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Lecture

Management of refractory Inflammatory Bowel Disease

S.S Goulas

SUMMARY

Medical management of active inflammatory bowel disease (IBD) depends on the extent and the severity of the disease estimated by both clinical and endoscopic parameters. Based on these parameters a flare of IBD, either of ulcerative colitis (UC) or of Crohn's disease (CD) can be mild, moderate or severe. Mild or moderate IBD is treated on an outpatient basis, while severe disease requires hospitalization. Although in the literature there is no clear cut definition of resistance, we characterize as refractory the disease that does not respond to drug treatment, consisting of salicylates and steroids in doses appropriate for the severity of the episode for a four week period in combination with topical therapy. In severe IBD the critical period is much shorter (5 days).

In refractory mild IBD, steroids (prednisone 20-40 mg) combined with a double dose of topical treatment are appropriate. In refractory moderate disease, therapeutic options are: the intensive scheme of severe disease, immunomodulators, Infliximab or consideration for surgery. In refractory severe cases cyclosporine (mainly for UC) or Infliximab either early or after cyclosporine failure appear to be effective approaches, which must be compared to surgical treatment in controlled clinical trials.

In conclusion, although refractory IBD is a challenge for the clinician there are several therapeutic options. Apart from old friends (steroids, immunomodulators, surgery) the new group of biologic agents, in the form of anti-TNF factor (Infliximab at present), has emerged as an option in the medical management of moderate, severe and refractory IBD.

Hepato-Gastroenterology Unit, "Helena Venizelou" Hospital, Athens Greece

Author for correspondence:

Spyros S Goulas MD, "Helena Venizelou" Hospital, 2, Pl Helena Venizelou, 11521, Athens Greece, Tel. & Fax: +30210-6427379, e-mail: spsgoulas33@yahoo.com

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Ulcerative colitis (UC) and Crohn's disease (CD) (collectively termed inflammatory bowel disease, IBD) share many common characteristics regarding etiopathogenesis, clinical presentation, natural history and management. Concurrently, the two diseases differ substantially. Treatment of IBD is medical (drugs, diet) and surgical. Drug treatment includes:

- Sulphasalazine, Aminosalicylates (Mesalazine/5-ASA, Olsalazine)
- Corticosteroids (Prednisolone, Prednisone, 6-methyl prednisolone, Budesonide)
- Immunomodulators (Azathioprine, 6-Mercaptopourine, Methotrexate, Cyclosporine, Tacrolimus)
- Antibiotics (Ciprofloxacin, Metronidazole)
- Biologic therapies (Infliximab, Adalimumab)

Ten years ago, the therapeutic strategy for IBD was standardized according to the results of many controlled trials and to long clinical experience. During the last decade, the introduction of the low bioavailability steroids (budesonide) and the new group of biologic therapies (especially anti-TNF, Infliximab) resulted in a revolution of medical management. Infliximab is a very efficacious drug for CD and has also been approved recently for the treatment of UC, based on the promising results of therapeutic trials. Biologic therapies and the whole spectrum of refractory IBD will be discussed in this review.

TREATMENT OF REFRACTORY ULCERATIVE COLITIS

UC is a chronic inflammatory disease of the colon of

unknown etiology. The clinical course can be:

Chronic relapsing, characterized by episodes of exacerbation and remission (60-75%)

Chronic active (5-15%)

Intermittent, characterized by an acute episode a long period of quiescent disease and relapse (5-10%).

Therapy points to the induction and maintenance of remission as well as the prevention of relapses and complications. Management depends on the extent and the severity of the episode estimated by both clinical and endoscopic parameters. UC can be divided into distal and extensive disease, according to the proximal margin of macroscopic inflammation. Distal disease refers to proctitis, or rectosigmoiditis. More extensive disease includes left sided colitis (up to the splenic flexure), extensive colitis (up to the hepatic flexure) and pancolitis. Disease severity is evaluated using a clinical activity index (the Truelove-Witts,[1] or the simple clinical colitis[2]). Patients with severe disease require hospital admission, while those with mild or moderate disease can be managed as outpatients. The endoscopic severity index with a score 0-5 (0=normal mucosa, 1=erythema, 2=friability, 3=bleeding, 4=ulcers and 5=diffuse ulceration) and the Powell-Tuck index with a combination of both clinical (number of diarrheas, blood, abdominal pain, anorexia, nausea, vomiting, fever, general condition, extraintestinal symptoms) and endoscopic parameters are also quite useful in clinical practice.

