Review

Axial spondyloarthritis: one year in review 2023

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ABSTRACT

Axial spondyloarthritides (axSpA) are a group of systemic autoimmune diseases, characterised by an inflammatory involvement of the axial skeleton, which, in the earlier phases, cannot be detected by conventional radiology, but only by magnetic resonance imaging, thus defining the so-called non-radiographic axSpA (nr-axSpA). The initial osteitis then tends to complicate into bone reabsorption and aberrant bone deposition, which then determines the ankylosis of the axial skeleton in the latest phases of the disease.

Peripheral joints may also be affected, enthesitis being its more characteristic manifestation. The radiographic form corresponds to ankylosing spondylitis which, with psoriatic arthritis, is the best-known subtype of SpA. AxSpA are rarely associated to laboratory abnormalities and are usually complicated by the presence of both extra-articular manifestations (particularly acute anterior uveitis, psoriasis and inflamatory bowel disease) and comorbidities, with a subsequent higher risk for patients of an impaired quality of life.

In this paper we reviewed the literature on axSpA of 2021 and 2022 (Medline search of articles published from 1st January 2021 to 31st December 2022).

Introduction

Axial spondyloarthritides (axSpA) are a group of systemic autoimmune diseases, characterised from an inflammatory involvement of sacroiliac (SI) joints or spine, which, in the earlier phases, cannot be detected using conventional radiology, but only by magnetic resonance imaging (MRI), thus defining the so-called non-radiographic axSpA (nr-AxSpA). The initial osteitis then tends to complicate into bone reabsorption and aberrant bone deposition, able to determine the ankylosis of the axial skeleton in the latest phases of the disease. Peripheral articular and periarticular structures may also be affected; in particular, enthesitis, a hallmark of axSpA, is typically associated with pain and morning stiffness. The radiographic form corresponds to ankylosing spondylitis (AS) which, with psoriatic arthritis (PsA), is the best-known subtype of SpA. AxSpA are rarely characterised by laboratory abnormalities and tend to be complicated by the presence of extraarticular manifestations, in particular acute anterior uveitis (AAU), psoriasis (PsO) and inflamatory bowel disease (IBD). These pathologies are usually associated with the development of several comorbidities, most often ranging from cardiovascular (CV) diseases, mood disorders, musculoskeletal complications and malignancies. Therefore, axSpA patients, have a higher risk of an impaired quality of life (QoL). During the last years many new drugs have emerged to treat axSpA, with comparable efficacy and safety profiles. Indeed, thanks to the improved knowledge of pathogenetic mechanisms at the basis of the disease, new targeted therapies and biological agents have been developed. Non-pharmacological treatments may also be effective in AxSpA and may act in synergy with the standard of care, with a consequent opportunity to significantly optimise patients' quality of care (1-4).

Methods

Following our regular annual reviews on different aspects of rheumatology (5-15) we will here provide a critical digest of the recent literature on AxSpA of 2021 and 2022 (Medline search of articles published from 1st January 2021 to 31th December 2022).

In particular, we performed an on-line search on MESH database, using as key terms "blood", "chemistry", "diagnosis", "diagnostic imaging", "drug therapy", "epidemiology", "metabolism",

"mortality", "prevention and control", "psychology", "therapy".

Genetics and pathogenesis

Genetic factors have been known to play a prominent role in AS pathogenesis. The most recognised genetically determined factor involved in susceptibility to the disease and therefore strongly associated with AS is human leukocyte antigen (HLA)-B27. However, it can only explain less than 50% of the total genetic risks for AS, and many studies have demonstrated that non-MHC genes may also contribute to AS susceptibility. Recently, several different studies tried to investigate the role of other potential genetic factors in AS pathogenesis. Bai and colleagues evaluated the association of endoplasmic reticulum aminopeptidase (ERAP)1 polymorphisms and AS susceptibility in an HLA-B27 positive population, since increasing evidence suggests that this gene may have a synergistic effect with HLA-B27. The results showed that the minor allele of rs2287987 was a protective factor for AS development in the HLA-B27 positive population, while no significant association emerged between the single nucleotide polymorphisms (SNPs) of rs30187, rs27044, rs10050860 and rs17482078 and AS susceptibility (16).

