Developments in therapies for spondyloarthritis

Joachim Sieper

Abstract | First-line therapy for spondyloarthritis (SpA) has not yet altered in the wake of new classification criteria; NSAIDs and physical therapy are recommended. Anti-TNF agents can be used when NSAIDs fail, but their efficacy has potentially been limited in previous trials by inclusion criteria requiring the presence of established, active disease. Now, not only patients with axial SpA (axSpA) with radiographic signs of sacroiliitis (that is, with ankylosing spondylitis), but also patients in whom structural damage is not—yet—visible radiographically (non-radiographic axSpA) can be included in trials of therapy for axSpA. TNF blockers, it seems already, are at least similarly effective in patients with non-radiographic axSpA as in those with established AS. Short symptom duration and a positive C-reactive protein test at baseline are currently the best predictors for a good response to TNF-blocking agents. Biologic agents besides anti-TNF therapies have so far failed in the treatment of axSpA. New bone formation seems currently to be best prevented by NSAIDs, not by TNF blockers. Whether earlier effective treatment of bony inflammation with anti-TNF therapy will be able to prevent ossification at a later stage has yet to be determined. New classification criteria for peripheral SpA will also allow treatment trials to be conducted more systematically than has previously been possible in this subgroup of patients.

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Introduction

Therapy for spondyloarthritis (SpA) has evolved considerably in the 21st century. Biologic agents have entered the armamentarium for persistent disease, and improved imaging techniques have facilitated the development of new classification criteria for subtypes of SpA. Diagnosis of non-radiographic axial SpA (axSpA) has become possible, enabling treatment to be initiated earlier in the course of this disease subtype. The diagnosis and classification of SpA,[1] and strategies for early referral,[2] are discussed in detail elsewhere in this Focus issue. In this Review, I describe current treatment strategies, recommendations and outcomes in SpA, and outline ongoing research aimed at delivering new therapeutic options. Therapy in pediatric patients is covered in a separate Review in this issue.[3]

The Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA[4] and peripheral SpA[5]—published in 2009 and 2011 respectively—overlap with the classification criteria for psoriatic arthritis (PsA),[6] for patients who happen to also have psoriasis. PsA is a heterogeneous disease with several subtypes. The SpA-typical subtype, for example, has axial involvement and/or peripheral manifestations, predominantly of the lower limbs and/or asymmetrically and mostly presenting as monoarthritis or oligoarthritis; another subtype resembles rheumatoid arthritis (RA), whereas other forms are unique to PsA (such as arthritis of digits in a row, of the distal interphalangeal joints, or arthritis mutilans). As nearly all clinical trials in PsA have enrolled patients with polyarthritis, which is not typical for SpA, the development of therapies for PsA will not be discussed in this article. Furthermore, as evidence of the efficacy of conventional DMARDs, such as sulfasalazine, methotrexate or leflunomide, in axSpA is lacking,[7] these compounds are not discussed in this Review.

First-line therapy for SpA has not yet changed in the biologic era; NSAIDs and physical therapy remain the recommended course of action upon initial diagnosis.[8] Nevertheless, international experts came to consensus on the use of anti-TNF agents in NSAID-resistant ankylosing spondylitis (AS) almost a decade ago.[9] Recommendations for the use of these compounds in AS have since been updated with experience,[10] and as the new classification criteria[4,5] have facilitated recommendations aimed at specific subtypes of SpA.[7,11] An overview of current therapies, seemingly inefficacious drugs, and treatments for which clinical trials are ongoing in patients with SpA is provided in Table 1.

