1. GENERAL DISCUSSION AND SUMMARY

Evolving treatment of Ankylosing Spondylitis.
The therapy of ankylosing spondylitis (AS) consisted for a long time of patient education, exercise therapy and non-steroidal anti-inflammatory drugs (NSAIDs) and nowadays these are still the cornerstones of treatment. Traditionally, NSAIDs are anti-inflammatory drugs that mainly affect symptoms. In contrary, the role of disease modifying antirheumatic drugs (DMARDs), which are characterized by changing the course of the disease and delaying structural damage, was always limited in AS. Over ten years now, the tumour necrosis factor (TNF)-blockers have dramatically changed the therapeutic options in AS and spondyloarthritis (SpA).

However, the traditional distinction between NSAIDs and DMARDs is not always clear in AS. There is some evidence that NSAIDs do not only modify symptoms, but also seem to delay radiographic progression. On the other hand the effect of DMARDs was often primarily measured as effect on symptoms and inflammation and it was doubted if TNF-blockers would have effect on radiographic progression. In addition, the clinical relevance of the growth of some syndesmophytes is debatable in patients who experience impressive relief of symptoms, following TNF-blocking therapy [1]. However, for clarity, in this chapter the traditional denomination of NSAIDs and DMARDs, as used in rheumatoid arthritis (RA), was followed.

The first part of this thesis consists of studies performed just before the TNF-blockers became available and the second part concerns several aspects of anti-TNF therapy itself. The TNF-blockers seem to have solved many of the problems in AS patients, but still many questions about drug therapy in AS remain outstanding: Do NSAIDs really have disease modifying effects? What is the role of DMARDs in AS? How do we assess the efficacy of medication? What is the effect of medication on extra-articular manifestations, especially anterior uveitis, and what is the effect on bone and cardiovascular disease? What is the effect of TNF-blockers and what are the main adverse events? What can we say about non-responders and do we know enough about long-term therapy? Is there still an unmet need for new drugs to treat AS?

These various aspects of drug therapy in AS are discussed in this chapter. Summaries of the previous chapters of this thesis and conclusions are shown in *cursive script*.

**NSAIDs.**
Non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2-selective inhibitors (coxibs), are recommended as first-line therapy for inflammatory back pain and stiffness in patients with AS [2]. Evidence that NSAIDs not only give
symptomatic relief but also have anti-inflammatory properties is supported by the
decrease of acute phase reactants (erythrocyte sedimentation rate (ESR)) and a
small effect on axial MRI bone lesions during treatment with etoricoxib in an open-
label study [3]. Continuous use of a NSAID, in contrast to on-demand use, proved
to retard radiographic ossification of the lumbar spine, especially in patients with
elevated acute phase reactants [4-6]. Hence, in addition to analgetic and antiflogistic
effects, NSAIDs might have disease modifying properties. Inhibition of bone
formation was seen also in the prevention of heterotopic ossification by coxibs and
effect on bone healing [4, 7]. Apparently paradoxical, NSAIDs seem to improve bone
mineral density [8]. Considering the continuous use of a NSAID, the likelihood of
radiographic progression in an individual patient has to be taken into account and
weighted against potential (gastrointestinal and cardiovascular) adverse events [9].
The best predictor of structural progression is the presence of syndesmophytes at
baseline [10]. In contrast, high levels of functional dickkopf-1 predicts protection
from syndesmophyte formation [11].

In summary NSAIDs are still the cornerstone of the treatment of AS. Continuous use
is recommended in patients with elevated acute phase reactants and progressive
disease.

DMARDs: sulfasalazine and mesalazine.
Sulfasalazine is not effective in AS with only spinal symptoms, but several studies
showed some efficacy of sulfasalazine in active AS/SpA with peripheral arthritis
(weighted mean difference in ESR -4.79 and morning stiffness VAS-100mm -13.89
compared to placebo) [12-15]. Presently, sulfasalazine is still the initial treatment
option for AS patients with peripheral involvement [2, 16].

