The Practical Use of Steroids in IBD

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In the daily management of IBD, glucocorticosteroids (GCS) still take an important and crucial position. In both Crohn's disease (CD) and ulcerative colitis (UC), GCS are usually initiated after failure of aminosalicylates, sulphasalazine and/or antibiotics and prior to treatment with immunomodulators and biological agents.
The European Crohn's and Colitis organization ECCO developed a consensus on CD management in 2004. According to this conference, 'the preferred treatment for mildly active localised ileocaecal Crohn's disease consists of Budesonide 9 mg daily. The benefit of mesalazine is considered to be limited and antibiotics cannot be recommended. Moderately active localized ileocaecal Crohn's disease should preferably be treated with budesonide 9mg per day or with systemic corticosteroids. Antibiotics can be added if septic complications are suspected. Severely active localized ileocaecal Crohn's disease should initially be treated with systemic corticosteroids. Active colonic Crohn's disease may be treated with aminosalicylates if only mildly active, or with systemic corticosteroids'(1).

GCS penetrate the cell wall and bind to the GCS receptors, after which they down regulate the synthesis of proinflammatory molecules (endopeptidase, endonucleases etc) and up regulate antiinflammatory molecules (phospholipase A2, cytokines such as TNF, iNOS etc.) at the nuclear level. This all leads to a global antiinflammatory action: reduced chemotaxis and tissue infiltration of neutrophils, reduced proliferation, differentiation and cytotoxicity of lymphocytes, reduced chemotaxis and phagocytosis by monocytes/macrophages, reduced expression of adhesion molecules by endothelial cells.

A review of all placebo-controlled trials in Crohn's disease by Bebb and colleagues (2) revealed that the success rate with prednisone amounted tot 60%, with a number of patients needed to treat of 3, versus 10 for mesalazine. Higher doses of GCS, e.g. as used in the GETAID trials (1mg/kd/day) led to response rates of even over 90 % (3) ! Nevertheless, it needs to be reminded that the antiinflammatory effects of a course of steroids often remains limited to only a few months. Both Munkholm and Faubion (4,5) demonstrated that after 12 months, only 26-32% of patients were still in remission, while more than half had relapsed and more than 20% had become 'steroid dependent'. Prolonged use of steroids can, however, not be recommended given the important toxicity associated with its use: Cushing's syndrome, osteoporosis, acne, weight gain, increased appetite, mood swings and many more.

The development of topically acting GCS has been a major advance in reducing GCS toxicity. Agents like enteric/colonic released budesonide even approach the 'ideal profile' of GCS: high receptor affinity (>100 times more than hydrocortisone), maximal concentration at the site of inflammation, high first pass effect in the liver and hence low systemic bioavailability (5-8 times lower than hydrocortisone). The goals of treatment with topical (non-systemic) GCS in IBD are as follows: induction of remission of mild to moderate active disease, maintenance of remission, minimalization of adverse events and improvement of quality of

life. The agents that have been studied and used in IBD include oral budesonide, topical budesonide and beclomethasone dipropionate for UC, oral fluticasone propionate and rectal tixocortol pivalate.

By far the most clinical experience is available for the two commercially available budesonide preparations Budenofalk and Entocort 'controlled ileal release' (CIR). Greenberg and colleagues demonstrated in 1994 that a dose of 9 mg/day was the optimal dose for induction of remission in ileocaecal CD (6). That dose was later compared with prednisone at a dose of 40 mg/day in a study which showed that budesonide CIR was almost as potent as prednisone, but with a much more favourable side effect profile: 48% of patients treated with prednisone have at least 1 side effect, versus only 29% of patients treated with budesonide (7). The most important differences were reported in the aesthetic side effects of acne and moon face. A comparable study compared methylprednisolone and Budenofalk 3x3 mg/day (8). In this study, all types of CD were treated and not just ileocolonic disease. Remission rates at 8 weeks were 73% with systemic versus 56% with topical steroids. Whereas the rapidity of action was similar with both agents, the side effect profile was in favour of Budenofalk. At least one typical steroid side effect was reported in 70% of patients with methylprednisone compared to 29% of patients treated with Budenofalk. The same study design was copied in a larger population 201 patients by Bar-Meir and colleagues (9). Remission rates were identical in both groups (56%), whereas remission without steroid side effects was observed in 41% of patients on prednisone versus 23% of patients on Budenofalk. Another study with comparable design included only paediatric patients and came to the same conclusions (10).