Another meta-analysis, conducted by Hu *et al*. explored whether tumour necrosis factor (TNF)-alpha gene polymorphisms were associated with AS susceptibility in an HLA-B27-positive population. TNF polymorphisms -238, -308, -857, -1031 and -863 were found to be associated with AS susceptibility only when comparing HLA-B27-positive AS patients with a random control population (17).

According to some other authors, TNF-α polymorphisms at positions -238, -308, -850, -1031 and rs769178 could have an influence on AS susceptibility, independently from HLA-B27 positivity. These results were only partially confirmed stratifying for Caucasians, but they were not consistent in the Latin-American and East Asian populations (18).

Considering once again the TNF-α gene, Gao *et al*. observed that rs1799724 polymorphism was significantly associated to a reduced risk of developing AS in Asians. After stratification by ethnicity, the polymorphism rs1800629 showed a significant association with a higher risk of AS in the Caucasian population and a decreased risk of AS in Brazilians and Mexicans. In addition, rs361525 and rs1800630 polymorphisms were linked to an elevated AS susceptibility in Asians (19). Other factors taken into account were interleukin (IL)-1 and IL-23 receptor (-R) genes.

Concerning IL-1, from a metanalysis of Chinese and English databases, it was found out that the IL-1A-889 (rs1800587) allele was significantly correlated with AS while IL1F7 exon 2 (rs3811047) G allele polymorphism was significantly associated to a lower risk of developing AS (20).

Another metanalysis evaluated the association between IL-23R polymorphisms and autoimmune diseases susceptibility. The results showed that IL-23R (rs10889677 A/C) A allele was a risk gene for AS in the general population, especially in Caucasians and that AA genotype increased the risk of AS in Mongolians (21). A role of IL-23 in the pathogenesis and in the level of activity of AS was confirmed by a meta-analysis by Lee and colleagues (22).

Recently, two separate metanalyses by Gao *et al*. analysed the role of toll-like receptor 4 and 9 and ERAP2 polymorphisms in AS susceptibility. In the first study, no significant associations were found between AS risk and TLR4-rs4986790, TLR4-rs4986791, TLR9-rs55704465 and TLR9-rs187084 polymorphisms (23). Similarly, ERAP2-rs2248374 and ERAP2-rs2549782 polymorphisms showed no significant association with AS development risk (24).

Finally, also cytotoxic T lymphocyte antigen (CTLA)-4 polymorphism was studied in terms of autoimmune diseases susceptibility. Regarding AS, this study indicates that CTLA-4 (+49 A/G) was correlated with a higher risk of developing the disease in Caucasians (25).

Some other have studies analysed the role of lymphocyte dysfunctions in AS pathogenesis. In particular, a Chinese metanalysis investigated how different proportions of lymphocytes subsets could facilitate AS onset. Interestingly, only the percentage of B cells was significantly increased in AS patients when compared to healthy controls. However, a significant increase in the proportion of CD4 T cells, Th17 cells, Tfh cells and Th1/Th2 ratio was observed, together with a significant decrease in Treg cells, thus implying how these imbalances could contribute to the pathogenesis of AS (26).

Trying to correct the dysregulation in lymphocytes subsets, an Iranian randomised controlled trial was designed to investigate the effect of symbiotics (nutritional supplements combining probiotic and prebiotics) supplementation in Ax-SpA patients. A reduction in IL17-expressing CD4þ T cells proportion and in IL-17 and IL-23 gene expression was observed, together with an increase in Treg cells levels (27). However, their results did not show any significant improvement in disease activity after the administration of symbiotics (28).

Another probable player in AxSpA onset could be the receptor activator of nuclear factor-kappa B ligand (sRANKL); indeed, its serum level was found significantly increased in Chinese patients with AS, apparently in relation with functional compromission of patients and disease duration (29).

It is well known that infections could act as a significant trigger in the onset of autoimmune diseases. Data from a recent meta-analysis showed a higher positive rate of Klebsiella pneumoniae in faeces, serum IgA and IgG in patients with AS than in healthy controls, suggesting that this bacterium could play a role in the disease onset (30).

