The broad spectrum of chronic inflammatory bowel diseases encompasses the two main entities: Crohn’s disease (CD) and ulcerative colitis (UC). The course of disease may be intermittent or chronic. Activity ranges from mild to severe and can in some instances be fulminant. Prognostic risk factors for a disabling course seem to be small bowel involvement, a stricturing or penetrating behaviour, perianal disease, onset at an age of less than 40 years and the need for systemic steroids for treating the first flare. The etiology of inflammatory bowel disease (IBD) is complex and many aspects still remain unclear. A healthy intestinal mucosa is in a state of controlled inflammation regulated by a delicate balance of pro- and anti-inflammatory cytokines. In Crohn’s disease the interaction of the intestinal mucosal immune system and the intestinal milieu seems to culminate in a sustained activation of an immune response with an uncontrolled deregulation of pro- and anti-inflammatory agents, resulting in ongoing mucosal damage. Understanding the mechanism of induction and maintenance of remission in Crohn’s disease at intestinal interfaces is a prerequisite to the evaluation of new therapeutic options.

Rapid action and long term duration is the goal in most therapeutic approaches in chronic inflammation for induction and maintenance of remission. The search for new drugs has resulted in the evaluation of new immunosuppressive and anti-inflammatory agents including biological therapies targeting specific molecules. Among these, particularly the TNF-α blockers infliximab and adalimumab have a record of a sustained and extended response in Crohn’s disease. Efficacy and safety were evaluated in several studies in the last decade (Present et al. 1999; Sandborn et al. 2002; Hanauer et al. 2002; Hanauer et al. 2006; Clark 2006;
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Sandborn et al. 2007; Colombel et al. 2007). At present, anti-TNF-alpha (TNF-α) antibodies are a mainstay in patients with severe, steroid-refractory Crohn’s disease and are also proposed as first line treatments in “top-down” strategies (Armuzzi et al. 2008; Hanauer et al. 2007; D’Haens et al. 2008). The hope of this approach is that early use of biologics in Crohn’s disease offers the potential to modify the course of disease in the long term thereby resulting in improved clinical outcomes.

Other therapeutic options in steroid-refractory Crohn’s disease are still limited, and a considerable number of patients remain refractory, lose response or are intolerant to these biologicals. An overall long lasting remission of less than 30% due to TNF-alpha blockers in patients with steroid-refractory Crohn’s disease seems common. Despite the reasonable progress in our understanding of the disease pathophysiology, new alternative biological therapies failed to demonstrate a convincing efficacy and safety profile so far.

Thus there is a strong need for other agents to expand our arsenal of rapid acting and ideally long lasting immunosuppressive regimes. The encouraging results of the first uncontrolled studies by Stallmach and co-workers (Stallmach et al. 2003) addressing cyclophosphamide pulse therapy in steroid refractory IBD accounted for our interest in this treatment. We initiated an uncontrolled open-label study to expand the body of evidence for cyclophosphamide pulse therapy in severely active, steroid-refractory or -dependent Crohn’s disease patients. In our cohort all patients received a median of 3 (range 2–6) monthly pulses of 750 mg cyclophosphamide intravenously. The main purpose was to evaluate the overall efficacy and safety of this regime. The most significant finding was the high short term efficacy of cyclophosphamide pulse therapy in these severely affected patients. Induction of remission was achieved in 67% of the patients and a steroid-free remission in 54% (Schmidt et al. 2009). Of note, cyclophosphamide pulse therapy was highly effective in the treatment of extraintestinal manifestations like episcleritis, erythema nodosum and peripheral oligoarthritis which was paralleled by remission of luminal disease.

The anti-inflammatory effects of cyclophosphamide pulse therapy could be observed following the first infusion. In our cohort 47% of the patients entered remission at week four, indicating the rapid-acting potential of this treatment. Furthermore, cyclophosphamide pulse therapy was well tolerated at cumulative doses of 1.5–4.5 g. A pitfall of this short-term treatment strategy was the high relapse rate after the induction of remission and stopping cyclophosphamide pulse therapy. Sixty percent of patients that entered remission relapsed at a median of 16 months (Schmidt et al. 2009).

In spite of these promising results further evidence is mandatory to support a regular use of this well known drug peradventure in steroid and anti-TNF-alpha refractory Crohn’s disease. Cyclophosphamide pulse therapy might be applied in patients that lose response or render intolerant to anti-TNF-alpha strategies. The main issue to be addressed in future studies is the long-term response to cyclophosphamide pulse therapy and to identify “surrogate markers” in patients who could benefit from this therapeutic option.

Analogous to the established Cyclops scheme for Wegener’s granulomatosis, a body weight-related dose of 13–15 mg/kg seems to be preferable (Vancavá et al. 2006). Accordingly, the inductive regime of cyclophosphamide pulse therapy in the first three months should regularly be followed by a consolidation of another three months of treatment to achieve a longer lasting remission. An individually optimization of the protocol is essential regarding single dosage, pulse frequency and duration of treatment. In addition long-term immunosuppression using azathioprine, 6-mercaptopurine or methotrexate after finishing cyclophosphamide pulse therapy should be mandatory to sustain the beneficial effects.

This therapeutic option should be kept in mind as a reasonable option to target the inflammatory process in severely disabled patients refractory or intolerant to earlier treatment strategies, including TNF-alpha antibodies.

The possible benefits versus individual risks have to be carefully addressed. The safety profile of cyclophosphamide is well known based on extensive studies in vasculitis patients over the past decades (De Groot et al. 2001).
In synopses of the recent data with cyclophosphamide pulse therapy in Crohn’s disease, all studies presented a safe and highly effective “new therapy” for induction and maintenance of remission in steroid-refractory and dependent course of disease (Schmidt et al. 2009, Schmidt et al. 2006, Barta et al. 2006). Nevertheless, there is a strong need for additional experience to improve the setting of the very encouraging cyclophosphamide treatment in Crohn’s disease.

References