Spondyloarthritis: From disease phenotypes to novel treatments
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General discussion and summary
Spondyloarthritis (SpA) is a disease with many different faces (axial disease, peripheral arthritis, enthesitis, ...) which results in highly heterogeneous phenotypes in different patients. The key question addressed in this thesis is whether this phenotypical heterogeneity reflects fundamentally different disease processes, this is whether different expressions of tissue inflammation are driven by distinct cellular and molecular pathways. If so, targeting a specific pathway would only be therapeutically beneficial in a specific subset of SpA (e.g. in ankylosing spondylitis (AS) but not in psoriatic arthritis (PsA) or undifferentiated spondyloarthritis (USpA)) or in a specific disease manifestation (e.g. in synovitis but not in enthesitis). Alternatively, these different phenotypes represent one single disease driven by shared or ‘public’ pathogenic pathways, with minor ‘private’ pathways determining the exact phenotypic expression of the disease. If this hypothesis is correct, targeting the public pathways should be effective in all the different phenotypes and tissue manifestations of SpA. This is how disease phenotypes and novel treatments in SpA, the initially perhaps seemingly unrelated two parts of this thesis, come together.

**DISEASE PHENOTYPES IN SPONDYLOARTHRITIS**

**Early disease**

Unraveling where and how disease is initiated is key to our understanding of the fundamental pathophysiology of SpA and its different phenotypic manifestations. However, it is very difficult to study this in humans since it is not easy to indicate a time point when the disease actually is starting. McGonagle et al. previously proposed a hypothesis postulating that the primary lesion of SpA is enthesitis (inflammation at the attachment sites of ligaments, tendons and joint capsules to bone) and that this could explain all signs of SpA, including synovitis, which would be secondary to the release of proinflammatory mediators from the enthesis. If this hypothesis is correct, pathophysiological studies should focus on experimental models of enthesitis rather than synovitis and translational research should aim to obtain and study entheseal biopsies rather than synovial biopsies. Moreover, clinical trials should then focus on specific treatments targeting primary enthesitis instead of pathways that are active in synovitis, since these last pathways might only be secondary and therefore not a good target to treat the disease.

In Chapter 3 we reevaluated this hypothesis by performing a combined imaging and histopathological study to assess the presence and extent of enthesitis and synovitis in early untreated SpA versus rheumatoid arthritis (RA) peripheral arthritis. The major findings of this study were that the frequency as well as the extent and localization of enthesitis are similar in SpA and RA. Moreover, the degree of synovitis as assessed by magnetic resonance imaging (MRI) and immunohistology was similar or even slightly increased in SpA versus RA. These results, which are in line with findings of earlier studies, challenge the hypothesis that enthesitis is the primary immunopathological lesion in SpA. In contrast to McGonagle et al., we propose that SpA can primarily affect a variety of tissues which are exposed to cellular stress (including but not restricted to mechanical stress), such as the enthesis but also the synovial tissue, the bone and extra-articular manifestations like the uvea, aortic root, skin and ileum. This hypothesis is supported by animal models where various tissues are involved in the early SpA phenotype. Two models have highlighted the role of enthesitis in SpA immunopathology.
Firstly, the ankylosing enthesitis model in DBA/1 mice demonstrates that entheseal stress can lead to osteoproliferation and mild inflammation reminiscent of heel enthesitis in human SpA. Secondly, a ground-breaking mechanistic study recently provided convincing evidence that interleukin (IL)-23 overexpression induces enthesitis (including involvement of the aortic valve, an enthesis-like structure) and SpA-like disease by acting on double-negative, enthesis-resident T lymphocytes. Surprisingly, however, an earlier report of the same overexpression model revealed a severely destructive polyarthritis which is more a model for RA instead of SpA. Furthermore our group demonstrated that in the human leukocyte antigen (HLA)-B27/β2 microglobulin transgenic rat model, which is presumably the most ‘physiological’ experimental model for SpA, the earliest histopathological signs of inflammation are found in the synovium of peripheral joints and in the connective tissues of the spine in the absence of enthesis. More recently, we also demonstrated that transmembrane tumor necrosis factor (tmTNF) overexpression induces experimental arthritis and spondylitis with radiographic and histologic proven new bone formation; in this model, early histopathological lesions include synovitis, enthesitis and osteitis (Van Duivenvoorde et al manuscript in preparation). Finally, some animal models such as the curdlan-induced disease in SKG mice indicate an important role of gut inflammation (ileitis) in the development of SpA-like musculoskeletal disease.