Take-home messages

- Some SNPs of both ERAP1/2, TNF-α, IL-1A, IL-23A-R and CTLA-4 genes seem to be associated with a higher probability of developing AS, with different pattern of risk based on ethnicity (16-25).
- An imbalance in lymphocytes subsets seems to be involved in ax-SpA pathogenesis and the administration of symbiotics does not seem to correct it (26-28).
- RANKL system could be related to AS onset (29).
- A Klebsiella pneumoniae infection may have a role in AS development (30).

Comorbidities

Comorbidities have an essential role in defining the disease burden in patients with SpA. In particular, CV risk could compromise both patients' survival and QoL.

A recent meta-analysis by Morovatdar *et al*. explored any relation between AS and the risk of developing cardiac arrhythmia and conduction disorders. The analysis showed that AS patient presented an increased risk of atrial fibrillation (RR: 1.85, 95% CI: 1.15–2.98) and atrioventricular block (OR: 3.46, 95% CI: 1.09–10.39) when compared to the general population. The authors emphasise systemic inflammation could represent the link between AS and the observed cardiac dysfunctions (31). Concerning major adverse cardiac events, a recent meta-analysis by Liu *et al*. reported a 36% increase of stroke risk in patient affected by any arthritis (rheumatoid arthritis, PsA, AS, gout) when compared to the general population, confirming the role of systemic inflammation as a pivotal causing factor (32). A recent paper by Deng *et al*. explored red cell distribution width (RDW) and mean platelet volume (MPV) values in subjects affected by AS. The analysis confirmed a positive association between higher values of RDW and AS, while no differences in MPV emerged when comparing these patients with the general population (33). A recent meta-analysis by Li and coworkers investigated the association between circulating homocysteine (HCY) levels and AS. No significant differences in HCY levels were found when comparing the entire AS cohort with the control group. Conversely, higher HCY values were found in AS patients treated with methotrexate (MTX) while patients treated with TNF-inhibitors had significantly lower HCY levels. In addition, no differences in HCY levels emerged when comparing patient groups divided by disease activity or methylenetetrahydrofolate reductase C677T genotype (34). Various systemic autoimmune disorders have been associated with audio-vestibular dysfunctions. Recently, Yan *et al*. observed higher odds of hearing loss in AS patients than controls; it can manifest as slight to moderate and tends to be associated with an impaired subjective well-being and a lower QoL, thus underlining the need for increased attention to audiologic manifestations in these patients (35).

Take-home messages

- AS seems to significantly increase the risk of atrial fibrillation, atrioventricular block and stroke (31, 32).
- AS patients tend to have higher values of red cell distribution width (33).
- As expected, AS patients treated with MTX seem to be at risk of having higher levels of circulating homocysteine (34).
- AS could represent a risk factor for the development of hearing loss (35).

Imaging

Musculoskeletal ultrasound (MSUS) is a largely available instrumental examination which enables clinicians to better assess disease activity in SpA patients. If the peripheral joints and periarticular structures has been largely investigated, only few studies have assessed the performances of the MSUS in the SI joint (SIJ) setting. A recent meta-analysis concluded SIJ MSUS showed an excellent performance for the diagnostic purpose but not for the disease activity monitoring. The higher sensibility of the exam could help in selecting patients who should undergo a second level evaluation, thus sparing costs and time (36).

MRI is currently the most accurate imaging tool used in axSpA regarding its diagnostic approach. Exploiting the potential of MRI, Ye and colleagues confirmed that tissue diffusion coefficient (Dslow) was the most reliable MRI parameter to detect the activity of sacroiliitis in axSpA patients (37).

The advantage of using MRI in SpA is linked to the possibility of an earlier diagnosis, with the consequently start of the most appropriate therapy. However, in order to avoid the tendency to overestimate inflammatory sacroiliitis in the clinical setting, Diekhoff and colleagues faced the problem of distinguishing this condition from another one named osteitis condensans ilii, which is often seen in healthy individuals, in particular in post-partum women and athletes as a stress-related lesion (38, 39). Interestingly, a French retrospective study showed that subchondral bone attenuation coefficient of the sacroiliac margins, evaluated during computed tomography imaging of the SIJ, could help clinicians in this differential diagnosis (40).

