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Therapy of steroid-resistant inflammatory bowel disease

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Abstract: BACKGROUND AND AIMS: Although systemic corticosteroids are successfully administered for the induction of clinical response and remission in the majority of patients with inflammatory bowel disease (IBD) presenting with a flare, a proportion of these patients demonstrate a primary nonresponse to steroids or in the case of an initial response, they develop a resistance or a steroid dependence. Long-term therapy with corticosteroids for treatment of IBD should be avoided, given the high frequency of adverse treatment effects. Knowledge about treatment strategies in case of steroid nonresponse is therefore highly relevant. **METHODS:** A systematic literature research was performed using Medline and Embase to summarize the currently recommended treatment strategies for steroid-resistant IBD. **RESULTS:** Treatment of steroid-resistant Crohn's disease is based on the introduction of immunomodulators such as azathioprine, 6-mercaptopurine or methotrexate, the anti-TNF drugs infliximab, adalimumab and certolizumab pegol. In the case of steroid resistance in ulcerative colitis, aminosalicylates, the above-mentioned immunomodulators, infliximab, adalimumab or calcineurin inhibitors such as ciclosporin or tacrolimus may be administered. **CONCLUSION:** This review summarizes the current evidence for treating steroid-resistant IBD.

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Therapy of steroid-resistant Inflammatory Bowel Disease

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Short title: Therapy of steroid resistant IBD

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Key words: Crohn's disease, ulcerative colitis, steroids-resistance, therapy

ABSTRACT

Background and Aims: Although systemic corticosteroids are successfully applied for induction of clinical response and remission in the majority of inflammatory bowel disease (IBD) patients presenting with a flare, a proportion of these treated patients demonstrate a primary non-response to steroids or in case of an initial response, they develop a resistance or a steroid dependence. Long-term therapy with corticosteroids for treatment of IBD should be avoided given the high frequency of adverse treatment effects. Knowledge about treatment strategies in case of steroid non response is therefore highly relevant.

Methods: A systematic literature research was performed using Medline and Embase to summarize the currently recommended treatment strategies for steroid resistant IBD.

Results: Treatment of steroid resistant Crohn's disease is based on the introduction of immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate, as well as the anti-TNF drugs infliximab, adalimumab, and certolizumab pegol. In case of steroid resistance of ulcerative colitis, aminosalicylates, the above mentioned immunomodulators, infliximab, adalimumab, or calcineurin inhibitors such as ciclosporin or tacrolimus may be applied.

Conclusion: This review summarizes the current evidence for treating steroid resistant IBD.

INTRODUCTION

Corticosteroids are used since the 1950s in inflammatory bowel disease (IBD) and remain one of the most effective treatments in a disease flare.[1] These drugs represent effective anti-inflammatory agents for inducing response and remission in IBD patients with moderate to severe disease activity. Corticosteroids act through inhibition of several inflammatory pathways such as suppression of interleukin transcription, induction of I κ B that stabilizes the NF- κ B complex, suppression of arachidonic acid metabolism and stimulation of lymphocyte apoptosis within the lamina propria of the gut.[2]

Precise evidence about the most effective dose and duration of therapy is missing. Sixty milligrams (mg) of prednisolone seems not to be more effective than 40 mg but is associated with a higher frequency of adverse events.[3] Guidelines suggest to start with an initial oral dose of 40-60mg (0.75-1mg/kg) prednisolone daily followed by a tapering.[4,5] A commonly used regimen for steroid tapering consists of reducing dosages above 30 mg daily in 10 mg steps per week and reducing dosages of 30 mg daily and below in 5 mg steps per week. Neither the long-term remission rates nor the duration of remission are influenced by the initial dose or the rate of steroid tapering.[5,6] The goal of every IBD therapy is the achievement of a steroid-free remission. Steroids have no role as maintenance therapy in either Crohn's disease (CD) or ulcerative colitis (UC).[7]