Implications of SpA classification criteria

Historically, a diagnosis of AS was dependent on the occurrence of structural damage in the sacroiliac joints (SIJ), because such changes are the only ones visible on plain radiographs. Radiographic sacroiliitis is essential for fulfillment of the modified New York (mNY) criteria for AS,[12] which have frequently been applied not only to the classification but also to the diagnosis of AS. The disease course, however, begins with inflammation—the development of structural, radiographic damage can take many years.[13]

Rheumatology, Department of Medicine, Charité Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany
joachim.sieper@charite.de

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The ASAS criteria for axSpA[4] now identify patients with radiographic signs of the disease (that is, patients with AS) as well as patients with earlier stages of non-radiographic axSpA; however, not all patients with early signs of disease will develop radiographic axSpA. Nevertheless, these criteria[4] allow patients to be included in clinical treatment studies much earlier in the course of their disease than was previously possible. Classification criteria have also been developed and proposed for peripheral SpA.[5] Almost no evidence-based data on the efficacy of drugs in patients with this subtype of disease exist—the new criteria are thus essential to facilitate interventional trials in patients with SpA with peripheral disease manifestations.

Better understanding of, and ability to stratify, the subtypes of SpA will ultimately aid the development and targeting of therapies. The implications of current criteria, including the treatment recommendations that have resulted from them, are discussed in the appropriate places throughout this Review.

Key points

- The term axial spondyloarthritis (axSpA) now includes patients with ankylosing spondylitis (radiographically visible sacroiliitis with or without syndesmophytes) as well as non-radiographic axSpA
- Responses to TNF-blockers are similar between patients with non-radiographic and radiographic axSpA
- Short symptom duration and elevated C-reactive protein levels are the best predictors for a good response to anti-TNF therapy
- Antibiotic treatment might be an interesting treatment option in a subgroup of patients with peripheral spondyloarthritis

Axial SpA

TNF-blocker treatments

The initial trials that demonstrated good to very good efficacy of TNF-blocker treatment in axSpA enrolled patients with AS with radiographic sacroiliitis according to the modified New York (mNY) criteria.[7,14] Thus, the next step was to investigate whether patients with non-radiographic axSpA would respond similarly well (or even better) to this class of drugs. This question has been addressed in three clinical trials.[15-17] In all of these studies the patients retrospectively fulfilled the new ASAS classification criteria for axSpA,[4] although these criteria were not yet available when the trials began.

In the first such study (published in 2008),[15] 46 patients with non-radiographic axSpA were treated with adalimumab or with placebo for 12 weeks; all patients were then switched to adalimumab and treated until week 52. The 40% improvement in ASAS criteria (ASAS40) response rate was reached by 54.5% of the patients in the adalimumab group versus 12.5% in the placebo group;[15] thus, the efficacy of adalimumab in non-radiographic axSpA is at least as good as that reported for the previous trials in AS.[14]

In another trial, this time of infliximab,[16] 40 patients with axSpA were included; all had symptom duration <3 years, active inflammation of the SIJ on MRI images, all were positive for HLA-B27, and all had the clinical symptom inflammatory back pain. Only ~12% of these patients had radiographic evidence of sacroiliitis according to the mNY criteria. A high percentage (55.6%) of patients in the infliximab arm reached the ASAS criteria for partial remission, compared with only 12.5% in the placebo group. Active inflammation as assessed by MRI also improved significantly better in those treated with infliximab as compared with the placebo group.[16]

Finally, in the third trial of anti-TNF therapy, 76 patients with axSpA (symptom duration <5 years) were treated in a 1-year randomized, prospective trial with either etanercept or sulfasalazine.[17] A significantly higher number of patients in the etanercept group showed an improvement of active subchondral bone marrow inflammation in the SIJ, spine, and peripheral entheses on whole-body MRI scans. Furthermore, 50% of these patients reached the ASAS partial remission criteria after 1 year of treatment, compared with 19% of the sulfasalazine group. Half of the patients had radiographic sacroiliitis at inclusion in the trial, whereas the other 50% did not; the effect of etanercept was similar in both halves of the cohort.[17]