After clinical and endoscopic evaluation, the disease is characterized as mild, moderate or severe. This distinction is critical for every patient with UC, as it is decisive for the selection of therapeutic scheme. It is also necessary to define refractory disease. Although there is no generally accepted definition, refractory is the disease, which does not respond to medical treatment, consisting of systemic aminosalicylates and steroids in doses appropriate for the episode, for four weeks (in conjunction with topical treatment). In cases of severe attack, therapy is parenteral, according to the intensive scheme, and assessment is made after 5 days.

Treatment of mild UC

In distal colitis (proctitis, rectosigmoiditis) initial treatment is usually effective. Mild distal UC is rarely refractory after 2-4 weeks of treatment. In these cases, prednisolone 20 mg per os can be added and local therapy is given in a double dose.

In mild extensive colitis, steroid treatment is continued at the same dose for 4 weeks and then the dose is gradually tapered and stopped. In refractory cases (20-30%) prednisolone in a dose of 40 mg is appropriate.[3-8]

Treatment of moderate UC

Treatment is usually administered on an outpatient basis except for cases characterized by dehydration, electrolyte disturbances or severe anemia requiring transfusions. The efficacy of the classic scheme for moderate disease is approximately 80%. In refractory cases the following steps can include:

- Sulphasalazine, Aminosalicylates (Mesalazine/5-ASA, Olsalazine)
- Hospital admission for the scheme of severe disease (steroids IV + salicylates + topical therapy, assessment on day 5 and addition of cyclosporine or consideration for colectomy, if there is no response)
- Immunomodulators (Azathioprine, 6-Mercaptopourine, or Methotrexate) if there is partial response
- Infliximab
- Surgical therapy (consideration in patients with long standing disease with frequent relapses, despite adequate treatment with immunomodulators)

In chronic active or steroid dependent UC (relapse when prednisolone is reduced to less than 20 mg, or less than 3 months after withdrawal) treatment with immunomodulators is indicated. Azathioprine is given in a dose of 1,5-2,5 mg/kg and 6-mercaptopurine 0,75-1,5 mg/kg. These drugs have a slow onset of action and are fully active after 3 months, therefore steroids must be continued during this period and then gradually tapered if clinical response is achieved. Alternatively, or in cases of failure or intolerance to Azathioprine, Methotrexate should be considered. The initial dose is 25 mg IM per week for 1-2 months and then 15 mg per week as a maintenance dose. Oral administration though more convenient is less effective.[9-12]

Treatment of severe UC

Patients are admitted to hospital for intensive intravenous therapy. These patients should be followed very closely by a specialized medical (gastroenterologist and surgeon with specific experience in IBD) and nursing team. The therapeutic scheme is discussed elsewhere. Initial evaluation is performed 3 and 5 days post admission: if there is improvement, therapy is continued; if there is deterioration or toxic megacolon, emergency colectomy is appropriate and if patient's clinical condi-

tion remains stable (steroid therapy ineffective), cyclosporine 2-4 mg/kg IV should be added (especially when surgery is not available or contraindicated). In all cases the possibility of infection or sepsis should be considered and if it occurs, treatment with antibiotics is required.

Cyclosporine is used in cases of severe UC, which do not respond to IV steroids, after the positive results of one classic double-blinded study in patients with severe refractory UC. The initial response was 82%, but 6 months later despite continuous treatment orally, 44% of initial responders needed colectomy.[13] In another study results were less favorable: treatment was efficient in 38% of patients and only 14% avoided colectomy in the long term.[14] Cyclosporine in a dose of 2mg/kg is equally effective to 4 mg/kg, and there is a trend for fewer side effects for the lower dose.[15] In a meta-analysis for the role of cyclosporine in severe refractory UC, the authors concluded that there is very limited evidence that the drug is superior to steroids. Although the advantage of a rapid onset of action is very attractive, the long-term outcome is less favorable, when the proportion of surgical procedures needed and the side effects are considered.[16] Continuation of cyclosporine orally for 3-6 months and addition of Azathioprine may improve the long-term outcome but this remains under investigation.