About half of the patients treated with steroids will suffer from side effects. Following the application of supra-physiological doses of steroids, cosmetic problems (such as acne, moon face, edema), diabetes, dyspepsia or sleep and mood disturbances may occur. Furthermore, patients under steroids are confronted with an risk for infections. Prolonged use of steroids has been associated with osteoporosis, osteonecrosis, myopathy and cataract. In addition, children and adolescents may suffer from growth retardation. Typical steroid-withdrawal effects include adrenal insufficiency, the corticoid withdrawal syndrome and raised intracranial pressure.[2]

The natural history of first exposure to corticosteroids shows a thirty-day outcome of complete remission in 48-58%, partial remission in 26-32% and no response in 16-20% for CD patients.[6,8] In UC immediate outcomes were complete remission in 54%, partial remission in 30% and no response in 16% of the patients.[8]

The phenomenon of steroid resistance is not confined to IBD suggesting it may be an inherent property of an individual becoming important in the presence of inflammatory disease.[1] Several molecular mechanisms of glucocorticoid resistance have now been identified, including activation of mitogen-activated protein (MAP) kinase pathways by certain cytokines, excessive activation of the transcription factor activator protein 1, reduced histone deacetylase-2 (HDAC2) expression, raised macrophage migration inhibitory factor, and increased P-glycoprotein-mediated drug efflux.[9]

Definition of steroid resistant and steroid dependent disease

Patients (MC or UC) who have still active disease despite prednisolone or an equivalent of up to 0.75 mg/kg/day over a period of 4 weeks are defined as having steroid-resistant or steroid refractory disease. Patients who are either unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting without recurrent active disease, or who have a relapse within 3 months of stopping steroids are considered as having steroid-dependent disease.[10-13]

Steroid resistance, dependence or primary non response should prompt medical treatment escalation or consideration of surgery.

Steroid resistance in Crohn's disease

Before escalating or changing therapy in steroid resistant Crohn's disease, complications such as an abscess or infection must be ruled out by appropriate imaging techniques or stool analyses. Furthermore, surgery should also be considered as an option, especially in CD patients with severe ileocaecal involvement. Different treatment strategies have been shown to be effective in case of steroid resistance; these will now be further discussed below.

Purine analogues

Thiopurine drugs, represented by mercaptopurine (6-MP) and its pro-drug azathioprine (AZA) have cytotoxic and immunosuppressive properties. The appropriate maintenance dose of AZA is 2-2.5mg/kg/day and 1-1.5mg/kg/day of 6-MP respectively. They are widely used in steroid-refractory or -dependent IBD patients. AZA and 6-MP have proven efficacy for the induction of remission in active Crohn's disease and for maintaining remission and having steroid sparing properties in quiescent steroid dependent CD.[14-17] In the recent SONIC study 30% of the 170 patients receiving AZA alone had a corticosteroid-free clinical remission after 6 months.[18] About 9% of IBD patients are resistant to thiopurines and between 15% and 28% experience adverse reactions.[19]

Methotrexate

Methotrexate 25mg/week (oral, subcutaneous or intramuscular) may be used as an alternative to thiopurines. It is an established therapy for induction and maintenance of remission in CD.[20,21] Injections might be preferred due to unpredictable intestinal absorption by the oral route.[22]

Anti-TNF therapies

There are currently three biologic agents licenced for the treatment of Crohn's disease in Switzerland: Infliximab (Remicade®) and Adalimumab (Humira®) are monoclonal IgG1 anti-TNF antibodies, Certolizumab Pegol (Cimzia®) is a pegylated anti-TNF Fab-antibody fragment. These three anti-TNF agents have proven efficacy in CD in various controlled trials. Most of these trials did not clearly address steroid resistance but were used in patients with moderate to severe disease.