Sulfasalazine is split in the large intestine in sulfapyridine and mesalazine
(5-aminosalicylic acid), having antibacterial and antiflogistic properties, respectively.
Mesalazine is the active drug in the treatment of inflammatory bowel disease.
The effect of mesalazine was investigated in 20 patients with active AS in an open
study for 24 weeks (chapter 2). There was a high rate of premature discontinuation
because of intolerance. Except for a small significant decrease in erythrocyte
sedimentation rate, treatment with mesalazine did not show improvement in other
disease variables.

The mode of action of sulfasalazine in AS is unknown. However in 1985, a high rate
of incidence of inflammation in the intestine was found in patients with HLA-B27
related arthritis [17]. In more recent studies, these numbers of intestinal involvement
were confirmed in axial SpA patients [18, 19], which might explain the beneficial
effects of sulfasalazine. Moreover the bacterial flora of the gut seems to be an
important factor in the role of HLA-B27 in the pathogenesis of AS [20]. When the role
of the bowel and its flora is more elucidated in AS, the intestines and the enteral microbes could again be important as targets for treatment.

*In AS patients with peripheral arthritis sulfasalazine is recommended. There is no evidence for use of only mesalazine in these cases.*

**Statins as antirheumatic drugs.**
Statins have anti-inflammatory properties, as demonstrated by lowering C-reactive protein and disease activity in rheumatoid arthritis [21].

*The effect of the statin rosuvastatin in AS was investigated in 15 consecutive patients with active disease in an open study during 12 weeks, followed by an observational period of 12 weeks (chapter 3). Treatment with rosuvastatin resulted in significant decreases of C-reactive protein and erythrocyte sedimentation rate after 12 weeks and a trend of improvement in several clinical variables. A randomised, placebo controlled trial is required to prove the anti-inflammatory and disease modifying properties of statins in AS. As could be expected, total and LDL-cholesterol levels were significantly reduced during treatment in this study.*

The improvement of the lipid profile is a favourable effect of statin therapy in AS, particularly in view of the increased cardiovascular risk in AS patients [22, 23]. Concerning this increased cardiovascular risk in AS patients, attention is also needed for cardio-respiratory fitness and other traditional risk factors for cardiovascular disease, as smoking, high blood pressure, diabetes and overweight [24, 25]. Moreover, effective treatment of inflammation has favourable effects on the cardiovascular risk in AS [26-28].

*In addition to treatment of inflammation, in AS patients attention is recommended for traditional risk factors for cardiovascular disease. Further studies on antirheumatic properties of statins are needed.*

**DMARDs: leflunomide.**
Leflunomide is proven to be effective in rheumatoid arthritis and psoriatic arthritis, but studies in AS were lacking so far [29, 30].

*The effect of leflunomide in AS was studied in a double blind, randomised, placebo controlled trial in 45 patients with active disease (chapter 4). The number of responders according to the Assessment of SpondyloArthritis international Society (ASAS) 20% definition was higher in the leflunomide group than in the placebo group, but the difference did not reach statistical significance. Although the study was underpowered, the differences between the treatment groups were small and therefore striking differences in a trial with higher numbers of patients are not likely.*
These data were confirmed by another small and open label study. In this study axial symptoms did not improve, but in patients suffering from peripheral arthritis the number of inflamed joints was reduced with leflunomide treatment [31]. The number of patients with peripheral arthritis in our trial was too small to draw any conclusion about the efficacy of leflunomide in this subgroup. If a difference in efficacy between these subgroups would exist, this might be explained by differences in pathophysiology. Significant higher MMP-3 concentrations, for example, are found in AS patients with peripheral disease compared to those with only axial disease [32].

In general, there is no place for leflunomide in the treatment of AS, but leflunomide might be considered in patients with peripheral arthritis resistant to other therapies.