No response to both steroids and IV cyclosporine after 10-12 days defines the severe cases as refractory to intensive treatment. 10% of UC patients have severe disease and 20-30% of severe UC is refractory, which means that 2-3% of patients with UC of any type do not respond to the intensive scheme. Patients of this group should be considered for surgical treatment or Infliximab. Early administration of Infliximab instead of cyclosporine may be an alternative option but there is no data at present on this topic.

The role of biologic therapy in refractory UC

Infliximab is a chimeric anti-Tumor Necrosis Factor/ TNF monoclonal antibody with potent anti-inflammatory effects. TNF is increased in both serum and bowel tissue of IBD patients compared to controls. The drug has been under investigation for treatment of UC since 1997. Initial studies were performed in patients with refractory UC but the number of patients was limited and there was no control group (single arm studies). Efficacy was reported as high as 50-70%. From those studies, it became evident that more than a single dose was needed to achieve remission (maintenance therapy). More recent large double controlled studies demonstrated that Infliximab is effective both in active as well as in refractory cases. In the first double controlled study including patients with steroid resistant UC, 5 mg/kg Infliximab administered on 0 and 2 weeks was compared to placebo and no statistical significant difference was evident after 6 weeks (clinical improvement 39% vs 30%, NS.)[17] The results of two multicenter double controlled studies (ACT-I and II) for the efficacy and safety of the drug in moderate and severe UC were published recently. In ACT-I 364 patients with moderate or severe UC refractory to steroids and immunomodulators were divided into 3 groups and treated with 5mg/kg, 10mg/kg or placebo at week 0, 2, 6 and every 8 weeks thereafter until week 46. In ACT-II 364 patients refractory to salicylates, steroids and immunomodulators were divided and treated in the same way for 23 weeks. 30% of patients were steroid refractory. In ACT-I, at week 8 (3 doses) clinical response in the 3 groups was 69%, 62% and 38% respectively and 77%, 68% and 35% for the group of steroid resistant cases ($p<0,001$). For ACT-II response was 65%, 69%, 29% for the three groups and 65%, 70% and 37,5% for the steroid resistant cases ($p<0,001$). Response started after 1-2 weeks and endoscopic healing was noticed in many cases. One year later 35% of patients on 5 mg/kg every 8 weeks were in sustained remission. Conclusively, Infliximab is effective in moderate and severe UC as it is associated with symptomatic improvement, remission and tissue healing. The recommended dose is 5 mg/kg IV at 0, 2, 6 weeks and every 8 weeks thereafter, as in CD. In refractory UC, the drug is also effective and remission is maintained after steroid reduction or withdrawal in a significant proportion of patients (steroid sparing effect).[18] Following this publication, Infliximab was approved for the treatment of moderate and severe UC in patients with inadequate response to classic therapy by the European Medicines Agent-EMEA.

TREATMENT OF REFRACTORY CROHN'S DISEASE

The severity of CD is more difficult to access than in UC. A clinical (Harvey-Bradshaw, CDAI) and an endoscopic index (CDEIS) are commonly used in studies; treatment decisions are based on the site, the activity (clinical, endoscopic) as well as the behavior of the disease. This was recently validated at the Consensus Meeting of Prague.[29] According to the Vienna classification CD can be inflammatory (B1), fibrostenotic (B2) or fistulizing (B3).[19] The management of the inflammatory type (B1) with an emphasis on refractory disease will be discussed here.

