Outline of this thesis
AIM AND OUTLINE OF THIS THESIS

In this thesis we aimed to study two major clinical challenges in spondyloarthritis (SpA) as described in the general introduction (Chapter 1). Part I of this thesis focuses on the disease phenotypes in SpA. Here we aimed to assess which tissue is primary affected in early SpA and describe and compare the different SpA subpopulations as classified by two types of criteria. Part II of this thesis focuses on novel treatment options in SpA where we investigated whether it is useful to extend the availability of tumor necrosis factor (TNF) inhibitors, which are known to be very effective in the treatment of the prototypic subtypes of SpA, to treat all the different subgroups described in Part I. Also we describe and evaluate novel therapeutic targets in the treatment of SpA.

PART I: DISEASE PHENOTYPES IN SPONDYLOARTHRITIS

Articular manifestations in SpA comprises involvement of the axial skeleton and of peripheral joints. The relative contribution of synovial versus enthesal versus bone inflammation in axial and peripheral SpA remains unclear. In Chapter 3 we revisited the hypothesis proposing that enthesitis is the primary peripheral joint lesion in SpA whereas synovitis is the primary lesion in rheumatoid arthritis (RA). In order to test the validity of this hypothesis we assessed enthesitis and synovitis in a combined magnetic resonance imaging (MRI) and histopathological study of early untreated SpA and RA. In the next two chapters we describe the clinical similarities and differences of various SpA subpopulations. In Chapter 4 we compared clinical features and disease activity of undifferentiated SpA with ankylosing spondylitis (AS) and psoriatic arthritis (PsA), using the classical phenotypic classification. In Chapter 5 we use the novel classification criteria developed by the Assessment of SpondyloArthritis international Society (ASAS) and assessed to what extent these criteria really reflect axial versus peripheral disease.

PART II: NOVEL TREATMENTS IN SPONDYLOARTHRITIS

The search for novel treatment options in SpA does not only consist of developing and testing new therapeutic compounds, but also concerns the optimal use of already existing therapies. In Chapter 6 we describe an investigator-initiated, randomized, placebo-controlled trial which aimed to investigate whether the TNF inhibitor adalimumab, which has been extensively studied in AS and PsA, is also effective in peripheral SpA patients who do not fulfill the criteria for AS and PsA. This group, which is described in Chapter 4, has not been included in most clinical trials and, accordingly, biologicals are not yet available in daily clinical practice for these patients. We also assessed whether TNF inhibition can lead to long-lasting remission in peripheral SpA, as sometimes observed in RA, or whether interruption of treatment leads to rapid disease relapse, as seen in AS (Chapter 7). Finally, we investigated in Chapter 8 whether anti-drug antibodies are associated with poor clinical response and/or rapid relapse in peripheral SpA treated with adalimumab.

The final chapters of this thesis study novel therapeutic options in SpA. In Chapter 9 we discuss the rationale for targeting the interleukin (IL)-23/IL-17 axis in SpA. One of the compounds targeting this axis is secukinumab, a monoclonal antibody directed towards IL-17A. In Chapter
we report the proof-of-concept randomized, placebo-controlled trial with secukinumab in AS and indicate that this is the first biologic drug beyond TNF blockers that reached its primary endpoint in a phase II trial in AS. Finally, in Chapter 11 we address the mast cell, the main cell type expressing IL-17 in SpA synovitis, as possible therapeutic target in SpA by conducting an investigator-initiated, proof-of-concept study with nilotinib, a tyrosine kinase inhibitor. In this randomized placebo-controlled clinical trial we investigated both the immunopathological and clinical effects of nilotinib on peripheral and axial SpA.