The key question is not which of these tissues is affected first in an individual patient or specific experimental model but rather which molecular and cellular pathways are locally activated during the initiation of the disease process. To address this issue, we need either to rely on animal models where a specific pathway is artificially deregulated (e.g. IL-23 and tmTNF) or to study the human target tissue longitudinally during disease initiation. The latter is feasible with sequential synovial biopsies but can medically and ethically not be performed on tissues such as entheses, uvea and aortic roots. It is the question whether the currently ongoing early SpA cohorts (often defined as disease duration less than 3 years) capture the appropriate patient population to address this issue, or whether we need to capture (future) patients in even earlier disease stages. For this purpose, we recently initiated a cohort study of seemingly healthy first degree relatives of SpA patients. Sequential biosampling and imaging in this cohort of individuals at risk of developing SpA will allow to define a temporal hierarchy of immune alterations leading ultimately to clinical SpA.

**Classical phenotypic classification**

In addition to studying SpA longitudinally to assess potential differences in immunopathology in different disease stages as discussed in the previous paragraph, we also aimed to study SpA cross-sectionally in order to identify differences in immunopathology between different disease phenotypes. This approach has been extensively used to study the two prototypical forms of SpA, AS and PsA, but data on other SpA subtypes are scarce. We therefore revisited the cross-sectional investigation of SpA phenotypes using two different types of classifications: the classical phenotypic classification (USpA versus AS and PsA) and the new Assessment of SpondyloArthritis international Society (ASAS) classification (axial versus peripheral disease).

The classical subdivision of SpA into the different phenotypic forms AS, PsA, inflammatory bowel disease (IBD)-related SpA, reactive arthritis (ReA) and USpA is still used in daily clinical practice.
these the prototypic subtypes AS and PsA are the best described and studied. However, increasing evidence indicate that all the different subtypes belong to a single disease with a heterogeneous phenotype rather than distinct disease entities. This concept is based on studies on genetic background, immunopathology, and animal models, as well as on the clinical observation that a single patient can express several phenotypes at once or can evolve from one phenotype to another over time. This would imply that fundamental insights in AS and/or PsA, such as the good response to TNF blockade, are likely to equally hold true in the other SpA subtypes.

This concept is now further supported by our clinical study described in Chapter 4, where we assessed the similarities and differences in patient characteristics, disease activity and response to TNF inhibitors between USpA and AS and PsA patients in a real-life outpatient setting. In this study we show that USpA: 1) is a common SpA subtype that presents at younger age than AS and PsA, 2) exhibits a mixed axial and peripheral phenotype, frequently with low-grade sacroiliitis, 3) has at least similar disease activity compared to AS and PsA and 4) appears to respond as well to TNF inhibitors as AS and PsA, underscoring that also USpA is an important subgroup of SpA. However, this subgroup is commonly excluded from clinical trials. This results in the clinical problem that, despite that data of our study, USpA patients do not qualify to be treated with effective therapies such as TNF inhibitors because these are not registered for USpA patients. Moreover, the same problem will persist in the future if USpA is not included in novel clinical trials with novel compounds. This urges us to advocate to replace the classical phenotypic classification by the new ASAS sub-classification into axial and peripheral disease according to the predominant disease manifestation. Recognition of the major disease manifestations, such as axial and peripheral disease, independently of specific ‘phenotypic’ features will allow to capture SpA in a more accurate way as both early and less prototypical forms of the disease will be included. This has already been well demonstrated for the non-radiographic forms of axial SpA (nr-axSpA), which do not (yet) display the radiographic sacroiliitis required to fulfil the modified New York criteria for AS but, as indicated by our study, also applies to the former ‘USpA’ with peripheral disease manifestations.