Other DMARDs.
Corticosteroids are effective when used intra-articular in peripheral or sacroiliac joints [33]. Oral corticosteroids were seldom studied in AS. A recent study showed short-term efficacy of a high dose prednisone when given for two weeks [34]. A 50% improvement of the Bath AS Disease Activity Index (BASDAI) was seen in 33% of the patients treated with 50 mg prednisone every day, versus 8% on placebo. More studies are needed to establish the role of corticosteroids. An option could be that corticosteroids are used in AS as bridging therapy, like in RA, awaiting the efficacy of another treatment.

Methotrexate (MTX) was studied in a few randomized controlled AS trials, but in low numbers of patients and only in low doses (7.5-10 mg/week). Thus far, insufficient evidence was found to support benefit of MTX in the treatment of AS [35]. Studies with higher doses of MTX are needed, also in the light of the possible role of MTX in reducing immunogenicity, as is discussed below.

A short course of therapy with corticosteroids could be considered in AS, but more studies are needed to investigate long-term treatment with corticosteroids and high doses of methotrexate.

TNF-blockers
From the beginning of this century tumour necrosis factor alpha (TNF) blockers were used in AS and proofed to be very effective on both a short-term and long-term basis. During treatment with TNF-blockers, improvement was seen in symptoms, including spinal pain, morning stiffness, functioning, spinal mobility, arthritis, enthesitis, extra-articular manifestations, sleep, quality of life and also in acute phase response, hemoglobin levels and inflammatory MRI lesions [1, 36-38]. Currently, five TNF-blockers are available for treatment of AS: infliximab, etanercept, adalimumab, golimumab and certolizumab [39-43]. In a meta-analysis the odds ratio
for being in ASAS40 response was 4.7 (95% CI 3.8 - 6.0) for patients taking a TNF-blocker compared with placebo [44].

The ASAS has published international recommendations for the use of TNF-blockers in patients with axial spondyloarthritis [45]. Treatment with TNF-blockers is considered the standard of care for AS patients with active disease, who fail to respond adequately to conventional treatment. Active disease is defined as at least four weeks of active disease, according to a Bath AS Disease Activity Index (BASDAI) score of at least 4 (0-10) and positive expert opinion. Conventional therapy is defined as treatment with at least two NSAIDs over a 4-week period in total, at maximum recommended or tolerated anti-inflammatory dose unless contraindicated. Moreover, patients with symptomatic peripheral arthritis must have had at least one local steroid injection and should normally have had a therapeutic trial of a DMARD, preferably sulfasalazine. Patients with peripheral enthesitis must have failed appropriate local treatment. The effect of treatment with a TNF-blocker is evaluated after at least 12 weeks. The response criteria are a 50% relative change or absolute change of 2 (0-10 scale) in BASDAI score and expert opinion in favour of continuation.

In a questionnaire among AS patients, recruited from a secondary care clinic, 64% reported a BASDAI score of at least 4 (scale 0-10). The authors concluded that there is a large unmet need for TNF-blocking therapy in AS, although an expert opinion was not available in most of these patients [46]. In a representative group of Belgian rheumatology offices about 40% of the AS patients were supposed to be eligible for anti-TNF therapy, for the most part according to the international recommendations [47].

A main disadvantage of this successful treatment are the high costs. In 2011 two TNF-blockers were on the first and second place of the top ten of expenses for drugs delivered by the public pharmacies in the Netherlands [48]. The expenses for the two drugs together were more than 350 million euros (total drug expenses 5001 million euros). Next to the registered TNF-blockers, so-called biosimilars have been developed, which may be more cost-effective. The first studies with a biosimilar of infliximab in AS showed equivalent efficacy compared to the original TNF-blocker [49].

TNF-blockers are often effective for most of the signs and symptoms of AS and have dramatically broadened the therapeutic arsenal in AS.

Immunogenicity of TNF-blockers.