Treatment of mild disease (T. Ileum/T. Ileum-Right Colon/ Colon)

If the disease does not respond to the initial therapy, prednisolone 20-40 mg or budesonide 9 mg are used. Treatment is continued for 8 weeks and then gradually tapered and stopped. Budesonide is effective in the area of the terminal ileum-right colon but not in the remaining colon, and thus it is not recommended in Crohn's colitis. It is slightly less effective than classical steroids, but is associated with fewer side effects due to its low bioavailability. In refractory cases, infection and sepsis should also be considered and if the suspicion is confirmed, antibiotics should be given.[3-6,20,28,29]

Treatment of moderate disease (T. Ileum/T. Ileum-Right Colon/ Colon)

In cases of treatment failure (20-30%) the next steps can be:[3-6,21,22,24-29]

- Hospital admission for the scheme of severe disease (steroids IV+ salicylates, assessment on day 5 and consideration for surgical excision if there is no response)
- Immunomodulators (Azathioprine, 6-Mercaptopourine, or methotrexate) if there is partial response
- Infliximab
- Surgical therapy (consideration in patients with long standing disease with frequent relapses despite adequate treatment with immunomodulators). The threshold for surgery for localized ileocaecal disease is lower than that of disease located elsewhere.

There are no comparative trials for all these alternative therapeutic options. Special diets (elemental, polymeric) or parenteral nutrition are complementary to the standard drug therapy.

Treatment of severe disease (T. Ileum/T. Ileum-Right Colon/ Colon)

Cyclosporine has not been studied adequately in severe CD refractory to steroids. There are no double controlled studies with IV administration, merely a few small and uncontrolled. According to a metaanalysis, the drug is of no therapeutic value in CD.[23] Other investigators suggest that it is moderately effective in severe disease but its role is substituted by Infliximab.[30-32] The experience with Tacrolimus is even more limited.[33,34] In any case of refractory severe disease the therapeutic dilemma is between a biologic agent and surgical therapy.

Small Bowel Disease

Steroids are used in a dose according to disease severity. Adequate nutritional support is essential, due to multiple deficiencies of nutrients that occur. In refractory disease, Infliximab is the treatment of choice especially in extensive disease, which precludes surgical excision. Surgery is indicated only for the management of localized fibrotic strictures. Extensive resections should be avoided.[29]

The role of biologic therapy in refractory CD

Infliximab has been used in the management of CD for a decade. It is indicated for inflammatory (B1) and fistulizing (B3) disease. In B1 type, the drug has emerged as an option for active moderate or severe disease and for steroid refractory and steroid dependent disease (particularly if there is intolerance or failure of immunomodulators to maintain remission). In any case, infection or septic complications should be excluded.

In a large multicenter trial, in which the role of Infliximab in CD has been established, one dose of 5mg/kg achieved remission in 48% of cases after 4 weeks and was superior to 10 or 20 mg/kg.[24] In another trial, 3 doses of 5 mg/kg at 0, 2, 6 weeks were better compared to a single dose (response rate 65% vs 52% after 10 weeks). Important advantages of the drug are the rapid onset of action (1-2 weeks) and total tissue healing noticed in responders. A negative response following administration of the first dose is predictive of treatment failure.[25-27] The large multicenter Accent I study in 573 patients demonstrated an initial response of 58% and that repeated doses of 5 mg/kg every 8 weeks, after the initial 3 doses at 0, 2, 6 weeks were superior to placebo every 8 weeks (remission rates 39% vs 21% at 30 weeks, reduction of surgical interventions and need for steroids). The study contains no data for steroid resistant groups.[25]

Other biologic agents

More than 75 agents are being evaluated in experimental or clinical trials. Each one inhibits a particular inflammatory mediator in the pathophysiologic process of IBD. However, only a few drug trials, except for Infliximab, have reached phase II or III. From the group of anti-TNF factors Certolizumab, a human monoclonal antibody which binds to polyethylene glucol, has shown some promising results, as well as Adalimumab in active refractory CD.[36,37] Adalimumab is being evaluated in trials phase II and III in refractory disease.

Other cytokine inhibitors have been studied for UC (inhibitor of the Receptor Interleukin-2/Dalizumab, Baxilizimab) and CD (inhibitor of Interleukin –12/MRA),

in addition to other anti-inflammatory cytokines (Interleukin 10,11). However, it is very early to draw any safe conclusions.[38,39]

In conclusion, the agents comprising the group of biologic therapies represent the future in the management of IBD, as they seem effective to induce and maintain remission and mucosal healing and might possibly change the natural history of IBD in the long term. Although most of them, except Infliximab, are at an early stage and are still being evaluated, growing evidence exists that we are not far away from the emergence of the best agents of this group.

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