These data clearly demonstrate that patients with axSpA show an at least similar, but mostly even better, response to TNF-blocker treatment as patients who fulfill the mNY criteria for AS, and that the response rate between patients with radiographic and non-radiographic axSpA is the same if symptom duration is similar. Accordingly, phase III trials are underway —of certolizumab pegol for axSpA (both AS and non-radiographic axSpA);[18] of etanercept for non-radiographic axSpA;[19] and of golimumab for radiographic axSpA[20]—to confirm the findings and enable extension of the labeled indications for these compounds from AS to the whole group of axSpA. Furthermore, a phase III trial of adalimumab in patients with non-radiographic axSpA has concluded, with the results published in 2011 as an Abstract.[21] 192 patients were randomized for a 12 week treatment with either adalimumab (40 mg subcutaneously) or placebo every second week, followed by an open extension phase in which all patients were treated with adalimumab. An ASAS40 response was reached in 36% of the adalimumab group versus 15% of the placebo group (P <0.001) at week 12; the best predictors of this outcome were short symptom duration (<5 years) and elevated C-reactive protein (CRP) levels.[21]

Long-term response

Long-term follow-up studies in patients with AS treated with infliximab, etanercept, or adalimumab over 8,[22] 5,[23] and 5[24] years, respectively, were published in 2010 and 2011. A rather constant drop-out rate of ~15% per year was reported; reasons for withdrawal from the studies included adverse effects, inefficacy and non-compliance. Importantly, no new safety signals became apparent; furthermore, disease activity and function continued to improve slightly over time in those patients who persisted with the anti-TNF medication.[22–24] 2-year follow-up MRI data on active inflammation of the spine in patients taking infliximab[25] or golimumab[26] are also

Table 1 | Treatment recommendations and drug trials in axSpA and peripheral SpA

Therapy by SpA subtype	AxSpA (ASAS criteria[4])	Peripheral SpA in the presence of axSpA	Peripheral SpA (ASAS criteria[5]) without axial manifestations
Current ASAS treatment recommendations[7,11]			
First-line therapy	≥2 NSAIDs, for ≥4 weeks, physical therapy	≥2 NSAIDs, for ≥4 weeks, physical therapy	≥2 NSAIDs, for ≥4 weeks, physical therapy
NSAID-resistant, active disease for ≥4 weeks (BASDAI ≥4)	Anti-TNF agent (adalimumab, etanercept, infliximab, golimumab)	One local corticosteroid injection, if appropriate; sulfasalazine or other conventional DMARD; anti-TNF agent (adalimumab, etanercept, infliximab, golimumab)	One local corticosteroid injection, if appropriate; sulfasalazine or other conventional DMARD (expert opinion, no clinical trials)
Loss or absence of efficacy of TNF blocker	Switch to another anti-TNF agent (2nd anti-TNF agent is more likely to be effective in case of loss of efficacy than absence of efficacy of 1st agent)	Switch to another anti-TNF agent (2nd anti-TNF agent is more likely to be effective in case of loss of efficacy than absence of efficacy of 1st agent)	–
Investigational therapies			
Therapies in ongoing clinical trials and/or with positive trial data	Tocilizumab and sarilumab (anti-IL-6R antibodies), ustekinumab (anti-IL-23/IL-12 antibody), secukinumab (anti-IL-17 antibody), anti-TNF agents	–	Combination antibiotics (doxycycline plus rifampin, or azithromycin plus rifampin), anti-TNF agents
Treatments with evidence of inefficacy	Conventional DMARDs, abatacept (inhibitor of T-cell co-activation), rituximab (B-cell depleting agent), anakinra (IL-1R antagonist)	–	–

Abbreviations: ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial SpA; BASDAI, Bath ankylosing spondylitis disease activity index; SpA, spondyloarthritis.

available; in general, inflammation is considerably reduced with therapy (by 70–80%).[25,26] Again, further small reductions in inflammation over time occur in those patients who continue to take the drug.

Prediction of response

The positive data I have discussed from trials of anti-TNF treatment in patients with axSpA with symptom duration <5 years raise the question of whether short symptom duration is a prognostic factor for a good treatment response for the whole group of patients with axSpA, including those with AS. Indeed, it became clear in an analysis of the early trials of TNF blockers in AS, published in 2004,[27] that symptom duration <10 years is associated with a better response to therapy, in comparison with patients with AS of duration >10 years. Furthermore, such an association was also found in other studies of anti-TNF drugs in patients with AS,[28] as well as in the trial of adalimumab in patients with non-radiographic axSpA,[15,21] for which symptom duration was not limited.