Trying to optimise the MRI evaluation of ax-SpA, particularly for the identification of the earlier signs of the disease, Bressem *et al*. observed that deep neural networks could detect both inflammatory and structural changes at the SI joints indicative of ax-SpA at MRI, with good sensitivity and specificity (41).

A comparison study on the sensitivity to change of different imaging scoring methods on patients with early ax-SpA, showed that MRI signs of inflammation at the SIJ were more sensitive to change than those localised at the spine. Taking into account the evaluation of structural damage, fatty lesions detected on MRI of SIJ had a significantly higher sensitivity to change than pelvic radiographs. Interestingly, this difference was not confirmed for the evaluation of structural changes at spinal level, where MRI was not superior to radiography (42).

The MRI study of patients belonging to the ACHILLES trial confirmed the central role of this technique also in the study of heel enthesitis. In particular, the authors observed more evident pathologies in the Achilles tendon area than in the plantar aponeurosis; moreover, it was observed that the most frequent lesions were intra-tendon hypersignal and retrocalcaneal bursitis (43).

Take-home messages

- Thanks to its high sensibility, sacroiliac joints US could be helpful for selecting axSpA patients who should undergo a second level evaluation (36).
- The tissue diffusion coefficient (Dslow) was the most reliable MRI parameter to detect the activity of sacroiliitis in axSpA patients (37).
- The subchondral bone attenuation coefficient of the sacroiliac margins, could help differentiate sacroiliitis from osteitis condensas ilii (38-40).
- The diagnostic role of MRI has been

confirmed also in early forms of ax-SpA, both for signs of inflammation or structural damage (41, 42).
- MRI could help to characterise the involvement of heel enthesis in ax-SpA (43).

Quality of life

It is well known that QoL may be significantly compromised in patients with ax-SpA. The Ankylosing Spondylitis Quality of Life (ASQoL) score has been validated in nr-axSpA for the assessment of patients' QoL (44), while a *post-hoc* analysis of a randomised controlled trial (RCT) observed a strong correlation between the Simplified Ankylosing Spondylitis Disease Activity Score (SASDAS) and the ASDAS. The authors suggest that, while the SASDAS is not intended to replace the gold standard ASDAS measure of disease activity in axSpA, it may be useful as a simplified tool in some situations (45).
Two recent meta-analysis showed that biological therapies, in particular TNF-inhibitors (TNFi) and anti-IL-17 agents, seem to be related to an improvement in Short-Form 36 (SF-36) and ASQoL scores of patients with AS, when compared to non biological treatments or placebo (46, 47). These data are of pivotal importance, in particular when considering how AS diagnostic delay still remains consistent, as demonstrated in a meta-analysis by Zhao and colleagues, who observed an estimated delay of 6.7 years (48).
Wearable technology and remote assessment could allow a better and more stringent home-based management of rheumatic disorders, including ax-SpA. AS patients well accepted the remote evaluation of patient-reported outcome measures (PROMs) (49); interestingly, a single-blinded RCT on AS patients evaluated the impact of 4 educational interventions via social networks given by research nurses, demonstrating a better control of depressive symptoms and an improvement of SF-36 sub-items score when matched to the placebo group (50). Moreover, a RCT by Molto *et al*. confirmed that home self assessment, dedicated training and educational formation given by trained nurses, could assure a better control of AS disease activity, with a significant reduction of BASDAI score (51).
Finally, wearable tools, such as monitoring wristbands, seemed to implement the home-based exercise programmes of AS patients, with subsequent better results of PROMs (52).

Take-home messages
- The Ankylosing Spondylitis Quality of Life score has been validated also for nr-axSpA and the new index Simplified Ankylosing Spondylitis Disease Activity Score could replace the ASDAS in certain conditions (44, 45).
- The Ankylosing Spondylitis Quality of Life score tends to be better in those patients treated with TNF-inhibitors and anti-IL17, than with non-biological DMARDs (46, 47).
- The diagnostic delay in AS patients continues to be consistent (48).
- Wearable technology and remote assessment seem to be valuable tools to improve the quality of care also in axSpA (49-52).