Classification into axial and peripheral disease
To what extent the novel classification in axial versus peripheral SpA as proposed by the ASAS would allow to better capture the full spectrum of SpA was investigated in Chapter 5 as we anticipated that many patients with SpA may present with both axial and peripheral disease. The ASAS criteria, however, do not include ‘combined’ disease and pre-specify that patients with combined disease should be considered as ‘axial SpA’. We investigated the clinical characteristics and disease activity of the different SpA subpopulations according to the ASAS criteria in a real life observational cohort study of 389 SpA patients who were diagnosed by the rheumatologist’s expert opinion (which is still considered as the gold standard) and fulfilled the European Spondyloarthropathy Study Group (ESSG) criteria. However, when we applied the ASAS criteria strictly (this is: whenever a patient reports active axial symptoms, even if minor in comparison with pronounced peripheral disease, he should enter the axial arm of the criteria) a substantial group of patients failed to be classified as SpA by the ASAS criteria. Moreover, it was striking that many of these patients had predominantly peripheral disease with additional but not predominant axial symptoms. If these
patients were allowed to enter the SpA classification through the peripheral arm of the criteria, 65% of these patients would now fulfill these ‘modified ASAS criteria’, which is an indication that the ASAS criteria might underestimate peripheral disease. This is further underscored by the finding that the cohort of patients classified as axial SpA according to the ASAS criteria in fact consisted of two separate groups of equal size: patients with exclusive axial disease and patients with combined axial and peripheral disease (active inflammatory back pain plus arthritis, enthesitis and/or dactylitis). Importantly, the latter subgroup showed the highest disease activity. That is why we propose a modification of the ASAS criteria so that patients with combined axial and peripheral symptoms could enter either the axial or peripheral arm of the criteria. This proposal should obviously be validated in other cohorts.

The finding that not all SpA patients are correctly classified by the ASAS criteria is in line with a previous study which concluded that the ASAS axial SpA criteria and rheumatology experts captured different patient populations. Moreover, previous studies which evaluated the performance of the ASAS criteria already illustrated that there is a lot of confusion how to actually apply these criteria, since all these studies used somewhat different definitions of the classified subgroups. This makes the comparison of results concerning sensitivity, specificity, prevalence and patient characteristics between studies very inaccurate.

It is crucial to emphasize here that the ASAS criteria are developed for classification of patients, which is fundamentally different from diagnosing. With our study we thus do not argue that the use of the new criteria would lead to diagnostic issues and do not insinuate that our proposed modification would solve this. Experienced rheumatologists will undoubtedly recognize the diagnosis of SpA in patients with combined axial and peripheral disease, even if they do not fulfill the ASAS criteria. Similarly to the older phenotypic classification discussed above, however, criteria are often quite strictly applied for registration of novel treatments and this may again have consequences for the treatment of patients in daily practice. Therefore, further optimization of diagnostic and classification criteria are mandatory to adequately capture the presence and severity of the different manifestations of this heterogeneous disease and to guide optimal treatment decisions.

