MANAGING ULCERATIVE COLITIS: THE GUIDELINES AND BEYOND

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ABSTRACT

Management guidelines offer clinicians clear, evidence-based and often succinct treatment advice. For ulcerative colitis these guidelines describe the use of 5-ASA, corticosteroids, thiopurines, cyclosporine, and anti-TNFα therapies. However, guidelines do have some drawbacks, mainly a lack of concrete advice concerning patients resistant to these aforementioned therapies. This review gives a short overview of current guidelines and addresses treatment alternatives for conventional therapies.

Keywords: Ulcerative colitis, management, therapy, 5-ASA, corticosteroids, azathioprine, 6-mercaptopurine, 6-thioguanine, cyclosporine, tacrolimus, methotrexate, mycophenolate mofetil, infliximab, adalimumab, golimumab, vedolizumab.

INTRODUCTION

The management of ulcerative colitis (UC) remains challenging to even the most seasoned clinician. This is partly due to the non-elucidated aetiology of the disease. Periodically updated guidelines are valuable instruments that aid clinicians in decision-making. However, the management of UC at an individual level remains challenging due to highly variable disease presentations that are not specifically covered by the guidelines. Decision-making can be difficult for patients intolerant to conventional therapy, or with treatment-resistant disease limited to only the rectum. Also, a patient's preference for certain treatments can result in more complicated decision-making, for example when patients refuse certain drugs or surgery.

In this review we will summarise the latest guidelines on the management of UC. Additionally, treatment options and evidence for patients that have exhausted the therapies suggested by the guidelines will be discussed and a strategy will be proposed for this particular subgroup. Furthermore, the limited evidence of several new biological therapies close to registration and approval will be examined.

THERAPIES FOR ACUTE REMISSION INDUCTION

The choice of therapy depends on disease severity and localisation. To properly describe severity and localisation, several classification systems exist. Most often the Mayo score or the Truelove and Witts' index is used to classify severity, whereas localisation is usually anatomically described as proctitis (rectum only), left-sided (beyond the rectum but distal of the splenic flexure), or extensive (extending beyond splenic flexure). Below, the appropriate conventional treatments are summarised. The 2012 European Crohn's and Colitis Organisation (ECCO) guidelines on UC give more thorough recommendations in different situations.[1]

Proctitis

Topical 5-ASA therapy is the first-line therapy for proctitis. There is evidence for topical treatment only,[2-12] with some evidence showing that topical 5-ASA treatment is superior to oral 5-ASA treatment alone.[13] Topical steroid therapy has been found to be inferior for remission induction[14] and should therefore be used as a second-line therapy in case of 5-ASA intolerance.

Left-Sided Disease

A combination of oral and topical 5-ASA has proven to be more effective than either agent alone in the treatment of left-sided UC.[15-18] If this fails, oral steroids might be added.

Extensive Disease

Combined oral plus topical 5-ASA remains the first-line of treatment. If this therapy fails, oral steroids can be added.[19-23] If steroid dependence occurs, thiopurine treatment is recommended.[24]

Severe Disease

Severe disease is potentially life-threatening and in most cases requires hospital admission and immediate treatment. All guidelines recommend high-dose intravenous glucocorticoids as the first treatment modality, even though only limited evidence exists.[25-27] Early consideration of salvage treatments is of great importance as a precautionary measure as the patient may not respond to steroid treatment.

Intravenous Steroid-Refractory Severe Disease

Intravenous steroid-refractory disease leaves clinicians with limited drug therapies. Salvage therapy should not be initiated simply to delay surgery, as such delays will lead to greater morbidity at surgery.[28] If clinical and biochemical parameters allow an attempt at salvage, the guideline recommends cyclosporine, infliximab or tacrolimus. High quality prospective evidence exists for the use of cyclosporine,[27,29-31] confirmed by several retrospective studies.[32-34] There is also prospective evidence[31,35-37] and some retrospective evidence[34] for infliximab as a rescue therapy. The prospective evidence for tacrolimus is less extensive,[38-40] containing heterogeneous populations and the use of tacrolimus is therefore not as strongly recommended by the guideline.

There is limited evidence for using infliximab as a rescue therapy to cyclosporine, or vice-versa.[41,42] The guideline recommends such a third-line therapy only in select cases treated by a multi-disciplinary team in specialist centres.

TREATMENTS AND ALTERNATIVES FOR STEROID-DEPENDENT DISEASE

Though intravenous steroid-refractory disease represents the most severe cases of UC, this presentation is relatively rare. In contrast, it is more common to see outpatients who reach remission but either fail to taper their steroids or relapse soon after tapering, making them steroid-dependent. In the following paragraph several options for the treatment of steroid-dependent disease and their respective evidence will be discussed.