The European Crohn's and Colitis Organisation (ECCO) states in their consensus statement from 2010 that patients with evidence of active disease refractory to steroids should be treated with anti-TNF therapy, with or without thiopurines or methotrexate (EL1a, RG B for infliximab).[4] They also state that all currently available anti-TNF therapies appear to have

similar efficacy and adverse-event profiles, so the choice depends on availability, route of delivery, patient preference, cost and national guidance.[4]

Infliximab

The SONIC Study Infliximab with or without AZA was assessed in a randomized, double-blind, active comparator study of 508 adult patients with moderate to severe Crohn's disease naive to biologics and immunosuppressants. Remarkably, at baseline only 27.4% of patients were under systemic corticosteroids. Patients were randomized to receive AZA monotherapy, infliximab monotherapy, or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily. The primary endpoint of the study was corticosteroid-free clinical remission at Week 26. Of the patients receiving combination therapy, at week 26 56.8% were in corticosteroid-free clinical remission, as compared with 44.4% receiving infliximab alone ($P=0.02$) and 30.0% receiving azathioprine alone ($P<0.001$ for the comparison with combination therapy and $P=0.006$ for the comparison with infliximab). Similar numerical trends were found at week 50.[18]

The GETAID trial evaluated the usefulness of short-term infliximab combined with thiopurines in steroid-dependent Crohn's disease patients. 113 steroid dependent patients with active CD were stratified into two groups: AZAMP failures and AZAMP-naive patients. Patients were randomized to infliximab 5 mg/kg or placebo at weeks 0, 2, and 6. All patients were treated with stable doses of AZAMP throughout the 52-week trial. Their primary endpoint was clinical remission (CDAI < 150) off steroids at week 24. Significantly more patients receiving infliximab plus AZAMP compared with patients receiving AZAMP alone were in steroid-free clinical remission at week 12 (75% vs. 38%; $P < 0.001$) and week 24 (57% vs. 29%; $P = 0.003$). They concluded that Infliximab plus AZA/6-MP was more effective than AZA/6-MP alone in steroid-dependent Crohn's disease patients.[23]

Adalimumab

In the CLASSIC-I trial, several dosage regimens were compared to placebo for induction of remission in 229 anti-TNF naive patients with moderate to severe CD. Patients were randomized to receive sc injections at weeks 0 and 2 with adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo. In the placebo group (n = 25) 34% were under steroids and 30% under immunomodulators (AZA or 6-MP or MTX) compared to 32% under steroids and 29% under immunomodulators in the verum group. The highest remission rate was observed with 36% (p = 0.001) in the 160 mg/80 mg group compared to 12% in the placebo group. The percentage of patients off steroids at week 4 was not assessed as an endpoint in this study. [24] In the CHARM trial, patients received open-label induction with therapy with adalimumab 80mg (week 0) followed by 40 mg (week 2). At week 4, patients were stratified by response (drop in CDAI of at least 70 points) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week (eow) or adalimumab 40 mg weekly through week 56. [25] End points were the % of randomized responders achieving clinical remission at week 26 and 56. The percentage of randomized responders in remission was greater in the adalimumab 40 mg eow and 40 mg weekly groups compared to placebo at week 26 (40%, 47%, and 17%, respectively; p < 0.001) and week 56 (36%, 41%, and 12%, respectively; p < 0.001). Forty-four % of patients were under steroids and 47% under immunomodulators (AZA or 6-MP or MTX). Of the randomized responders at week 26, 3%, 35%, and 30% of patients treated with placebo, adalimumab 40 mg eow, and adalimumab 40 mg weekly, respectively, achieved a corticosteroid-free remission (p < 0.001 for each adalimumab group compared to placebo). At week 56, 6%, 29% and 23% of patients treated with placebo, adalimumab 40mg eow, and adalimumab 40 mg weekly, respectively, achieved corticosteroid-free remission (p < 0.001 for adalimumab 40 mg eow vs. placebo and p = 0.008 for adalimumab 40 mg weekly vs. placebo).