**NOVEL TREATMENTS IN SPONDYLOARTHRITIS**

**Optimal usage of existing effective therapies**

As already described above effective biological therapies are only available for AS and PsA patients and not for the other SpA subgroups. This has a big impact on the management of the disease since the therapeutic arsenal for SpA is already very limited compared to the RA field. In axial SpA, the therapeutic arsenal is limited to non-steroidal anti-inflammatory drugs (NSAIDs) and TNF inhibitors in case of axial SpA. For peripheral SpA, it comprises intra-articular corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine, leflunomide and methotrexate, although the evidence supporting the use of these DMARDs is very weak. TNF inhibitors and, more recently, ustekinumab (targeting the p40 subunit of IL-23 and IL-12) and apremilast (a small molecule targeting phosphodiesterase 4) were approved for PsA but not for other forms of peripheral SpA. There is thus a high unmet medical need
for 1) novel biologic therapies besides TNF blockade for axial SpA, 2) more solid evidence for (or against) the use of DMARDs in peripheral SpA, and 3) evidence supporting the use of TNF blockers in non-psoriatic peripheral SpA.

In Chapter 6 we describe a study addressing the latter issue. Performing an investigator initiated randomized double-blind, placebo-controlled clinical trial with adalimumab in patients with active peripheral SpA not fulfilling the criteria for AS or PsA, we show that adalimumab but not placebo induced a rapid and significant decrease in disease activity. This is in line with previous small studies, and was recently confirmed in the ABILITY-2 trial, a large phase III trial with adalimumab in peripheral SpA. As already underscored in Chapter 4 it is important not to exclude these less typical phenotypes such as USpA from clinical trials and registration of effective therapies, since clinical trials in USpA are feasible and USpA respond similarly to effective anti-TNF therapy as AS and PsA. We have now demonstrated this not only cross-sectionally (Chapter 4), but also in a randomized controlled trial (Chapter 6). This indicates that TNF inhibitors are effective and safe in peripheral SpA, including USpA, and therefore this therapy should be made available for these patients. Moreover, this also underscores that all types of patients with SpA should be included into clinical trials with novel compounds. In axial SpA this is already starting to happen. It has been shown recently that TNF inhibitors are equally effective in nr-axSpA as in AS, especially in those patients with active inflammatory lesions on MRI or with elevated C-reactive protein (CRP). We advocate that this trend to be more inclusive in trials and registration of TNF blockers as well as novel drugs in the field of SpA should not only apply to axial but also to peripheral disease.

A major issue in determining the efficacy of therapeutic compounds in SpA as a whole (including axial and peripheral disease) is that there is no generally accepted definition for treatment success or failure or disease remission. Outcome measurements for axial SpA, including the original ‘Bath’ measurements (BASDAI, BASFI, BASMI) and the more recent ASAS tools (ASAS20 response, ASDAS, ...) are broadly available and well validated. In contrast, we do not have such tools for peripheral SpA. PsA studies have often used outcome measurements from the RA field, such as ACR 20/50/70 responses. These tools, however, have been developed for polyarticular synovitis and do not capture appropriately oligo-arthritis, enthesitis, dactylitis and axial disease. More specific peripheral SpA outcome parameters have only started to emerge recently. Our study described in Chapter 6 and the subsequent ABILITY-2 study now allows us to test and validate appropriate outcome parameters for this patient population. One can anticipate that this will require a composite index of patient reported outcomes and more objective biomarkers of inflammation (e.g. CRP and calprotectin) as well as structural damage (e.g. vascular endothelial growth factor (VEGF) and calprotectin). Ideally, such outcome parameter would not only be applicable at the group level for clinical research but would be sufficiently reproducible and discriminative to be applied to individual patients in clinical practice.

Biologic-free remission

Once disease remission has been achieved, the next question is whether this remission can be maintained after dose tapering or discontinuation of the treatment. This would reduce the chance of possible side effects of the treatment and would save costs. In Chapter 7 we show that
unfortunately more than 70% of peripheral SpA patients who were included in a follow-up study from the study in Chapter 6 relapse within 16 weeks after interruption of TNF blockade. Even patients with complete remission of arthritis or reaching Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease did rapidly flare. This is in line with previous studies in axial SpA.\textsuperscript{56-63} Recently a study reported better percentages for biological-free remission in patients with early axial SpA, where about half of the patients remained in partial remission 24 weeks after stopping the TNF inhibitor, although also here the disease activity gradually increased over time.\textsuperscript{64}