In RA it has been shown that several TNF-blockers can induce an immune response and the formation of antidrug antibodies. The antibodies were associated with low serum drug levels and reduced response to treatment [50].
Serum drug levels and antidrug antibodies were studied in 38 AS patients treated with infliximab for 54 weeks (chapter 5). At the end 53% of the patients met the 20% ASAS response criteria. The mean serum trough infliximab level for responders was significantly higher compared to the non-responders (8.2 mg/l versus 6.3 mg/l). In addition, anti-infliximab was significantly more often found in non-responders (59% versus 5%). As shown in other studies, antibodies against the TNF-blocker were in our study associated with increased risk of infusion reactions [51].

Antidrug antibodies, associated with reduced treatment response, were also shown in 31% of 35 AS patients treated with adalimumab for six months [52]. In RA, co-administration of methotrexate (MTX) reduces the immunogenicity of the TNF-blocker in a dose-dependent manner. The overall Odds Ratio was 0.20 (95% CI 0.12-0.34) to develop antibodies against adalimumab in RA patients using MTX compared with patients without MTX [53]. In AS, the same effect was suggested in a small open label controlled study in which infliximab in combination with MTX seemed to be more efficacious than infliximab alone [54]. Despite the fact that evidence for effect of MTX on AS disease activity is lacking, it might be interesting to conduct studies on the effect of MTX and other immunosuppressive drugs on antibody formation against TNF-blockers and the influence on the response rate in AS.

In case of insufficient response or adverse events during TNF-blocking treatment, switching to another TNF-blocker can be effective. Overall the response rates among switchers are lower, but about half of them achieve treatment response [55-57]. Information about drug serum levels or antidrug antibodies could be helpful in these situations.

Antidrug antibodies, associated with reduced treatment response, are found in 29-31% of AS patients treated with infliximab or adalimumab. Further studies are needed to determine the effect of immunosuppressive drugs on antibody formation and to define the role of antibody determination in clinical decision making.

Adverse events of TNF-blockers.
In placebo controlled trials, the most frequent adverse events of TNF-blockers were injection site reactions (or infusion reactions) and mild infections [39-43]. In this paragraph the risks of serious infections, malignancy and liver problems are discussed in more detail.

In assessing the risk of serious infections one has to keep in mind that patients with immune mediated inflammatory disorders have an increased risk of infections not only due to medication, but also because of the disease itself. In a meta-analysis, RA patients on TNF-blockers had an increased risk of serious infections (adjusted hazard
General discussion and summary

Next to the role of TNF in host defence, it plays an important role in the pathobiology of cancer [61]. Therefore, malignancy has been considered as a possible adverse event of TNF-blockers. Regarding the risk of malignancy during TNF-blocking therapy, the possibility of a higher risk for certain malignancies by the inflammatory disease itself has to be taken into account. Patients with RA appear to be at higher risk of lymphoma and lung cancer compared with the general population, but overall the malignancy risk is almost similar [62].

Data on a possible increased risk of malignancy during treatment with TNF-blockers are conflicting, but in a Swedish register TNF-blockers were not associated with a further increase of the risk for lymphoma in RA [63]. In another study TNF-blocking therapy in RA was associated with an increased risk for non-melanoma skin cancer [64].

Less is known about the incidence of malignancy in AS patients, with and without TNF-blocking therapy. In a Belgian cohort, a tendency towards a higher incidence of malignancy in SpA patients treated with a TNF-blocker was seen, compared to the general population. However, the numbers were too small to draw definite conclusions [61]. In a Taiwanese cohort with matched controls, an increased risk of cancer, particularly lung or head and neck cancer, (aHR 1.38) was found in TNF-blocker naïve AS patients [65]. The risk of malignant lymphoma in AS was not elevated in a national register and not affected by the use of TNF-blockers [66]. The overall malignancy rates for adalimumab-treated patients with AS or other inflammatory disorders was as expected for the general population in a meta-analysis of clinical trials [59].