A Scandinavian study by Thompson et al. then compared budesonide CIR (9 mg/day) with mesalazine (4 gram/day) in active CD. Remission rates after 8, 12 and 16 weeks of therapy were clearly higher with budesonide (60-70 %) than with mesalazine (40 %). Three per cent of the patients on budesonide had to discontinue treatment during the trial versus 9% on mesalazine. In addition, serious adverse events occurred more frequently with mesalazine (11).

The benefit of systemic corticosteroids to *maintain* remission in CD was analyzed by Steinhart in his Cochrane study based on 3 controlled clinical trials. Odds ratios for relapse were 0.71 at 6 months, 0.82 at 12 months and 0.72 at 24 months (12). These findings led to the conclusion that active GCS treatment is not superior to placebo in the maintenance setting. The situation is somewhat comparable with topical steroids. Several trials using Budesonide 6 mg/day as maintenance therapy demonstrated that the time to the next relapse can be prolonged, but at the end of one year this benefit was not found to be significant (13,14). In the subgroup of patients who are dependent on systemic steroids, however, Cortot et al. were able to show that a successful switch to topical steroids is possible in the majority of patients, leading to a reduction in the number of side effects by 50 % (15). Mantzaris compared mesalazine and budesonide in the same type of study design and demonstrated that after one year, significantly more patients were still in remission with budesonide 6 mg/day than with mesalazine 3 gram/day ($p= 0.045$) (16).In conclusion, it can be stated that oral budesonide (CIR) and budesonide pH modified treatments are not able to maintain medically induced remission neither to prevent relapses after surgically induced remission. Oral budesonide (CIR) is a valuable alternative to conventional steroids, however, in cortico-dependent patients.

Corticosteroids also play a major part in the management of moderate to severe ulcerative colitis. Many patients with UC relapses who are refractory to 5-ASA preparations will need

GCS therapy. If oral therapy appears to be ineffective, patients are usually admitted to the hospital for intravenous treatment. This approach is successful in more than 60 % of the patients (17). In case of failure, additional therapy with cyclosporine, infliximab or even colostomy should be considered. Patients with left-sided disease can be treated with topical therapy. For this indication, budesonide enemas have been as effective as 5-ASA enemas (18).

Finally, doctors treating IBD patients should always pay attention to the bone system, since GCS indeed induce osteopenia or osteoporosis if no appropriate action is taken. A multicentre study looked at bone mineral density (BMD) in relation to budesonide and prednisolone in Crohn's disease in a randomized controlled trial (19). Patients with active ileocolonic CD were treated with either steroid preparation, tapered in case of improvement and reintroduced as clinically indicated. Patients were followed for a total duration of 24 months. The population was divided in three groups: steroid-dependent patients, patients who had received steroids previously and steroid-naïve patients. BMD was assessed by dual X-ray absorptiometry (DXA). At the end of the two years, the BMD was clearly lower in patients who were steroid-naïve and also in patients who had previously received steroids, but not in steroid-dependent patients. Importantly, the most significant bone loss occurred with the first steroid course! The following recommendations should therefore be kept in mind with regard to GCS treatment in IBD: DEXA-scans before a first treatment with corticosteroids is initiated, minimalization of steroid use and maximal use of topical steroids. In case of normal BMD, Ca and Vit D should be considered in conjunction with steroids. In patients who already have osteopenia/osteoporosis, biphosphonates should be given in addition to Ca and Vit D.

As a general conclusion, we have to say that GCS and topical steroids are highly effective in IBD. A sufficiently high dose needs to be given when this therapy is initiated and tapered as soon as remission has been attained. Maintenance steroid therapy cannot be accepted any more, given he availability of immunomodulatory and biological agents that are steroid sparing. And, finally, when using GCS: always beware of the bones!

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