Collectively these data indicate that discontinuation of TNF inhibitors is probably not a good option in SpA. However, dose tapering after achieving an initial remission is certainly a treatment strategy that should be further explored. Opponents of this strategy proclaim that lower doses and/or higher intervals of dosing may promote the induction of anti-drug antibodies (ADAbs) towards the TNF inhibitor, which in turn may result in loss of response to treatment by either an increased clearance of the drug or neutralization of the active component of the therapeutic compound.\textsuperscript{65,66} However, it has been shown that patients effectively respond to retreatment in case of flare of disease symptoms.\textsuperscript{60,63,67} Moreover, we show in Chapter 8 that at least in peripheral SpA: 1) trough serum adalimumab levels are heterogeneous but do not correlate with clinical response to treatment or relapse after anti-TNF treatment discontinuation, 2) anti-adalimumab ADAbs are found in 1/4 patients but also do not correlate with clinical response to treatment or relapse after discontinuation of the TNF inhibitor, and 3) low titer ADAbs can be masked by circulating adalimumab but also ‘unmasked’ ADAbs show no clear relationship with clinical efficacy. Moreover, the potential detrimental role of ADAbs has now been pretty well established in RA (at least at the group level; whether measurements in individual patients can guide treatment decisions remains to be determined), but the data are less robust and consistent in AS and PsA.\textsuperscript{68} Whereas the role and relevance of immunogenicity to biologic drugs should certainly be further investigated in SpA, our study illustrates well that novel findings and concepts such as immunogenicity and drug-free remission cannot automatically be extrapolated from RA to the SpA field.

Novel promising treatment options
The management of SpA has improved tremendously since the introduction of TNF inhibitors for this disease over a decade ago, but these drugs also have their limitations. Firstly, a substantial amount of patients (approximately 40% depending on with which outcome parameter this is determined) does not adequately respond to anti-TNF treatment either due to inefficacy or adverse reactions.\textsuperscript{17} Secondly, it is not possible to maintain drug-free remission after stopping the TNF inhibitor and patients stay dependent on this expensive therapy with possible side effects, as discussed above in Chapter 6.\textsuperscript{56-63} And finally, TNF blockade can halt joint destruction\textsuperscript{69} but fails to significantly inhibit pathological new bone formation in SpA.\textsuperscript{70-72} Therefore, there is still a high unmet need for new and better drugs, even in prototypical AS and PsA.

In Chapter 9 we discuss the rationale of targeting the IL-23/IL-17 axis in SpA and give an overview of the recent results of clinical trials inhibiting (parts of) this axis in SpA. One of the key trials is described in Chapter 10, where we show that inhibiting IL-17A in AS profoundly modulates signs and symptoms of disease in a small size, short term, proof-of-concept trial. 60% of patients in the secukinumab group, of whom 45% received prior anti-TNF-treatment, reached the
primary endpoint of ASAS20 response at week 6, indicating a 99.8% probability that secukinumab was more effective than placebo. Favorable changes in secondary clinical outcomes, including acute-phase parameters, MRI scores and quality-of-life measures, further supported clinical efficacy. The clinical response to secukinumab was also significantly associated with genetic polymorphisms in the ERAP1 gene, and showed a trend towards association with polymorphisms in the IL23R gene. This is the first randomized double-blind placebo-controlled phase II trial which reached its primary outcome in AS since the introduction of TNF blockers. Moreover, this is the first example of a targeted therapy where a strong association is demonstrated between pathway-related genetic risk factors and clinical response to therapeutic targeting of the pathway, which is a robust indication that the IL-23/IL-17 axis is a pivotal pathway in the pathophysiology of SpA. Phase III trials are currently ongoing to confirm these observations and investigate the long term efficacy and safety of IL-17 blockade in AS and PsA. The phase III trials will also reveal whether secukinumab is equally effective in anti-TNF incomplete responders as in anti-TNF naive patients, which would be of major relevance for daily clinical practice. And, finally, long term results will show whether osteoproliferation is halted by targeting the IL-23/IL-17 axis. In parallel with these phase III trials addressing key clinical questions, we initiated a mechanism of action trial where sequential biosampling (including synovial biopsies) will allow us to study in more detail how IL-17 blockade affects the immunopathology of SpA and whether or not the biological effects are distinct from those observed with TNF blockers, as we obtained similar samples in our adalimumab study described in Chapter 6.

