Chemokine receptor blockade in rheumatoid arthritis
Vergunst, C.E.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
General discussion
This thesis focuses on the feasibility of targeted blockade of receptors involved in chemotaxis in rheumatoid arthritis (RA), in particular C5aR, CCR1, CCR2, and CCR5.

**Background**
In the past three decades important breakthroughs were made in the treatment of RA. First, the discovery of low dose methotrexate as an effective treatment. Second, the insight that early immunomodulatory treatment is key in controlling the disease and its long term destructive effects on joints. More recently, targeted treatments directed against TNF, IL-6 receptor, B cells, and co-stimulatory molecules have become useful additions to available treatments for RA (1). The success of these treatments has also paved the way for the development of new targeted therapeutic strategies. Although these developments have raised the bar considerably for the efficacy of new treatments, the fact that roughly one third of RA patients does not respond to currently available treatments leaves a major challenge in RA research.

For several reasons, chemokine receptors form an attractive group of potential future targets for therapies against RA (2;3). First and foremost, they seem to be crucial in the migration of monocytes into synovial tissue. Although RA's firestarter has yet to be identified, the inflammation that ensues is in part dependent on monocyte/macrophage infiltration. Second, the 7 transmembrane G-coupled structure of chemokine receptors allows for the relatively uncomplicated chemical engineering of blocking small molecules. This would overcome an important issue in the currently available mono-target treatments, as these are monoclonal antibodies, which are immunogenic due to their structure as large proteins. Production of monoclonal antibodies is more complicated and relatively expensive.

**MAIN FINDINGS**

Chapter 2 reviews the available literature with regard to chemokines and RA. Chemokines are best known for their ability to direct migration of cells expressing matching receptors. The chemokine/receptor pairs, of which more than 50 have been discovered to date, can functionally be categorized into three groups: inflammatory, homeostatic and angiogenic/angiostatic. Histological features associated with these functions are infiltration with inflammatory cells, lymphoid neogenesis, and hypervascularization. Since all three are present in RA synovial tissue, it comes as no surprise that chemokines of all three functional categories are present. The role of inflammatory chemokines may be the most prominent. Research investigating the potential of blocking inflammatory chemokines as a therapeutic strategy in RA has reached the stage of proof of concept studies in patients.

Although C5aR is not a member of the chemokine family, functionally it can be considered an inflammatory chemokine receptor. Chapter 3 describes the results of a multi-center, double-
blind, placebo-controlled phase II study with a C5aR antagonist PMX53. Treatment did not reduce the inflammatory infiltrate in the synovial tissue of RA patients, although results of in vitro experiments suggest that an adequate dose of the antagonist was administered to the patients. The results of a trial using anti–C5a antibodies in RA support the notion that C5aR antagonism is probably not a useful approach in ameliorating RA (4). Although C5a blockade could dramatically reduce symptoms in PNH patients (5;6), no beneficial effect was observed using the same antibodies in RA patients.

Chapter 4 describes the results of a larger multi-center, double-blind, placebo-controlled phase II study with a CCR1 blocking small molecule. Patients did not benefit from the treatment compared to placebo. With the results from this trial, research with regard to CCR1 antagonism in RA has now taken an interesting turn: a previous trial using a different CCR1 antagonist showed a clear reduction in synovial infiltrate (7). With two trials pointing in opposite directions, more clinical research is required to decide whether or not CCR1 is a good therapeutic target in RA. The most important question remains what level of receptor blockade is required to obtain a beneficial effect on inflammation and how to accomplish this level.

Chapter 5 describes the results of a multi-center, double-blind, placebo-controlled phase II study with a monoclonal antibody against CCR2 (MLN1202). Treatment did not ameliorate disease, as reflected by clinical scores and synovial tissue analysis. As results in animal studies interfering with CCR2 function are contradictory, clinical research is essential in unravelling the actual role of CCR2 in RA. Negative results from a previously reported trial blocking CCR2’s ligand CCL2 could possibly be explained by an unintended raise in circulating CCL2 due to formation of immune complexes consisting of CCL2 and infused CCL2-antibodies (8). Although it remains unknown whether the receptor occupation required for complete functional blockade was reached, the current study makes the CCL2/CCR2 axis less likely to be a suitable mono-target in the treatment of RA. Our results are confirmed by a recent trial in RA using an orally dosed CCR2-antagonist (9).

Chapter 6 describes the results of a multi-center, double-blind, placebo-controlled phase II study with a CCR5 blocking small molecule. This small study was the first ever in RA patients using a CCR5 antagonist. CCR5 antagonism has been a highly anticipated therapeutic strategy for RA. Although the results of this study are not promising in terms of efficacy, the treatment was well tolerated. An independent study with a different CCR5 antagonist confirmed these negative findings (10).

Chapter 7 presents data on in vitro chemotaxis experiments using monoclonal antibodies against CCR2 and CCR5. The Fc parts of the anti-CCR2 antibodies used in these experiments
are identical to the Fc part of MLN1202, the antibody used in the trial described in Chapter 5. Similar experiments were done with monoclonal antibodies against CCR5. Anti-CCR2 antibody treatment blocked CCL2/MCP-1-induced chemotaxis of monocytes, whereas anti-CCR5 antibody treatment blocked CCL5/RANTES-induced chemotaxis in vitro. However, none of the blocking antibodies was able to block SF-induced monocyte chemotaxis. The results support the notion that redundancy might indeed account in part for the observed chemokine receptor blockade failure in clinical trials, where the goal was to inhibit cell migration towards the inflamed compartment.

CONCLUSIONS AND FUTURE RESEARCH

This thesis presents negative results in proof of concept trials antagonizing CCR1, CCR2, CCR5, and C5aR in RA. In all but one of the trials discussed here, an innovative trial design was used; instead of reaching statistical power by maximizing the number of patients included, the amount of information per included patient was maximized, allowing us to gain important information out of relatively small trials (11).

The interpretation of negative results in phase 2 clinical trials can be difficult when the question whether the compound was dosed adequately for the aimed pharmacodynamic effect cannot be answered with certainty. Nevertheless, looking at possible other reasons for a lack of efficacy can be useful while contemplating future research. First and foremost the question whether sufficient levels of receptor blockade were reached in the studies reported in this thesis remains relevant. This goes especially for the case of CCR1 receptor blockade. Redundancy, one important characteristic of the chemokine system, comes to mind as an alternative explanation for the negative results. Redundancy of the chemokine system is reflected by the fact that multiple receptors can interact with multiple chemokines. The result of this redundancy in blocking a single type of receptor could be that the binding chemokine will simply activate another type of receptor with which it can also form a functional pair, or, that other chemokines become more important in the process of the infiltration of immune cells into the tissue. Feasibility of mono-target therapies was established with other targets, e.g. anti-TNF anti-IL6 receptor antibody therapy (although the cytokine system is also characterized by redundancy). Thus, the possibility that redundancy of the chemokine system is an important reason for the lack of positive results should be considered. Equally important questions are whether the right chemokine receptors were blocked and if so, if they were blocked at sufficient levels. Future research with regard to chemokines in RA should therefore be aimed at optimizing receptor blockade 24 hours a day. Beside that, it should be aimed at possibilities to overcome redundancy, for instance by poly-chemokine (receptor) blockade. Finally, an alternative approach worth investigating is to promote cell egress rather than inhibiting cell influx (12).
REFERENCE LIST