Therapy

TNF-alpha inhibitors

In recent years, the use of biosimilars has become routinary and data about their safety and efficacy are being collected.
Cao, Zeng, Su, Li and colleagues observed a substantial overlap between adalimumab (ADA) originator and its biosimilars HS016 and TQ-Z2301, for efficacy, pharmacokinetics and safety in Chinese patients with AS (53-56).
Deodhar observed that therapy with golimumab (GOL) could be more efficacious in patients with early AS onset, than in those with late onset, thus confirming the central role of a prompt diagnosis and treatment in assuring a better control of disease activity (57).
Reveille and colleagues not only confirmed these data, but also highlighted a sustained improvement in health-related quality of life (HRQoL) and productivity of patients with AS (58).
A well-known cause of reduced efficacy of TNFi is the synthesis of antidrug antibodies. In a study by Eser on infliximab (IFX), it was observed that increased body weight, serum C-reactive protein (CRP), antidrug antibody concentrations, decreased serum albumin and elevated serum glucose levels were predictors of a higher clearance of the drug. Interestingly, the authors also noticed that baseline IFX clearance and body weight were the only predictors of early detection of antidrug-antibodies (59). Accordingly, Wang and colleagues suggested that some AS patients' characteristics could vary the TNFi response; the probability of a major response increased with higher CRP levels and decreased with body mass index (60). A higher risk of disease flares in axSpA patients also seemed to be associated with a reduction in the dose of TNFi therapy, with no significant differences in infection rates or injection/infusion reactions (61).
Some working-groups investigated the efficacy of TNFi throughout the application of imaging techniques.
A recent MRI-study showed the superiority of etanercept (ETN) to celecoxib in decreasing the Spondyloarthritis Research Consortium of Canada (SPARCC) scores of both SIJ and spine in AS patients (62). Finally, Khoury and colleagues observed that in axSpA patients there was no sufficient evidence to distinguish the difference between changes in MRI related to TNFi effects and those due to the alternation between periods of disease flares and remission (63).

Anti-IL17

Nowadays, IL-17 inhibitors (IL-17i) are often prescribed to treat SpA, thanks to a generally favourable efficacy and safety profile both on the axial, peripheral and cutaneous domains of the disease. In some phenotypes of patients, they could be recommended even over TNFi (64).
A recent metanalysis of RCTs on AS confirmed their efficacy; moreover, it was also shown that ixekizumab (IXE) had a slightly higher risk of non-serious adverse events (AEs) than secukinumab (SEC); as expected, a higher number of infections than placebo was registered; nasopharyngitis, in particular, seemed to be more common in patients receiving SEC (65).
Enthesitis is a hallmark of AS, being

one of the disease domains most associated with pain, fatigue, morning stiffness and worse QoL. A *post-hoc* analysis of four RCTs on SEC, focusing on the efficacy of the drug in reducing the inflammatory process at the entheseal sites, showed a meaningful reduction of overall and axial Maastricht Ankylosing Spondylitis Entheses Score (MASES) scores. However, improvement of the peripheral and Achilleus enthesitis, even if sustained, was not statistically significant (66).

Interestingly, data from registrational studies on SEC revealed a great and sustained non-steroidal anti-inflammatory drug (NSAID) sparing effect in AS patients, thanks to an optimised control of disease activity, permitting the patients to avoid the long-term side effects of this class of drugs (67).

Fatigue is a common feature of many rheumatic diseases, with a strong impact on patients' QoL and working ability. A subgroup analysis of the MEASURE-1 and 2 studies showed that therapy with SEC was able to significantly reduce patients' fatigue, with a sustained response for up to 3 years. The response was higher in TNFi-naive patients and correlated with a better control of disease activity and with an improvement of the Working Productivity and Activity Impairment (WPAI) as well (68). Similarly, Walsh and colleagues observed an improvement in QoL of patients with a nr-axSpA during therapy with IXE (69).

Another typical feature of AS, shared with the other inflammatory arthritis, is reduced bone mineral density (BMD), related to an increased risk of fractures. In AS patients treated with SEC, Braun and colleagues observed an increased BMD, especially at vertebral sites, (without any radiographic progression of the disease that could misrepresent this finding); no relationship was found with the markers of bone metabolism (70).

A sub analysis performed by Braun and colleagues on nr-axSpA patients revealed that the improvement in the axial involvement after treatment with SEC was higher in males and in those patients with higher CRP values and worse MRI signs of inflammation at SIJ, with no differences between loading and non-loading dose groups (71).