Also in PsA several trials have now demonstrated that blocking IL-17 with secukinumab or brodalumab as well as blocking upstream IL-23/IL-12 is clinically effective, leading to the registration of ustekinumab for the treatment of PsA. Moreover, proof-of-concept trials with new compounds targeting the IL-23/IL-17 axis are currently ongoing (www.clinicaltrials.gov). These include briakinumab (another IL-12/IL-23 inhibitor targeting the common p40 subunit), tildrakizumab and guselkumab (both monoclonal antibodies targeting the p19 subunit of IL-23), apilimod (a small molecule that selectively suppresses the synthesis of IL-12 and IL-23) and fezakinumab (a monoclonal antibody directed against IL-22). Also, small molecules targeting this axis, including compounds targeting IL-23R, Janus kinases (JAKs) and RAR-related orphan receptor gamma (RORγt), are in preclinical or clinical development. Whether therapeutics targeting the IL-23/IL-17 axis or other axes will inhibit new bone formation still needs to be awaited. Likewise, head-to-head clinical trials with TNF inhibitors are necessary to see the future position of these compounds: should it be used as second line treatment after failure on TNF inhibitors, should it be used as alternative for TNF inhibitors, or can it perhaps be used simultaneously as combination treatment for a synergistic effect?

Two recent randomized controlled trials with novel therapeutic target have not been discussed in Chapter 9: the studies with apremilast (an oral phosphodiesterase (PDE) 4 inhibitor) in AS and PsA and our own proof-of-concept investigator initiated clinical trial with nilotinib in axial and peripheral SpA (Chapter 11). The phase II and III clinical trial with apremilast in SpA showed a significantly better American College of Rheumatology criteria for 20% improvement (ACR20) response in the treated group (31-44%) compared to placebo. However, in AS this effect was less clear since the primary end point of the phase II study was not met, although there was a numerically improvement in disease activity measurements in the treated group.
In Chapter 11 we studied the mast cell as potential therapeutic target in SpA based on the following rationale. Firstly, the infiltration of the synovial membrane by c-Kit+ mast cells is markedly higher in SpA than in RA.25 Secondly, this infiltration is already observed in early disease and is not affected by effective anti-TNF treatment.25 Thirdly, mast cells are the major IL-17 expressing cells in peripheral SpA and the proportion of mast cells expressing IL-17 is significantly higher in SpA than RA synovitis.25 Fourthly, as mentioned previously, IL-17A blockade with secukinumab effectively down-modulates inflammation and clinical symptoms in AS (Chapter 10) and PsA.21 Finally, sulfasalazine, the only DMARD with proven efficacy in peripheral SpA,10 has shown to inhibit degranulation and TNF secretion by mast cells.81,82 Mast cells can be targeted in vivo by tyrosine kinase inhibitors such as imatinib and nilotinib, which are registered for the treatment of chronic myeloid leukemia (CML).83,84 Originally developed to inhibit c-Abl on malignant leucocytes, these drugs also appeared to inhibit c-Kit, the receptor for stem cell factor, thereby inducing apoptosis of mast cells, including synovial mast cells.85 Accordingly, we recently demonstrated in ex vivo biopsy tissue cultures that imatinib strongly reduced spontaneous production and secretion of pro-inflammatory cytokines including IL-6, IL-8 and IL-17 by SpA synovium.25 In line with this data, a small open label trial with imatinib in 6 SpA patients showed a decrease in clinical and serum markers of disease activity upon 3 months of treatment.86 The study described in Chapter 11 supports the role of mast cells in synovial inflammation by demonstrating histological, biological and clinical effects of nilotinib treatment in peripheral SpA. In agreement with previous ex vivo studies demonstrating that imatinib reduced the spontaneous production of proinflammatory cytokines by the synovial tissue25 and induces apoptosis of synovial mast cells,85 