B cells and B cell directed therapies in rheumatoid arthritis: towards personalized medicine
Thurlings, R.M.

Citation for published version (APA):
SUMMARY IN ENGLISH

RHEUMATOID ARTHRITIS (RA) is a chronic inflammatory disease which is characterized by inflammation of the joints, but other tissues can be affected as well. The inflammatory process gradually results in progressive damage of cartilage and bone, resulting in increasing disability. RA occurs in around 1% of the population.

During the last fifteen years the diagnostics and treatment of RA have much improved. Tests have been developed facilitating early diagnosis, and patients are treated earlier with more effective drugs. Because of these reasons the disease process can currently be halted in an early phase in most patients. As a result, damage of cartilage and bone and severe disability occur less frequent. The basis for this progress has been formed by increasing knowledge of the inflammatory process in RA, which has resulted in the development of a number of new drugs which are all effective in a proportion of patients. Since every drug is only effective in part of RA patients it is important to be able to predict beforehand which patient will benefit from which treatment. This is called personalized medicine. To make personalized medicine a reality it is necessary to discover whether RA has a different pathogenetic mechanism in different patients. Furthermore, it is necessary to understand in detail the mechanism of action of new treatments. In this thesis I focused on treatment with rituximab. This is a drug that depletes B cells (B of bone marrow or bursa), white blood cells that are involved in RA in at least a proportion of the patients.

THE ROLE OF B CELLS IN THE IMMUNE SYSTEM. The immune system is formed by white blood cells and inflammatory mediators that work together to battle infections caused by microorganisms (bacteria, viruses, parasites, yeasts, fungi). There are multiple types of white blood cells and inflammatory mediators. They can be subdivided into groups with specifically evolved functions.

The first subdivision is made between ‘innate’ and ‘adaptive’ immunity. The innate immune system is evolutionary the oldest. It consists of white blood cells and inflammatory mediators that fight most infections very effectively. During evolution, however, bacteria and viruses evolved that can escape from the innate immune system. Therefore, adaptive immunity has developed. This consists of white blood cells and mediators of inflammation that direct the innate immune system and increase its effectiveness. Adaptive immunity has two characteristics: 1. It consists of white blood cells that have evolved to recognize unknown microorganisms much more effectively compared to the innate immune system; 2. After an infection with a microorganism small numbers of the white blood cells that have best recognized the microorganism persist in small numbers in the lymphoid tissue. In case of a new infection with the same microorganism, they will direct the innate immune system to attack it again, but with a faster, stronger response.

The adaptive immune system is divided into two parts: cellular and humoral immunity. Cellular immunity is directed against for instance infections of cells by viruses. Humoral immunity is directed against infections of tissues by bacteria, yeasts, fungi and parasites. Antibodies belong to the most important players in humoral immunity. They are produced by B cells and serve as mediators recognizing microorganisms very effectively. When they bind to a microorganism they can direct the innate immune system to kill it.

During life B cells are continuously being formed in the bone marrow and they circulate through the blood and the lymph nodes. When they encounter a microorganism, the B cells that recognize the microorganism the best start to divide and the daughter cells produce large amounts of antibodies. These differentiated cells are called plasma cells.

B CELLS IN THE INFLAMED JOINT TISSUE OF RA PATIENTS. There are various lines of evidence indicating that B cells are involved in the inflammatory process in the joints of RA patients. First, in around 70% of RA patients antibodies are present that recognize substances which are present in the inflamed joint. These antibodies are called rheumatoid factors and anti-citrullinated protein antibodies (ACPA). It is currently not known why these specific antibodies are involved in RA, but it has been suggested that ACPA can be formed in response to non-specific stimuli (such as bacteria found in the gingiva or smoking) in individuals with a specific genetic predisposition. Moreover, the inflamed joint tissue of RA patients contain clusters of B cells and plasma cells. Intriguingly, these clusters are only found in a subset of the patients. In other patients the joint tissue does not contain B or plasma cells.

In chapter 2 we show in a cohort of 100 RA patients that patients with B cell clusters in the joint tissue do not have a more severe disease subtype, characterized by for instance more joint damage. Furthermore, B cell clusters are observed equally in the joints of patients with or without rheumatoid factors or ACPA. This indicates that there is a different cause for the presence of B cell clusters in the synovial tissue in the joints of a proportion of the patients. Possibly, these clusters are formed because of a certain genetic predisposition. Interestingly, as we show in chapter 3, patients with B cell clusters in their synovial tissue have increased synovial inflammation and they are enriched in their clinical response the anti-TNF antibody infliximab.

B CELL DIRECTED TREATMENTS. Rituximab is an antibody that has been developed to deplete the B cells during a period of several months. Rituximab has originally been developed as a treatment for non-Hodgkin’s lymphoma, a type of B cell cancer, but it also turned out to be an effective treatment for RA patients. It is currently not completely understood why rituximab improves synovial inflammation, and whether the current treatment schedule is optimal for treatment of RA. Rituximab is currently given as a course consisting of 2 infusions during a 2-week period.

In the blood rituximab destroys B cells within hours. In chapter 4 and 5 we show that the B cells do not disappear from the inflamed synovial tissue of all RA patients. In chapter 6 we show that plasma cells, which are derived from B cells and produce antibodies, only disappear in patients who exhibit reduced synovial inflammation after rituximab treatment. This suggests that there are two possible explanations for why some patients do not respond to rituximab: 1. B cells and plasma cells persist in these patients because the administered rituximab dose is too low or the antibody should be administered more frequently. The data presented in chapter 8 suggest that the dosage is probably sufficient; 2. Rituximab is not able to deplete the specific B cells driving the disease process in these patients due to the presence of protective factors. We are currently investigating why B cells may be resistant to rituximab in a proportion of the RA patients.

In chapter 7 we investigate whether there are differences in the biological mechanisms driving the inflammatory process in RA between patients who respond compared to patients who do not respond to rituximab treatment. The white blood cells in the peripheral blood are highly...
activated in a subset of the RA patients. When analyzing this activation pattern it seems like these white blood cells are activated by interferon I. This is a protein playing a role in viral infections. Of interest, interferon I has been shown to be involved in several rheumatological diseases, including Sjögren’s syndrome, systemic lupus erythematosus and dermatomyositis. The precise role of interferon I in these conditions is currently unknown, but interestingly, interferon I stimulates survival of B cells. In chapter 7 we show that patients with a strong interferon I activity overall respond less well to rituximab treatment than those with less IFN I activity. This suggests that rituximab might perhaps be combined with drugs that block interferon I or reduce B cell survival in these patients.

Another possibility could be to re-administer rituximab before B cells return. We have not formally tested this possibility, but data presented in chapter 9 and 10 suggest that this approach may only work in patients who have responded to some extent to the first rituximab treatment course. When these patients receive a second course 6 months after the first course their synovial inflammation continues to diminish. Patients who have not responded at all to the first treatment course (around 30% of patients) do not exhibit robust clinical improvement after the second course either. These patients are candidates for treatment with drugs with a different mechanism of action.

In chapter 11 we conduct a clinical trial with a new B cell directed drug, atacicept, which was tested for the first time in RA patients. Atacicept blocks survival factors of both B cells and plasma cells. In this trial in 73 RA patients we show that atacicept can be given safely to RA patients. Furthermore, it induces clear effects on B cells, rheumatoid factors and ACPA. Some of the patients experienced decreased joint inflammation. Larger clinical trials are currently being conducted to investigate the right dose, safety and effectiveness atacicept treatment.