Regarding the safety of SEC, a study analysed both clinical trial and post-marketing surveillance data to assess the incidence rate of malignancies in PsO, PsA and AS patients, comparing them with the rates in the US general population. No differences were highlighted between the treated patients and the control group, nor between the two dosages of the drugs. The most frequent type of cancer was non melanoma skin cancer (NMSC), while haematologic malignancies were rare. About 10% of those who suffered from a previous malignancy had a recurrence, mainly NMSC, thus confirming a reassuring safety profile of the drug (72).

A network meta-analysis comparing indirectly SEC and IXE for efficacy and safety did not show any statistical differences between the two anti-IL17, while both of them appeared superior to ADA for efficacy outcomes (73).

In a recent randomised withdrawal-retreatment study on nr- and r-axSpA, it was observed that more than 80% of the patients who regularly took IXE remained flare-free. Together with IXE withdrawal, other risk factors for disease flares were the presence of anti-drug antibodies, an abnormal BMI and higher values of CRP or ASDAS (74).

Taking into account how the gender differences might have an impact on SpA outcomes, van der Horst-Bruinsma and colleagues observed that male patients had a better and more rapid response to IXE than women, who experienced worse outcomes, especially those with a diagnosis of nr-axSpA (75).

Brodalumab is an IL-17 receptor antagonist that inhibits the signalling of a higher number of cytokines, such as IL-17A/F, IL-17C and IL-17E. Its efficacy and safety in an Asian cohort of both r-axSpA and nr-axSPA patients were assessed in a double blind RCT *versus* placebo, which showed a significant improvement in the control of disease activity, without any differences between the TNFi-naive *versus* TNFi-experienced patients, together with a good safety profile; in particular, no deaths or new IBD diagnosis were reported (76). Another drug active on the broad spectrum of the IL-17 axis is bimekizumab, an IL17 A/F dual variable domain inhibitor, which, in AS patients, revealed a great efficacy profile, together with an improvement of the HRQoL outcomes. The safety profile did not differ from the other IL-17-inhibitors, in particular for candidiasis or development of IBD; a lower incidence of AAUs was registered, in comparison with IXE or SEC, but further data are needed to better investigate these data (77). Interestingly, Cao and colleagues recently observed the superiority of bimekizumab to IL-23 and IL-6 inhibitors in controlling disease activity in AS patients (78).

JAK-inhibitors

The class of Janus Kinase-inhibitors (JAKi) is a recent group of drugs studied and used in a large number of diseases, including all the chronic inflammatory arthritis. A review of 3 RCTs compared the results that tofacitinib (TOF), filgotinib (FIL) and upadacitinib (UPA) showed *versus* placebo in AS patients refractory to NSAIDs, assuring a shared good control of disease activity, together with an improvement of radiologic outcomes and physical functioning; no differences in serious AEs rates were highlighted among them (79). A more recent meta-analysis confirmed these findings (80).

Similarly, a recent RCT on AS patients treated with TOF, showed the effectiveness of the drug, with no differences between the TNFi-naive or experienced patients (81). On the same RCT, an analysis of QoL, fatigue, working ability, pain and functioning of patients was performed, showing an early improvement in all the investigated outcomes (82).

UPA is one of the most recent JAKi; it was engineered to inhibit JAK-1 with a higher affinity than TOF or baricitinib. The first RCT on UPA in AS patients is the SELECT-AXIS, which showed an early and significant improvement in all the efficacy outcomes, together with a rapid and constant improvement of the patients who switched from placebo. Regarding the safety profile, the most frequent AEs were upper respiratory tract infections, rhinopharyngitis

and elevation in serum creatine kinase; only few uveitis and HZ cases were reported, without any cases of thromboembolic events, MACEs, serious infections, IBD, renal dysfunctions or deaths (83). The efficacy trend of UPA was confirmed in the extension study, which also showed a multi-domain action of the drug, with a parallel improvement of both fatigue, pain and working ability.

Finally, the treatment was associated with a reduction in MRI scores and in the rate of radiographic disease progression. No significant safety warning emerged, with one case of both pulmonary embolism, uveitis, colitis and HZ that were reported (84). A sub-analysis of the SELECT-AXIS1 showed an early and sustained reduction of pain in AS patients treated with UPA, also confirmed in those who switched from placebo, similarly to other JAKi (85). UPA showed comparable efficacy and safety profiles also in TNFi or IL-17i experienced patients (86).

