ, MCINNES IB *et al*.: Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Res Ther* 2019; 21: 111.
100. CHIMENTI MS, FONTI GL, CONIGLIARO P *et al*.: One-year effectiveness, retention rate, and safety of secukinumab in ankylosing spondylitis and psoriatic arthritis: a real-life multicenter study. *Expert Opin Biol Ther* 2020; 20: 813-21.
101. WILLIAMS T, WADELEY A, BOND D, CAVILL C, FREETH M, SENGUPTA R: Real-world experience of secukinumab treatment for ankylosing spondylitis at the Royal National Hospital for Rheumatic Diseases, Bath. *Clin Rheumatol* 2020; 39: 1501-4.
102. GOEREE R, CHIVA-RAZAVI S, GUNDA P, JAIN M, JUGL SM: Cost-effectiveness analysis of secukinumab in ankylosing spondylitis from the Canadian perspective. *J Med Econ* 2019; 22: 45-52.
103. PURMONEN T, TÖRMÄLEHTO S, WAHLMAN H, PUOLAKKA K: Budget impact analysis of secukinumab versus adalimumab in the treatment of ankylosing spondylitis. *J Med Econ* 2019; 22: 151-7.
104. SCHREIBER S, COLOMBEL JF, FEAGAN BG *et al*.: Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. *Ann Rheum Dis* 2019; 78: 473-9.
105. VAN DER HEIJDE D, GENSLER LS, DEODHAR A *et al*.: Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2020; 79: 595-604.
106. DEODHAR A, VAN DER HEIJDE D, GENSLER LS *et al*.: Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. *Lancet* 2020; 395: 53-64.
107. ERDES S, NASONOV E, KUNDER E *et al*.: Primary efficacy of netakimab, a novel interleukin-17 inhibitor, in the treatment of active ankylosing spondylitis in adults. *Clin Exp Rheumatol* 2020; 38: 27-34.
108. DEODHAR A, GENSLER LS, SIEPER J *et al*.: Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol*

2019; 71: 258-70.
109. 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.
110. SLOAN VS, SHEAHAN A, STARK JL, SURUKI RY: Opioid use in patients with ankylosing spondylitis is common in the United States: outcomes of a retrospective cohort study. *J Rheumatol* 2019; 46: 1450-7.
111. UNAL C, FADILOGLU E, TANACAN A, ZAIM OC, BEKSAC MS: Retrospective evaluation of pregnancies with ankylosing spondylitis in a tertiary center in Turkey. *Int J Rheum Dis* 2020; 23: 101-5.
112. LEE JS, OH JS, KIM YJ *et al*.: Effects of pregnancy and delivery methods on change in ankylosing spondylitis treatment using the Korean health insurance review and assessment service claims database. *J Korean Med Sci* 2019; 34: e238.
113. MENA VÁZQUEZ N, MANRIQUE-ARIJA S, CABEZUDO-GARCÍA P *et al*.: Incidence and case fatality rate of COVID-19 in patients with inflammatory articular diseases. *Int J Clin Pract* 2021; 75: e13707.
114. SAIKALI W, GHARIB S: The first non-radiographic axial spondyloarthrits with COVID-19. *Immun Inflamm Dis* 2021; 9: 628-31.
115. EL HASBANI G, JAWAD A, UTHMAN I: Axial and peripheral spondyloarthritis triggered by sars-cov-2 infection: a report of two cases. *Reumatismo* 2021; 73: 59-63.
116. MARZO-ORTEGA H, WHALLEY S, HAMILTON J, WEBB D: COVID-19 in axial spondyloarthritis care provision: helping to straighten the long and winding road. *Lancet Rheumatol* 2021; 3: e11-e13.
117. ERPEK E, SOLMAZ D, BAYRAKTAR D, AKAR S: Depression and anxiety might not be increased during COVID-19 pandemic in patient with axial spondyloarthritis. *Clin Rheumatol* 2021; 40: 4773-4.
118. CIUREA A, PAPAGIANNOULIS E, BÜRKI K *et al*.: Impact of the COVID-19 pandemic on the disease course of patients with inflammatory rheumatic diseases: results from the Swiss Clinical Quality Management cohort. *Ann Rheum Dis* 2021; 80: 238-41.
119. GLINTBORG B, JENSEN DV, TERSLEV L *et al*.: Impact of the COVID-19 pandemic on treat to target strategies and physical consultations in >7000 patients with inflammatory arthritis. *Rheumatology (*Oxford) 2021; 60 (SI): S13.