Thiopurines

A prospective study[43] has shown that azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP) are highly effective in achieving steroid-free remission, with persistent long-term results found in observational studies.[44]

Anti-TNFα

In case of failure or intolerance to thiopurines, anti-TNFα therapy is considered the next step. Several large trials[45] and a Cochrane meta-analysis[46] have conclusively proven the efficacy of infliximab in this setting. Though less extensively studied,[47,48] adalimumab has also shown efficacy in steroid-dependent disease and in patients intolerant to thiopurine treatment.

UNCONVENTIONAL THERAPIES

If conventional therapies fail, colectomy becomes a valid treatment option for patients with UC. Clinical experience shows a profound difference in acceptability of colectomy in hospitalised patients compared with outpatients, though no formal studies have examined this issue. It is not uncommon for outpatients to refuse colectomy, despite being informed of the possible benefits of such intervention. In these situations a clinician may need to resort to either enrollment in clinical trials or initiation of an unconventional therapy in the hope of controlling a patient's symptoms. The provided algorithm (Figure 1) may help clinicians in their decision-making regarding these therapies, which are described in more detail below.

Therapy-Resistant Proctitis

A subset of patients with disease limited to the rectum is surprisingly treatment-resistant to topical 5-ASA and/or topical steroid therapies. This may present clinicians with a treatment dilemma: escalate to systemic therapies, with all associated adverse effects, or accept the limited disease localisation. There is a paucity of prospective controlled trials within this patient subgroup.

