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CHAPTER 2

OUTLINE AND AIMS OF THE STUDIES DESCRIBED IN THIS THESIS
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Despite the wide range of available medical and surgical therapies for perianal fistulizing CD nowadays, treatment of perianal fistulas is far from satisfactory. Achieving complete closure of the fistula tract is a long process with in many cases multiple relapses. Chapter 3 elaborates on the effect of different treatment strategies for perianal fistulas on response, remission and relapse rates. A disappointing remission rate of only 37.0% at the end of a median follow-up of 10 years was observed. Therefore, we concluded that there is an unmet need for effective medical options for patients who do not respond to the conventional strategies. Local cellular therapy with both adipose and bone marrow-derived MSC has been reported to be a safe, feasible and effective treatment for refractory perianal fistulizing CD. However, none of these trials was really placebo-controlled. Chapter 4 describes our early phase II, double-blind, placebo-controlled, randomized clinical trial performed to address the use of allogeneic bone marrow-derived MSCs in the treatment of refractory perianal fistulizing CD. The aim of this trial was to evaluate the safety and preliminary efficacy of allogeneic MSCs in the treatment of perianal fistulas. The possibility to create a stock with ‘off-the-shelf’ treatment potential from MSCs harvested from young healthy donors is a major advantage of an allogeneic cell source. In total, 21 patients with refractory perianal fistulizing CD were included in this trial who received locally either $1 \times 10^7$ (n=5), $3 \times 10^7$ (n=5), or $9 \times 10^7$ (n=5) MSCs, or placebo (n=6). To be able to reliably assess efficacy of local MSC therapy, all procedures were standardized. MSCs were injected after removal of setons in situ, curettage of the fistulous tract(s), trimming the mucosa and skin of the internal and external opening and closing the internal opening, respectively. In all patients, MSCs suspension or placebo was equally divided and injected in the wall around the closed internal opening. In chapter 5 we elaborate on the protocol that was executed in this clinical trial as a standard for such procedures in this setting.

Although the results of the clinical trial of local MSC therapy for perianal fistulizing CD are very encouraging, the exact mechanism of action of these cells remain to a large extent unknown. One of the questions to be answered is the optimal time of administration to achieve maximal efficacy of MSC treatment. In chapter 6 we evaluated whether the timing of MSC administration and the presence of an ongoing inflammatory response are important to reach treatment efficacy in experimental colitis. Dextran sulphate sodium (DSS) was given to C57BL/6 mice resulting in either mild or severe colitis depending on the percentage of DSS added to the drinking water. MSCs were injected intraperitoneally before or after the introduction of DSS to examine if the moment of injection is important to alleviate colitis. In addition, the effect of MSCs on colitis when multiple MSC injections were given during the disease course was compared to a single injection at the start of the experiment. To investigate the mode of action of the MSC-mediated immunosuppression
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