Short symptom duration overlaps considerably with young age as a predictor of good treatment response. For example, in the trial of adalimumab for active AS, 50% of patients aged <30 years reached ASAS partial remission, compared with 39% of patients aged 30–39 years and ~18% of patients >40 years old.[28] Moreover, in the trial of adalimumab for non-radiographic axSpA, 87% of patients aged ≤30 years reached the ASAS40 criteria, compared with only 16.7% of those aged >40 years.

Besides age and/or short symptom duration, the second predictor of a good response to anti-TNF treatment in nearly all analyses has been positivity for CRP at inclusion, in comparison with the CRP-negative group.[15,21,27–29] Positive HLA-B27 status, active bony inflammation on MRI images, and good function have been only partly, and less consistently, associated with a favorable treatment response.[15,21,27,28,30] Thus, patients with short disease duration and/or objective signs of inflammation—positive CRP seems to be a better indicator of active inflammation than MRI findings[15,21,30]—respond especially well to TNF-blocker therapy.

Attempts have been made to combine predictive factors into a prognostic tool. For example, using data from 635 patients with AS in 2 placebo-controlled trials, it was shown that ~50% of patients with elevated CRP levels, HLA-B27 positivity, young age, and good physical function would reach ASAS remission, whereas the remission rate was as low as ~5% if all these parameters were negative.[29]

Analyses such as these have been based on the presence or absence of predictive factors at baseline. Taking a broader approach, an analysis published online in 2011 of 5-year follow-up data from patients with AS treated with adalimumab took not only baseline parameters but also 12-week response data into account.[24] The investigators looked for parameters that were predictive of sustained ASAS remission over several time points, or of the presence of ASAS remission after 5 years. The best predictor of both these outcomes was being in ASAS

remission at week 12.[24] Taking all the available data into account, it seems that CRP levels, short duration of symptoms, and a good response to treatment in the first 3–6 months are the best predictors of response to TNF-blocker therapy in patients with axSpA. Nevertheless, it should also be stressed that a relevant number of patients who are negative for these predictors can also show a reasonable treatment response, as is evident from the data presented above.

Anti-TNF treatment recommendations

Before the 2010 update of the ASAS recommendations for the use of anti-TNF medication in axSpA,[11] such therapy was confined to patients fulfilling the mNY criteria for this disease subtype. The updated recommendations extend use of these drugs to patients who fulfill the new ASAS classification criteria for axSpA, enabling use of these compounds earlier in the disease course than was previously advised.[4,11] Another substantial change is the period for which NSAID therapy, with at least two such drugs, should be tried before a biologic agent is prescribed, which has been shortened from 3 months to 4 weeks (in patients with peripheral disease a conventional DMARD such as sulfasalazine should be tried after failure of NSAID therapy, but this step does not apply in axSpA). Besides these changes and a few more minor refinements, the updated recommendations are largely similar to their predecessors, and require the presence of active disease for ≥4 weeks.

As in the first ASAS recommendations,[9] high disease activity is defined in the updated advice by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 on a 0–10 scale; expert opinion that the patient is a suitable candidate for treatment with a TNF blocker is also required. The expert is usually a local rheumatologist familiar with SpA and TNF-blocker treatment, who will assess objective signs of inflammation, such as elevated CRP levels or active bone inflammation on MRI images. It is important to stress that an elevated BASDAI alone is often insufficient evidence that a patient's symptoms are caused by inflammation—a necessary condition for a good response to anti-TNF therapy—rather than being attributable to other causes, such as structural damage or fibromyalgia. Adaptations to national recommendations for the use of anti-TNF agents in patients with axSpA can be expected, particularly when the results of the phase III trials in patients with non-radiographic axSpA become available.