Serious liver problems were rarely seen in trials with TNF-blockers [40, 43]. [Gorman, 2002; Landewé, 2014] In clinical practice, however we observed several AS patient with liver enzyme elevations during treatment with etanercept. This prompted us to study this systematically (chapter 6). Of 105 consecutive AS patients treated with etanercept for at least three months, 15 patients had significant elevation of liver enzymes (defined as more than 1.5 times the upper normal limit) more than once. In nine cases the elevation was probably or possibly related to treatment with the TNF-blocker. An increased risk of elevation of liver enzymes was found in patients with a higher body mass index (BMI). This observation might be explained by an increased
vulnerability of a liver with steatosis, whereas on the other hand a favourable effect of TNF-blockers on fatty liver disease is expected [67].

The definite risk of hepatic disturbance during treatment of TNF-blockers can only be determined by comparison with a control group. In some placebo controlled trials of several TNF-blockers, increases of liver enzymes were seen 2-3 times more frequent in patients using the TNF-blocker than those using placebo [41, 42, 68]. Also the mean increase of liver enzymes was higher compared to the placebo-treated patients and therefore it is likely to be ascribed to TNF-blockers.

The most important adverse event of TNF-blockers is an increased risk of infections. This risk seems to be lower in AS patients than in RA. To assess the risk of malignancy in AS patients, treated with a TNF-blocker, more studies in large cohorts are required.

Increase of liver enzymes in TNF-blocker treated AS patients was seen in 9% of the patients. Therefore, regular testing of liver enzymes in these patients is recommended (for example every three months in the first year of therapy). Patients with higher BMI appear to be more prone to this side effect.

Measuring physical function and TNF-blocking.
The efficacy of TNF-blockers in AS is determined by the improvement in several disease parameters during treatment. The most important outcome parameters in AS are disease activity, function, spinal mobility and quality of life [1]. These parameters are interrelated and are assessed for a great part by self-reported, disease-specific, visual analogue scale (VAS) based questionnaires and physical functioning is commonly assessed with the Bath AS Functional Index (BASFI) questionnaire [69, 70]. However self-reported outcome measures are susceptible to under- or overestimation [71].

Previous studies suggested that performance-based tests of functioning and the BASFI questionnaire are only moderately associated, indicating that these methods measure different aspects of physical functioning [72]. Further evaluating this subject, the improvement of performance-based assessment of physical function was established in 82 patients treated with a TNF-blocker for three months (chapter 7). Improvement of performance-based physical function tests was seen in 48% of the patients that were categorized as non-responders according to the ASAS20 response criteria and in 56% of the patients showing no improvement in self-reported physical functioning. Therefore the discrepancy between a performance-based and a questionnaire-based assessment of response was confirmed.

Additional studies are needed to show the clinical relevance and the underlying mechanisms of these differences. In knee-osteoarthritis it was observed that self-
reported physical function was more influenced by pain than by performance-based function [73]. In AS, the influence of cardiovascular fitness on perceived disease activity was seen and, in AS patients with peripheral joint impairment, two questionnaires of functioning performed differently [74, 75]. Another study showed worse BASFI scores in AS patients compared with control subjects, but they reported and objectively performed the same amount of physical activity [76]. It is proposed to use a combination of measurements in evaluating different aspects of functioning of AS patient, keeping in mind feasibility. Similarly, a lack of correlation is sometimes seen between spinal inflammation and reported level of disease activity [77]. Therefore, disease activity in AS is preferably assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS), which includes an objective measure of inflammation (ESR or CRP) in contrast to the BASDAI questionnaire [78].