in vivo treatment with nilotinib induced a decrease in the number of synovial mast cells and in c-Kit mRNA expression in peripheral SpA. This was associated with a decrease in infiltrating macrophages, synovial expression of pro-inflammatory cytokines such as IL-6 and IL-23, systemic CRP levels, and clinical disease activity parameters. Importantly, the immunomodulatory effect of nilotinib was consistent across biological and clinical measurements and was not observed in the placebo group. Together with the published small open label study with imatinib,86 these data indicate that tyrosine kinase inhibitors targeting mast cells can suppress inflammation in peripheral SpA and thereby confirm the potential role of mast cells in SpA pathogenesis. Strikingly, the beneficial effects seen in peripheral SpA were not seen in axial SpA, which is possibly a sign that peripheral and axial SpA are driven by slightly different mechanisms. This concept is further supported by previous observations that the major cellular source of IL-17 in peripheral SpA are mast cells and to a lesser degree neutrophils,25 while in axial SpA neutrophils and myeloperoxidase (MPO)+ cells are the major IL-17 expressing cells.87 Furthermore, sulfasalazine, which also targets mast cells,81,82 has proven clinical efficacy in peripheral but not axial disease.80 Another important observation from this trial was that the placebo response in axial SpA was extremely high, indicating that we should be very careful in interpreting results of open-label clinical trials80,89 and that we should aim to always include a placebo-arm in our trial design.
CONCLUDING REMARKS AND FUTURE DIRECTIONS

Over the past years more insights have been gained in the disease phenotype of SpA and promising novel therapeutic compounds have been developed and tested for this disabling disease. However, only when full understanding of SpA is achieved, successful novel drugs and strategies can be introduced. The research included in this thesis has tried to contribute to the existing knowledge on this disease and support the hypothesis that SpA is one single disease driven by shared or ‘public’ pathogenic pathways, with minor ‘private’ pathways determining the exact phenotypic expression of the disease. The coming period validation studies will follow to fine-tune the classification criteria for SpA. Perhaps diagnostic criteria will follow which can provide a reliable and early diagnosis to prevent a long diagnostic and therapeutic delay. The hypothesis that the different phenotypes and tissue manifestations of SpA belong to one disease implies that they do not have to be treated separately but can be targeted all together. This underscores that the less typical SpA subtypes should not be excluded from clinical trials and that SpA should be approached as a whole.

Improvements in treatment should not only be achieved by optimizing currently available therapies, but more importantly also by novel targeted therapies. Especially the IL-23/IL-17 axis is a promising target in the treatment of SpA. Novel therapeutic options recently discovered will have to prove their efficacy on the long term. Also their possible remission-inducing and disease modifying capacities on osteoproliferation have to be investigated. Time will tell whether these novel therapeutics can fulfill the high unmet medical need for extra therapeutic options besides the currently available drugs. Additionally head-to-head comparisons with TNF inhibitors have to demonstrate whether these should stay the first line of targeted therapy or whether the novel targeted therapies are perhaps even more effective. Alternatively, clinical trials which treat patient with both TNF inhibitors and one of the new potential therapeutics simultaneously are also awaited. Furthermore, proof-of-concept studies with these novel therapeutics will provide further clues regarding the pathophysiologic mechanisms in SpA and are thereby likely to contribute to the development of unifying translational concepts and even better targeted therapies.

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