Immunogenicity, efficacy and switching

The induction of anti-drug antibodies—with potential loss of therapeutic efficacy—has been reported in patients with AS treated with TNF blockers, especially with the monoclonal antibodies infliximab[31] and adalimumab.[32] It has been discussed that a combination of TNF-blockers, especially of infliximab, with another disease modifying drug such as azathioprine[33] or methotrexate could suppress such an anti-drug immune response. However, three clinical trials comparing infliximab alone to a combination of infliximab and methotrexate found no superiority in terms of efficacy and allergic adverse events for the combination therapy.[34–36] Thus, no evidence currently supports the use of such a regimen.

If an anti-TNF drug is initially inefficacious and/or induces a neutralizing response, switching to an alternative agent can be effective, although response rates tend to be lower than those for a first anti-TNF therapy. For example, an ASAS40 response to a 12-week course of adalimumab was reached by 38% of patients who had received previous therapy with infliximab or etanercept, whereas the rate was 59% in patients with no prior exposure to anti-TNF therapy.[37] In those patients for whom adalimumab was not the first TNF blocker tried, a better response was more likely if their response to the first drug had been lost over time, rather than if no response had occurred.[37] Similarly, a study of 514 patients with AS taking a TNF blocker for the first time, 77 of whom switched therapies, found that a subsequent 2-point decrease of the BASDAI occurred in patients who switched to the second and/or third anti-TNF therapy, in comparison with a decrease of 3 BASDAI points in patients taking their first such drug.[38]

Other biologic therapies

Although TNF blockers have proven to be fairly effective in axSpA and AS, 20–40% of patients with these diseases do not respond, or respond inadequately, to these agents. Furthermore, remission is not reached in many patients, and bony inflammation as assessed by MRI is only reduced by ~70% in patients who continue to take the therapy. Thus, demand exists for novel, more efficacious treatments not only for patients who do not respond to TNF-blocker therapy (although the need is clearly greatest in this group), but for all patients with SpA.

Several biologic agents with targets other than TNF have been successfully tested in other diseases, including RA and psoriasis; indeed, a few have already been approved for some indications. Anakinra, an IL-1 receptor antagonist with approval for RA, was not effective in a study in 20 patients with NSAID-refractory, TNF-naive AS.[39] A prospective open-label trial of the B-cell depleting agent rituximab also showed no therapeutic effect in 10 patients with AS refractory to anti-TNF therapy, although it did show some efficacy in 10 patients not previously treated with biologic therapy.[40] In a similarly designed, open-label study of the T-cell modulating agent abatacept, efficacy was demonstrated in neither 15 anti-TNF-naive patients with active AS, nor in 15 patients for whom such therapy had previously failed.[41] This lack of efficacy of abatacept in axSpA has since been confirmed in another small trial.[42]

Monoclonal antibodies directed against the IL-6 receptor, which include tocilizumab (quite effective in the treatment of RA), seem to lack efficacy in patients with AS, in contrast to some earlier positive case reports. Detailed results of two placebo-controlled trials of these antibodies in patients with active AS are expected in the near future.[43,44]

Besides IL-1 and IL-6, two other cytokines, IL-23 and IL-17, are attracting interest among researchers in SpA.

IL-23, produced mostly by cells of the macrophage/monocyte lineage, stimulates type 17 T helper (T_H17) cells to secrete IL-17. This pathway seems to have a role in chronic immune responses, including autoimmune disease. My group has shown that IL-17$^+$ cells are found in an increased number in the subchondral bone marrow of patients with AS in comparison with osteoarthritis controls, although IL-17 was produced mostly by neutrophils and not by T cells in this setting.[45]

Ustekinumab is a monoclonal antibody directed against the p40 chain common to both IL-23 and IL-12, and therefore blocks both cytokines. Ustekinumab[46] and secukinumab (AIN457),[47] which recognizes IL-17, have shown reasonable efficacy in patients with psoriasis. A small phase II trial of AIN457 in patients with AS produced promising results in comparison with placebo;[48] the drug will therefore now be investigated in a large placebo-controlled trial. The efficacy of ustekinumab in AS is also currently being tested in a small study.[49]

Together, these results clearly indicate that axSpA is mechanistically different to RA, and that the efficacy of any promising new drug for the latter must be tested in patients with axSpA or AS. Conclusions based on trials in other chronic inflammatory diseases are of only limited value, and major demand exists for new drugs that are effective in patients with active axSpA.

