Gene therapy for arthritis: progress towards a clinical trial
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1 General Introduction
Rheumatoid arthritis (RA) is chronic, systemic, inflammatory disease primarily affecting the synovial tissue in multiple joints. It is characterized by swelling of the joints and inflammation of the synovial membrane, leading to invasion of synovial tissue into the adjacent matrix with degradation of articular cartilage and bone as a result.\(^1\) The disease usually presents itself with a symmetric polyarthritis involving the small joints of the hands and feet, but other joints are often involved as well. The primary manifestations are pain, swelling, and limited motion of joints. The disease afflicts about 1% of the population worldwide, women three times more often than men. Some patients may experience mild symptoms, but it has been estimated that 55–70% of RA patients have progressive disease resulting in joint destruction and disability. RA is still associated with long-term morbidity and early mortality despite major developments in antirheumatic therapy.

The etiology of RA is still incompletely understood. Autoimmunity plays an essential role in both chronicity and progression.\(^2\) A better understanding of the pathophysiology of RA has led to important and innovative approaches to its treatment. In the case of confirmed diagnosis the recommended gold standard is to initiate methotrexate, which can be in combination with other conventional disease-modifying antirheumatic drugs (DMARDs) and/or corticosteroids.\(^3\) If disease activity cannot be controlled by conventional treatment, further treatment consists of biologicals, such as anti-tumor necrosis factor (TNF), anti-CD20, and anti-interleukin (IL)-6 antibody therapeutics or treatment with anti-cytotoxic T-lymphocyte-associated protein 4-Ig fusion protein (CTLA4-IG).\(^3,4\) During the last two decades, the use of these new biological treatments, together with an improved timing and dosing of conventional therapy, has significantly improved the outcome of RA in many patients, but not all. Remission is achieved in only a minority of the patients, leaving most with at least monoarticular or oligoarticular disease activity. Moreover, not all patients are eligible to receive these biologicals and a need for repetitive treatment remains. Furthermore, there is still an unmet need for optimal local, intra-articular treatment in patients with monoarthritis or oligoarthritis who do not necessarily need systemic biological treatment. The clinical experience with intra-articular corticosteroid injections highlights the potential of local treatment of inflammatory arthritis.\(^5\) However, not all patients respond to intra-articular corticosteroids or tolerate (intra-articular) corticosteroids. The application of more than four corticosteroid injections into the same joint per year is advised against because of the risk for procedure and steroid-associated side-effects.

Gene therapy could provide a solution to this problem by providing local treatment for arthritis, with prolonged expression of therapeutic proteins after a single injection. Moreover, local administration in a joint will ensure maximal treatment selectively at the site of inflammation, while reducing systemic exposure, potentially limiting the side-effects compared with systemic antirheumatic treatments. Therefore, we investigated in this thesis several aspects of this new innovative treatment modality. The gene therapeutic product consists of a recombinant adeno-associated virus (rAAV) vector serotype 5 containing DNA encoding for the immunomodulatory protein interferon beta (IFN-\(\beta\)) under control of an inflammation-inducible promotor (ART-I02).

In Chapter 2 we describe the concept of intra-articular gene therapy, including different delivery methods, viral- and non-viral vectors and potential therapeutic targets for rheumatic diseases, specifically RA. One potential payload is IFN-\(\beta\). Interferons comprise a family of naturally secreted proteins with immunomodulatory functions. Interferon-\(\beta\) has anti-inflammatory properties, plays
a role in bone homeostasis and may inhibit angiogenesis. Of special interest is the ability of IFN-β to reduce the secretion of TNF, IL-1β, and IL-6, which are all key players in the pathogenesis of RA. Furthermore, IFN-β can enhance production of IL-10 and IL-1 receptor antagonist (IL-1Ra) by monocytes. In Chapter 3 the rationale for IFN-β as a novel therapeutic approach is briefly discussed.

Part I of this thesis focuses on the preclinical development of ART-I02, including transduction efficacy of the vector in different cell types and safety in animal models of arthritis. Part II of this thesis describes a mechanistic clinical trial evaluating intra-articular administration of a therapeutic compound, and provides a literature overview of the current developments in rAAV gene therapy with a focus on arthritic diseases.

PART I: PRE-CLINICAL STUDIES FOR THE DEVELOPMENT OF ART-I02

Development of a gene therapy vector involves the preclinical assessment of safety, biodistribution and efficacy in in vitro studies as well as in vivo in animal models. Part of the studies performed with ART-I02 are described in this thesis. In Chapter 4 we describe the expression and potency of human IFN-β after transduction of fibroblast-like synoviocytes (FLS) from different species with ART-I02. Furthermore, vector biodistribution was investigated in a rat model of arthritis. In Chapter 5 biodistribution, safety, and initial efficacy of ART-I02 were assessed in a larger animal model, namely collagen-induced arthritis (CIA) in rhesus monkeys. As the activities of human IFN-β are highly species-specific, rodent models cannot be used for efficacy studies with ART-I02. In the rhesus monkey, human IFN-β is biologically active. Therefore, we employed the rhesus monkey CIA model to evaluate ART-I02. In Chapter 6 we present evidence that the presence of macrophages in the inflamed joint might hamper efficient AAV mediated gene delivery. We show the influence of administration of agents that influence macrophage activity and numbers as well as of empty rAAV capsids on rAAV5-transgene expression in the joints of arthritic mice.

PART II: CLINICAL ASPECTS OF THE DEVELOPMENT OF INTRA-ARTICULAR GENE THERAPY

Prior to the clinical evaluation and application of the gene therapy product ART-I02, we wanted to obtain more experience with evaluation of the effects of intra-articular treatment in a clinical trial in RA. Therefore, we assessed the effects of intra-articular administration of the TNF soluble receptor construct etanercept in a randomized, double-blind placebo-controlled clinical trial (Chapter 7). The treatment effect of etanercept on the target joint was evaluated using a composite change index (CCI), a combined clinical score. In Chapter 8 the responsiveness and discrimination of the CCI as a single-joint assessment were investigated. This study also gave us the opportunity to explore TNF as a possible therapeutic target for intra-articular blockade by gene therapy that can be tested in future studies. The final chapter of this thesis addresses both the potential as well as hurdles of development of gene therapy. In Chapter 9 we summarize the current status of developments in the field of viral gene therapy using adeno-associated virus as a vector, with a special focus on arthritis.

Chapter 10 consists of a summary and general discussion on the findings of this thesis.
REFERENCES