The latest JAKi, FIL, with a selective affinity for JAK-1, has not yet been approved for SpA treatment. Some data about its use in AS patients come from the TORTUGA trial, which showed a significant slowing down in the progression of the erosions and a higher backfill trend at SIJ level (87). Analysing the effect of FIL on the vertebral setting, Maksymowych *et al*. noted a significant improvement of the CANDEN-MRI inflammation score (88).

Apremilast

So far, some efficacy and safety data on the use of this oral phosphodiesterase 4 inhibitor in ax-SpA have emerged. A phase II study, showed that AS patients did not appear to reach a maximum clinical response (89). Moreover, Taylor and colleagues conducted a phase III trial on APR in active AS and did not find any significant clinical benefits for patients, with safety and tolerability profiles respectively characterised by nasopharyngitis, upper respiratory infections, diarrhoea and nausea (90).

Bisphosphonates

In the past, some authors observed a certain efficacy of bisphosphonates use in AS. A meta-analysis by Eun and colleagues definitely clarified that therapy with bisphosphonates could neither improve disease activity, nor prevent bone loss in patients with AS (91).

Non-pharmacological therapy

It is well known some non-pharmacological therapies could represent an added value to the pharmacological standard of care for axSpA patients.

Calik *et al*. investigated the effect of adding aerobic training to spinal mobility exercises in AS; they observed significant improvements in both clinimetric parameters, aerobic capacity and respiratory muscle strength, thus suggesting that an aerobic exercise programme should be added to the individual exercise prescription of AS patients. Moreover, Harpham *et al*. found that training programmes with aerobic components were associated to a reduction in CRP values and improved scores of self-assessed disease activity (92, 93). Also the addition of a soft-tissue mobilisation to the training programme of AS patients seemed to significantly improve the levels of disease activity and the physical function of patients (94).

Moreover, Lim *et al*. observed that home-and-workplace combined exercise could improve both spinal mobility and pulmonary function, with a significant reduction in absenteeism and overall work impact due to ax-SpA (95).

Take-home messages

- In Chinese AS patients, adalimumab originator seems to be substantially comparable to its biosimilars HS016 and TQ-Z2301 (53-56).
- Golimumab confirmed its efficacy in AS, even in improving the health-related QoL and productivity of patients, particularly if prescribed in the earlier phases of the disease (57, 58).
- The clearance of infliximab from anti-drug-antibodies could be predicted by body weight and some other clinical characteristics of patients, that also seem to be able to generally influence the response to TNF-inhibitors (59, 60).
- A dose reduction of TNF-inhibitors could induce disease flares in axSpA patients (61).
- Secukinumab in AS patients could be efficacious in improving enthesitis in the Maastricht Ankylosing Spondylitis Entheses Score, showed a good NSAID sparing effect and could improve vertebral bone mineral density (66, 67, 70).
- Both secukinumab and ixekizumab seem able to improve axSpA patients' QoL and both showed better efficacy than adalimumab (68, 69).
- In axSpA patients treated with ixekizumab, a withdrawal of the drug, the presence of anti-drug antibodies, an abnormal BMI and higher values of C-reactive protein or ASDAS were shown to be risk factors for disease flares. Moreover, female sex and a diagnosis of nr-axSpA seem to be associated with reduced efficacy of the drug (74, 75).
- Brodalumab was effective and safe in Asian patients with both r- and nr-axSpA (76).
- Bimekizumab showed great efficacy in AS, and seemed to be superior to IL23 and IL6-inhibitors, with a safety profile that did not differ significantly from secukinumab or ixekizumab (77, 78).
- Tofacitinib, filgotinib and upadacitinib showed good efficacy in AS patients, with no significant differences in the occurence of serious adverse events (79, 80-88).
- Apremilast did not show significant efficacy in AS (89, 90).
- An aerobic exercise programme and soft-tissue mobilisation should be added to the individual exercise prescription of AS patients (92-94).
- Home-and-workplace combined exercise could improve the work productivity of AS patients (95).

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