Can structural damage be prevented in axSpA?

NSAIDs and TNF-blocking agents do have, beyond any doubt, a good effect on the signs and symptoms of axSpA. This success raises the question as to whether these drugs also prevent structural damage. Structural damage in AS is mostly defined by new bone formation, because ankylosis of the spine has the most important impact on long-term restriction of spinal mobility and disability.[50] Erosive bony damage, although it does occur in the SIJ and the spine, and usually precedes new bone formation, is considered less functionally important; the effect of drugs on this aspect has not been investigated.

Rather surprisingly, a study published in 2005 showed that continuous, daily intake of NSAIDs could indeed retard the growth of syndesmophytes, as measured by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), in comparison with an on-demand intake of the drugs.[51] This study confirmed results dating back to 1976, which showed that phenylbutazone, an NSAID used frequently at that time, could retard spinal ossification.[52] A more recent analysis of data from GESPIC (the prospective German SpA inception cohort) similarly demonstrated that patients with a high NSAID intake over 2 years had less new bone formation in the spine than patients with low NSAID intake over this period.[53] Interestingly, this protective effect was nearly exclusively seen in patients with elevated CRP levels over time and the presence of syndesmophytes at baseline, the strongest risk factors for the growth of syndesmophytes.[53] To calculate NSAID consumption, the investigators used an ASAS index of NSAID intake that was published in 2011.[54]

The apparent protective effect of NSAIDs is probably attributable not to their anti-inflammatory capacity, but rather to their inhibitory effect on osteoblast function, which is controlled by prostaglandins.[55] By contrast, no retardation in mSASSS advancement was found in analyses of patients with AS treated for 2 years with infliximab,[56] etanercept,[57] or adalimumab,[58] in comparison with a historical control group.[7] These findings have initiated an intense discussion about the sequence of events that lead to structural damage in AS, and how this outcome can be prevented. On the basis of 1-year and 2-year MRI and X-ray studies of patients with axSpA, the pathological sequence has become increasingly clear. Firstly, inflammation—best visualized using short tau inversion recovery (STIR) MRI sequences[59,60]—occurs, followed by the replacement of subchondral bone marrow with fatty tissue (visible best as fatty lesions in T1-sequence MRI images).[60] Finally, new bone formation (syndesmophyte growth) ensues,[61] which is best visualized radiographically.[62–64] The exact timescale over which these events occur is not clear yet, and is a topic for future research.

Ongoing studies will confirm (or modify) this sequence of events. Subsequently, combined MRI and X-ray studies will help to clarify whether early intervention with TNF-blocking agents—before fatty lesions are visible using MRI—can in fact prevent the occurrence of syndesmophytes, despite their apparent failure to do so in patients with established disease. Moreover, whether other drugs, such as NSAIDs, can prevent progression from fatty lesions to syndesmophyte formation could also be examined. In this context, a trial of the effect of TNF-blockers in combination with NSAIDs on syndesmophyte growth would be of special interest.

Peripheral SpA

As mentioned in the Introduction, placebo-controlled trials of therapy for peripheral SpA, except polyarthritic PsA, have mostly been lacking. Nevertheless, analyses of data from clinical trials in AS of the subgroup of patients with—in addition to their predominant axial disease—peripheral manifestations such as peripheral arthritis or peripheral enthesitis have suggested that conventional DMARDs, such as sulfasalazine,[65,66] and TNF blockers,[67] might be effective for these symptoms. The 2011 ASAS criteria for peripheral SpA[5] will now enable more systematic trials of drugs in patients with peripheral manifestations.