_Disease parameters in AS show correlations as well as discrepancies between self-reported and performance-based tests. Performance-based tests should be further developed. For good understanding of the cause and degree of the problems of the patient several tests have to be used, including performance-based tests._

**Extra-articular manifestations and TNF-blockers.**

In AS extra-spinal and extra-articular manifestations regularly occur, in particular psoriasis, inflammatory bowel disease and anterior uveitis. One or more extra-articular manifestations were seen in 42% of AS patients in a Belgian study [47]. Other studies found even higher incidences and extra-articular manifestations can also affect the bone, heart, lung and kidney [79]. The mean prevalence of anterior uveitis was 33% in a systemic review [80]. The anterior uveitis in AS is usually acute, unilateral and often recurrent. Inadequately treated the sequels for the eye can be vision-threatening. The primary therapy of anterior uveitis is treatment by the ophthalmologist with topical corticosteroids in combination with pupil dilating eye drops.

_The effect of the TNF-blocker adalimumab on the occurrence of anterior uveitis was studied in 77 consecutive AS patients with active axial disease treated for at least 12 weeks (chapter 8). Compared to the year before treatment, the number of attacks per 100 patient years was 80% reduced and the number of uveitis attacks per year decreased with 72%._

TNF-blockers appear to differ in the degree of their effect on extra-articular manifestations, especially uveitis and inflammatory bowel disease [81]. Part of this difference could be explained by the observation that the soluble receptor blocker etanercept has less effect on granulomas than the other TNF-blockers, which are monoclonal antibodies. This might explain why etanercept is not effective in inflammatory bowel disease. On the other hand this difference is favourable for the
soluble receptor blocker with respect to the risk of tuberculosis during therapy with 
TNF-blockers [82]. Despite the positive effect of TNF-blockers in general on extra-articular 
manifestations, an apparent paradoxical effect can sometimes be seen when uveitis, 
psoriasis or inflammatory bowel disease occur during treatment with TNF-blockers 
[83-85].

TNF-blockers have favorable effects on several extra-articular manifestations of AS, 
but in this respect the several TNF-blockers differ in efficacy.

Bone and TNF-blockers.
Interestingly, AS is characterized by the paradox of new bone formation 
(syndesmophytes and ankylosis) on the one hand and bone loss and increased risk 
of fractures on the other hand [8].

The influence of a TNF-blocker on bone was studied in 49 AS patients treated with 
etanercept (chapter 9). After two years of treatment the bone mineral density (BMD) 
of hip and spine was increased significantly (2.2%, resp. 7.0%). However, an increase 
was also seen in vertebral fractures (from 6 to 15 patients) and new bone formation 
(radiological score from 12.1 to 18.5). No significant changes were found in several 
markers of bone turnover.

In AS a decreased BMD is seen, although measurement of BMD of the spine 
with dual-energy X-ray absorptiometry (DEXA), in contrast to the hip, can be 
overestimated in case of new bone formation along the spine. A decreased BMD 
in AS is probably related to inflammatory factors. The expected positive effect of 
strong anti-inflammatory drugs, like TNF-blockers, on BMD was also demonstrated 
in other studies [86, 87]. It is unknown what the influence of TNF-blockers is on the 
ultimate outcome, namely fractures (without or with symptoms). In our study the 
number of vertebral fractures increased during treatment with the TNF-blocker, but a 
control group was lacking.
In addition, there is lack of knowledge about the effect of anti-osteoporotic drugs 
like bisphosphonates on BMD and fractures in AS. The effect of bisphosfonates is also 
interesting because of the claimed anti-inflammatory activity in AS [88-90].

