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EDITORIAL

Budesonide: a useful tool in the maintenance treatment of Crohn's disease?

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Maintaining remission over a long period of time is a great challenge in the management of Crohn's disease. For a long-time corticosteroids were the mainstay of pharmacological treatment of active Crohn's disease. In fact, corticosteroids have been used in inflammatory bowel disease (IBD) rather successfully as induction therapy since the 1950s.[1] However, for maintenance treatment this class of drugs is not considered to be very effective. Although some 80% of IBD patients respond to corticosteroids, there is a considerable loss of efficacy on maintenance treatment, which might be explained by the selection of steroid-resistant populations of lymphocytes in the gut mucosa. Some patients are unable to stop taking corticosteroids because of loss of well-being and risk for flares, which might be explained by withdrawal symptoms and other effects on the central nervous system. The major disadvantage of long-term maintenance treatment is the side effects related to corticosteroids, the worst being irreversible osteoporosis eventually leading to vertebral fractures.[2]

The topically active synthetic steroid budesonide has far fewer side effects because of a high first pass effect in the liver after oral administration, and is therefore considered to be safer than prednisolone. When it was introduced, clinicians hoped that besides effective induction therapy, which will not be discussed in this editorial, they would have access to a new tool for safe and effective long-term treatment.

In a large multicentre international study focused on budesonide treatment in Crohn's disease from our group, we found it hard to recruit Dutch patients on longterm steroid treatment.[3] This was probably due to the extended use of immunosuppressants such as azathioprine and methotrexate in the last decade of the last century. These drugs are particularly effective for long-term treatment and only a small group of IBD patients are intolerant to both. Methotrexate is more effective than placebo in maintenance, but the results are less convincing than with azathioprine. Azathioprine has been shown to decrease the relapse rate at one year from 40% on placebo to 5 to 10%.

The introduction of anti-TNF-α inhibitors led to other perspectives for long-term treatment of Crohn's disease. These drugs appear to be very effective in the maintenance treatment of Crohn's disease. As with every medical treatment, there have been concerns about loss of efficacy, side effects and safety.[4] In the light of these developments, the role of corticosteroids is changing. Currently, the conservative pharmacological step-up approach is shifting towards a top-down or a more rapid step-up approach as patients with a shorter disease history and younger patients tend to respond better and longer.[5] Treatment of Crohn's disease in this aspect is comparable with treatment of rheumatoid arthritis patients.

In this issue De Jong *et al.* describe an impressive, large multicentre study conducted both in the Netherlands and Germany.[6] A total of 160 Crohn's disease patients in remission were included and were randomised to a maintenance regimen of 6 or 9 mg/day of budesonide controlled-release (Budenofalk®). There was no difference in the one-year relapse rate, and the time to relapse was similar. However, the one-year relapse rates were very low (24 *vs* 19%).

Are the results of this study surprising? In the predetermined pooled analysis of four randomised controlled trials with budesonide 3 or 6 mg *vs* placebo in patients with medically induced remission, time to relapse was prolonged but without a difference in one-year relapse rate![7] Thus, it would have been surprising if budesonide 9 mg were to have been more effective than 6 mg for the long-term relapse rate after one year.

In addition, low-dose oral budesonide cannot be recommended for the prevention of postoperative relapse in Crohn's disease.[8] Oral budesonide, 6 mg/day, offered no benefit in prevention of endoscopic recurrence after surgery for ileal/ileocaecal fibrostenotic Crohn's disease

but decreased the recurrence rate in patients who had undergone surgery for disease activity.[9]

What is the clinical impact of the results? This study confirms that budesonide is equally potent in prolonging the time remission in both a 6 or 9 mg/day dose. This study demonstrates that a 9 mg dose is no better than 6 mg for this purpose. In the study by de Jong *et al*. a low one-year relapse rate was found, most likely due to an inclusion of patients whose Crohn's disease followed a relatively mild course. In view of these findings, it is unlikely that new large placebo-controlled studies with budesonide controlled-release will ever be performed. Presently, the number of potential new drugs for IBD exceeds the number patients available for these studies.

In patients with mild to moderate ileocaecal Crohn's disease, budesonide controlled-release is effective for remission induction therapy but the effect of maintenance therapy after remission is medically achieved in doses of up to 9 mg daily is in my opinion doubtful.

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