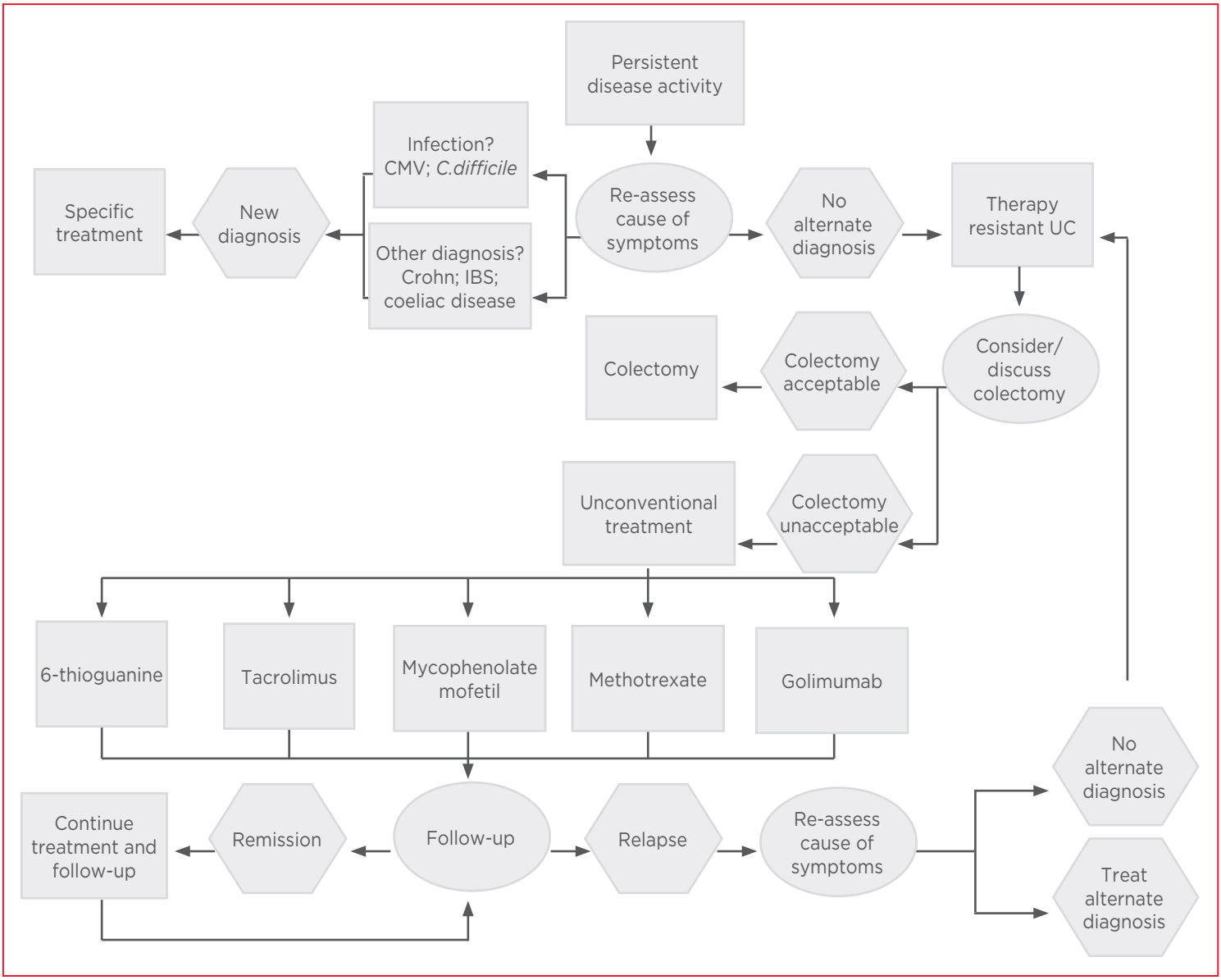

Figure 1. Management algorithm for therapy-resistant ulcerative colitis.
UC: ulcerative colitis; CMV: cytomegalovirus; IBS: irritable bowel syndrome.

There is only one randomised, placebo-controlled trial remotely addressing this issue.[49] This study investigated the efficacy of cyclosporine enemas in left-sided disease (disease extent ranging from 10 to 60 cm ab ani). No significant difference in remission rate between cyclosporine and placebo was found.

Two open-label pilot studies investigated the efficacy of topical tacrolimus for treatment-resistant proctitis. The first,[50] applied tacrolimus ointment in ulcerative proctitis patients who failed previous 5-ASA, steroid, immunosuppressant, and infliximab therapy. 75% (6 out of 8) achieved remission after 8 weeks, with reduction or cessation of steroid usage in five of the responders. The second,[51] treated 12 patients with ulcerative proctitis resistant to topical 5-ASA and/or topical steroid therapy. This study used tacrolimus suppositories and assessed efficacy after 4 weeks of treatment. Clinical remission was achieved in 83% (10 out of 12) with complete endoscopic healing in 33% (4 out of 12). These promising pilots warrant further investigation of topical tacrolimus in treatment-resistant ulcerative proctitis.

Even retrospective data are scarce. One study[52] retrospectively investigated the efficacy of infliximab in patients with proctitis resistant to at least 5-ASA and steroids. Clinical response was seen in 85% (11 out of 13) after infliximab induction therapy. Two patients suffered from adverse events. Other retrospective studies[53-55]

regarding infliximab contain only a few subjects with proctitis, and their response is not individually reported.

Mycophenolate Mofetil

No randomised studies have been performed, but the results of one retrospective and three open-label prospective studies have been published. The first study[56] retrospectively examined the effectiveness of mycophenolate mofetil (MMF) in 70 steroid-dependent inflammatory bowel disease (IBD) patients, of which 19 had UC. After an unclear treatment time (the average treatment time amongst all study subjects was 28 months), 35% (6 out of 17) of UC patients was in steroid-free remission. 65% (11 out of 17) failed to respond to MMF or were intolerant.

The three prospective studies consist of two uncontrolled, open-label studies, and one unblinded pilot study. The first open-label study[57] examined 24 IBD patients, of which 13 had UC with moderate-to-severe steroid-dependent disease. Patients were treated with combined MMF and high-dose steroids with tapering. In the first 3 months, 46% (6 out of 13) of patients achieved remission, but after steroids were tapered, the disease relapsed in all UC patients. The other open-label study[58] treated 14 patients with IBD resistant to conventional therapy. They included five patients with UC (or IBD unclassified), all of which were steroid-dependent and intolerant to thiopurines. One patient suffered from side-effects and ceased MMF treatment; the other four reached remission at 8 weeks and ceased steroid treatment. Follow-up at 12 months showed a maintained remission in 67% of all patients, but the exact data for UC patients at that time point are not reported.

Lastly, in the only controlled study[59] MMF was compared to azathioprine in 24 UC patients. Both groups received steroids in a tapering dose. Notably, this study excluded patients with current steroid usage. After 4 weeks of treatment, 67% (8 out of 12) in the MMF group reached remission and five remained in remission throughout the whole follow-up period of 1 year. However during the entire study, the remission rates were higher in the azathioprine group than in the MMF group, though no significance value is provided by the authors.