TNF-blockers reduce MRI-detected spinal inflammation [38]. Previously, it was 
demonstrated that inflammatory MRI lesions predict the development of new 
syndesmophytes, although other studies show a less clear association [91, 92]. 
Despite the anti-inflammatory effects of TNF-blockers, new bone formation during 
treatment was seen in comparison with the progression in TNF-blocker naïve 
historical cohorts [93-95]. These somewhat disappointing results raise questions 
about the mechanism of (un)coupling of inflammation and bone formation [87]. It
is hypothesized that, although TNF-blockers can decrease inflammation, they do not directly inhibit the formation of new bone. Bone formation might be the result of a repair mechanism, driven by mesenchymal tissue responses which are triggered by the resolution of inflammation and perhaps also triggered by mechanical stress [96]. Recent long-term studies however, demonstrated that finally less pathological bone formation occurs in AS patients treated with TNF-blockers, probably because of the reduction of new inflammatory lesions [97-99]. More studies are needed to unravel the effect of early treatment on radiographic progression before irreversible changes have occurred. Moreover, it would be interesting to study the effect of continuous use of NSAIDs or other therapies on the progression of new bone formation during (the first years of) treatment with TNF-blockers. This should be done by controlled and long-term studies, because of the slow rate of radiographic progression in AS [100].

During treatment with TNF-blockers bone mineral density increases in AS, but so far there is no evidence that TNF-blockers reduce the number of new vertebral fractures. Radiographic progression in AS is probably retarded by TNF-blockers on the long-term.

**Early treatment with TNF-blockers?**

TNF-blocking has shown to be effective in patients with early axial SpA in comparison with placebo or NSAID, although in many of these studies a considerable amount of the patients already meet the radiographic criteria of AS [43, 101-104]. In case of high disease activity, AS can be treated with TNF-blockers in the early (pre-radiographic) phase of the disease and possibly radiographic progression can best be retarded by early treatment. The classification criteria of axial spondyloarthritis (SpA) can be helpful to diagnose and treat the disease early [45]. Another argument to treat non-radiographic axial SpA and AS in the same way, is their similar burden of disease, defined as disease activity, functional impairment and quality of life [105, 106]. On the other hand little is known about the long term prognosis of the whole group of axial SpA [107]. Not all cases of non-radiographic axial SpA finally evolve to definite AS and partially non-radiographic axial SpA has features of a distinct disease entity [108, 109]. When considering therapy in axial SpA patients, it has to be taken in account that a higher response rate is seen in patients with radiographic features and in patients with objective signs of inflammation, reflected in MRI lesions or acute phase response [102, 104, 106, 110].

Patients with (early) non-radiographic axial SpA can be treated with TNF-blockers, especially when objective signs of inflammation are present as MRI lesions or raised acute phase response.
**Duration of treatment with TNF-blockers?**
Several studies show persistent favourable clinical results in AS patients treated with TNF-blockers for many years [111, 112]. Early remission is the best predictor for long-term remission through 5 years of treatment [113].

What is known about the necessary duration of therapy with a TNF-blocker? Discontinuation of the TNF-blocker in a patient with a favourable response seems to lead to a relapse in many cases [114, 115]. However, in part of the patients (32-47%) it is presumably possible to maintain low disease activity with TNF-blockers in reduced doses [116, 117]. Dose reduction might be possible in case of high serum drug levels. Predictive characteristics for successful discontinuation or dose reduction are not yet known; disease duration, age or duration of remission could be such factors.

Another question is whether non-radiographic axial SpA patients are less prone to develop a flare after stopping TNF-blocking therapy than patients with definite AS. After two years follow-up only 8% of patients with early axial SpA reached permanent drug-free remission after treatment with etanercept for one year [118]. In 24 patients with non-radiographic axial SpA and good response after treatment with adalimumab for 1 year, only 17% experienced no disease flare during 2 years after withdrawal of the drug [119]. However, in another study about 43% of the axial SpA patients remained in remission during 6 months in those patients who reached partial remission after treatment for 28 weeks with either infliximab plus naproxen or naproxen alone in the preceding period [120]. An attempt to discontinue treatment in good responders seems justified, because the response to retreatment with the TNF-blocker seems well in AS and non-radiographic axial SpA [119, 121].