TNF-blocker treatments

In a placebo-controlled trial published in 2010, 20 patients with peripheral SpA with enthesitis of the heel confirmed by MRI were treated for 12 weeks with either etanercept or placebo.[69] The patients would all have fulfilled the new ASAS criteria for peripheral SpA,[5] although they were not yet published when the trial began. A significantly greater improvement in the primary outcome parameter (patient global assessment) was demonstrated in the etanercept group, compared with the placebo group. Indeed, in the latest management recommendations for both AS[7] and PsA,[70] TNF blockers are recommended for patients with peripheral enthesitis if treatment with NSAIDs fails.

Antibiotic therapy

If a triggering event such as a preceding infection is known to have occurred in patients with peripheral arthritis (or reactive arthritis), treatment with antibiotics might seem logical. However, several trials of antibiotic therapy, often over a period of 3 months, have failed to show an effect on the course of arthritis in this setting.[71,72] Only when *Chlamydia* spp. have been identified as the causative agent have positive signals been reported in trials of antibiotic therapy.[73] For a long time, it has been assumed that in many patients presenting with peripheral SpA, a triggering event that is not clinically apparent, such as a latent infection, has occurred. In support of this assumption, chlamydial DNA was identified by PCR significantly more frequently in a study of samples from 26 people with chronic undifferentiated SpA than in control samples from patients with osteoarthritis.[74]

Whereas previous trials have tested single antibiotics, a study published in 2010 used a combination of two antibiotics (either doxycycline plus rifampin, or azithromycin plus rifampin), and only included patients in whom chlamydial DNA could be detected in either the joint or peripheral blood; furthermore, antibiotic treatment was prolonged to 6 months.[75] Most patients presented with a clinical picture of SpA, according to the authors, although an exact definition was not given. 63% of patients treated with antibiotics showed a 20% improvement of their symptoms, versus 20% of the placebo group. Moreover, remission was reached in 22% of participants who were treated with antibiotics, compared with 0% in the placebo group.[75] These data indicate that a causative treatment approach might be possible in some patients presenting with a clinical picture of peripheral SpA.

SpA-associated uveitis

Current or prior anterior uveitis affects 30–40% of patients with AS; annual flares of the eye inflammation are reported in 15–20% of patients with AS. No controlled trials of treatment for active anterior uveitis in patients with SpA are available; however, the flare rate is reduced by ~50% in patients with AS treated with a TNF blocker—infliximab[76] reportedly has a slightly better effect than adalimumab[77]or etanercept[78] although new onset of uveitis has also been reported if SpA patients were treated with TNF-blockers.[79]

Conclusions

It is increasingly clear that patients with axSpA can—and should—be diagnosed earlier. Furthermore, patients who have not yet developed radiographic sacroiliitis seem to respond at least similarly well, if not better, to TNF-blocker therapy as patients with radiographic sacroiliitis fulfilling the criteria for AS. Anti-TNF treatment is currently the only effective therapy for patients in whom conventional therapy with NSAIDs has failed. The best drugs or combinations of drugs for preventing new bone formation in axSpA are yet to be determined, as is the potential impact of earlier treatment on bone pathology. Finally, more treatment trials are needed in the near future in patients with peripheral spondyloarthritis, a subgroup that has been rather neglected in the past. Classification criteria for SpA subtypes will facilitate such efforts; further advancements in therapeutic options for patients with any manifestation of SpA are expected to follow in the coming years.

Review criteria

Original articles published between 2006 and 2012 were searched for focusing on subject in MEDLINE and PubMed. The search terms used were "anklyosing spondylitis", "spondyloarthritis", "treatment", "therapy" and "TNF-blocker"; each of the last 3 keywords were used in combination with "ankylosing spondylitis" or with "spondyloarthritis". All papers identified were English-language full text papers. The reference lists of identified articles were also searched manually for further papers of interest. Abstracts were included only if of great importance to the topic of this article.

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