Certulizumab pegol

In the Precise II trial, patients with moderate to severe CD received induction therapy with 400mg certolizumab pegol sc. at weeks 0, 2, and week 4.[26] Patients with a clinical response (CDAI reduction of at least 100 points from baseline) at week 6 were stratified according to their baseline CRP level and randomly assigned to 400 mg of certolizumab pegol or placebo every 4 weeks through week 24 with a follow-up through week 26. Sixty-four % of patients showed a response at week 6, the response was maintained through week 26 in 62 % of patients with a baseline CRP of at least 10 mg/L receiving certolizumab pegol compared to 34% in the placebo group ($p < 0.001$). In the placebo group 21% of patients were under corticosteroids and 25% under immunomodulators compared to 22% under steroids and 27% under immunomodulators in the certolizumab group. The percentage of steroid free patients at week 26 was not reported in this trial.

Steroid resistance in ulcerative colitis

Steroid-dependency in ulcerative colitis defines a patient, who fails to taper steroids below 10mg within 16 weeks (starting dose 0.75-1 mg/kg oral prednisone-equivalent) or who relapses within 12 weeks after discontinuation of steroids. A patient not responding to 0.75-1mg/kg of oral prednisone-equivalent within 4 weeks is defined having steroid-refractory or steroid-resistant ulcerative colitis.[10,27] This classification is made after exclusion of infection by appropriate stool tests and is best re-assessed by sigmoidoscopy/colonoscopy with biopsies to confirm the diagnosis and/or to rule out complications like CMV colitis or cancer. The universal goal, as in Crohn's disease is to withdraw steroids completely whenever possible.

Practical treatment algorithms for moderate to severe ulcerative colitis are provided in recent Swiss consensus recommendations.[28]

In steroid-refractory ulcerative colitis in a patient in clinically stable condition without the need for rapid induction, thiopurines (AZA 2-2.5mg/kg or 6-MP 1-1,5mg/kg) can be added.[29] Different as in CD, efficacy of thiopurines in UC has been proven for maintenance therapy,

but only as alternative treatment.[30] It may be worth trying to optimize conventional treatment, especially to maximise the dose of 5-ASA treatment or to add topical 5-ASA.[22]

If the patient is still clinically stable but not responding after 12 to 24 weeks, biological therapy must be considered.

Efficacy of infliximab in UC was demonstrated in two large clinical trials. In the Active Ulcerative Colitis Trial (ACT)-1 and ACT-2 studies, patients with moderate-to-severely active UC received induction with infliximab at weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks. Infliximab was superior to placebo for achieving clinical response, clinical remission, mucosal healing, and reducing corticosteroid use through week 30 (ACT-2) and 54 (ACT-1).[31]

The ACT-1 and -2 extension studies could show that long-term treatment with infliximab was effective and well tolerated for up to 3 additional years.[32] In a retrospective multicentre study primary non response to infliximab was noted in 22%.[33]

Recently, also adalimumab was shown to be more effective than placebo in inducing and maintaining clinical remission in patients with moderate-to-severe ulcerative in a large trial with 494 patients.[34] Adalimumab was given subcutaneously 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week.

In the severely ill, hospitalised patient with need for rapid induction, steroids will be given intravenously, such as 60mg of methylprednisolone or 400mg of hydrocortisone daily.[29] An overall response rate of steroids can be expected to be 67%.[35] A close teamwork between the gastroenterologist and the experienced colorectal surgeon at the latest at this stage of the disease is mandatory, in order not to miss the best timing for colectomy.

In case of resistance to iv-steroids, especially in the AZA-naïve patient, intravenous cyclosporine at a dose of 2mg/kg can be started.[28] If the patient is responding, AZA is added and cyclosporine orally continued for at least three month as a bridging therapy.[28]

If the severely ill patient had failed prior therapy with AZA/6-MP, due to the lack of good exit strategy, infliximab at 5mg/kg at weeks 0, 2, 6 and then every 8 weeks can be started.[28]

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