*Relapse of the disease is seen in many AS/SpA patients after discontinuation of successful therapy with a TNF-blocker. However, dose reduction and discontinuation should be attempted and studied further.*

**Other biologicals?**
Overall, about 30% of the AS patients do not respond to treatment with TNF-blockers. This might be explained in several ways. One reason could be that the patient has no active inflammation and the symptoms are caused by other mechanisms. This is not always clear, because objective signs of inflammation are often absent in AS. In many patients blood inflammatory markers are low and MRI is not always conclusive. Another explanation might be that the inflammation is TNF-driven, but the TNF-blocker is not tolerated or TNF is not adequately blocked, for example because of antibodies against the drug. Also, the role of TNF in the inflammation could be limited. Therefore, there is need for disease modifying drugs which modulate other pathways of inflammation than TNF-blockade.
Open label trials failed to demonstrate efficacy of anakinra (IL-1 antagonist) and abatacept (T cell inhibition) in AS [122, 123]. The B cell inhibitor rituximab was not effective in an open trial, although effect was seen in the subgroup of TNF-blocker naïve patients [124]. Placebo-controlled trials failed to show efficacy of tocilizumab in AS [125]. Another interleukin (IL)-6 inhibitor, sarilumab, neither showed efficacy in a placebo-controlled study in AS [126]. Apremilast, an oral inhibitor phosphodiesterase 4, showed some improvement compared to placebo in a pilot study, but further testing is needed [127].

Ustekinumab, a monoclonal antibody that inhibits IL-12 and IL-23, proofed to be efficacious in treating psoriatic arthritis [128]. In AS ustekinumab reduced signs and symptoms in an open-label study [129]. Presently, the most promising results in AS patients are found in blocking of IL-17. In animal models intestinal interleukin-23 and subsequent stimulation of IL-17/22 was found to be involved in development of spondyloarthritis syndrome [130]. TNF-independent increase in IL-17-expressing mast cells may contribute to synovial inflammation in peripheral SpA [131]. The anti-IL-17a antibody secukinumab was superior to placebo in reducing signs of AS in a small, randomized, double-blind study [132].

Because not all AS patients respond to therapy with a TNF-blocker, there is still need for other therapies. Most promising are results of agents blocking interleukin 23/17, but larger controlled studies are needed for further evaluation of these new therapeutic options.

Some future research suggestions.
NSAIDs are still the cornerstone of the drug treatment of AS. Prospective long-term studies are needed comparing continuous use with on demand use. The rate of radiographic progression in these groups can be compared, as well as the adverse events. This can be done in patients without TNF-blocking therapy, as well as in patients using TNF-blockers, because after the start of TNF-blocking treatment new bone formation is still going on.

Sulfasalazine is used in AS patients with peripheral arthritis. Furthermore, the role of the traditional DMARDs in AS is limited. There is an unmet need for controlled studies with higher doses of methotrexate, eventually in combination with a pulse dose of corticosteroids, to determine the effect on disease activity and also the effect on antibody formation against TNF-blockers. The antirheumatic properties of statins have to be studied in a controlled trial, as well as the effect of cardiovascular risk screening and management in AS. The effects of bisphosphonates in AS on bone mineral density, as well as on disease activity and radiographic progression have to be studied in placebo controlled trials.
TNF-blockers are an important advancement in the treatment of AS. Accurate (nationwide) registration of efficacy, extra-articular manifestations and adverse events of the different TNF-blockers and biosimilars would be very informative. The role of antibodies against TNF-blockers has to be elucidated and especially their role in predicting successful dose reduction, stopping and switching of therapy. Performance-based tests should be further developed and incorporated in the current outcome parameters of efficacy of therapies. Long-term follow-up is needed of patients with axial SpA, especially those without radiographic signs, because the long term outcome of non-radiographic SpA is largely unknown.

It would be very interesting to investigate the characteristics of patients not responding to treatment with a TNF-blocker. For part of these non-responders studies for other (biological) therapies are needed. Undoubtedly ongoing pathophysiologic research is needed in the search for new therapies.