Methotrexate

Few prospective studies have been performed on methotrexate (MTX) in UC. One study in 1996[60] examines the effectiveness of MTX versus placebo in steroid-dependent UC. No difference in remission rates was found (47% in the MTX group), which is similar to the results of several case series[61-63] (45-54%). However it has been argued[64-65] that the studied dose of 12.5 mg/week is considerably lower than the 'modern' dose of 20 to 25 mg/week.

Upcoming results of the French METEOR study and the North American MERIT-UC study may shed some light on the use of MTX in UC. Both investigate the effectiveness of MTX 25 mg/week for remission induction in treatment-resistant and/or steroid-dependent UC. It should be noted that whilst according to www.clinicaltrials.gov the MERIT-UC study is currently recruiting, the METEOR study already ended in November 2010, but as of yet no results have been published.

Tacrolimus

Several retrospective studies[66-73] have analysed the effects of tacrolimus on severe, therapy-resistant UC. Outcome parameters, concomitant medication, tacrolimus dosage, and target trough levels varied amongst these studies. However, all studies show a high clinical response rate, varying between 61% and 90%. Reported clinical remission rates vary between 33% and 72%.

The only randomised, controlled trial[38] concerning tacrolimus in UC randomised 62 patients with steroid refractory, moderate-to-severe UC. Changes in the tacrolimus dose were made to achieve a target trough level of 10-15 ng/mL. This study shows a 50% clinical response at 2 weeks, with a clinical remission rate of 9% (3 out of 32), with greater response amongst patients who reached the target trough level. After a 2 week open-label extension period, the clinical remission rate increased to 29% (6 out of 21).

6-Thioguanine

6-Thioguanine (6-TG) is a metabolite of 6-mercaptopurine. Because of polymorphisms in the enzyme thiopurine methyltransferase, the conversion of 6-MP to 6-TG can differ markedly between patients. Directly administering 6-TG should therefore remove dosing issues whilst in theory achieving similar results to AZA and 6-MP treatment.

However there is little published data that study 6-TG treatment directly. Of additional interest is the use of 6-TG in patients with intolerance to AZA or 6-MP. An open-label pilot study was performed in 49 patients with Crohn's disease, of whom 23 patients had pancreatitis after AZA or 6-MP administration.[74] None of these patients had recurrence of their pancreatitis after switching to 6-TG.

A database analysis[75] was performed regarding UC patients receiving 6-TG after becoming intolerant to conventional thiopurine treatment and/or being steroid-dependent. 46 UC patients were examined, of which 83% (37 out of 46) were on steroids when 6-TG therapy was initiated. 80% (37 out of 46) of patients remained in remission after a median follow-up time of 22.4 months, 13% (6 out of 46) were intolerant, and the remaining 7% (3 out of 46) failed therapy and underwent colectomy. The amount of patients in steroid-free remission is not described.

A prospective, open-label study[76] treated 16 UC outpatients who had steroid-dependent or refractory disease. After 3 months, 31% (5 out of 16) had complete response, and 38% (6 out of 16) a partial response.

The measurement of 6-TG levels in the setting of monitoring AZA and 6-MP therapy has been studied extensively and has been found to be useful in meta-analyses.[77] If these results are extrapolated to direct treatment with 6-TG, it is likely that the clinical efficacy of 6-TG is similar to AZA and 6-MP treatment, as long as sufficient serum levels are achieved.

Summary Regarding Disease Resistant to Conventional Therapies

When treating patients with UC resistant to conventional therapies, the first step is to ensure that it is indeed the UC that is causing the symptoms. Critical re-assessment of the patient to rule out any other pathology is highly important. Secondly, good communication is key since the 'rescue' therapies described above have low remission rates and only weak supporting evidence. Patients should be well informed on the potential benefits and risks of these agents. Specifically, patients should be aware that failure of these therapies will increase the likelihood of requiring colectomy.

Figure 1 summarises our recommendations, whilst Table 1 shows recommended dosage, laboratory tests, and contraindications. 6-TG and tacrolimus have the highest reported remission rates; therefore, we would recommend these agents over MMF, MTX or LDN. The other three agents are still useful in specific circumstances, for instance LDN is the most suitable agent for females who wish to become pregnant.

Table 1. Recommended dosage, laboratory tests, and absolute contraindications for 6-thioguanine, tacrolimus, mycophenolate mofetil, and methotrexate.

Agent	Dosage	Contraindications	Laboratory and functional tests		Comments
			Preliminary	Follow-up	
6-thioguanine	OD, oral, 0,3 mg/kg	Liver insufficiency Pregnancy	CBC, LF, RF	CBC, LF	Consider TPMT enzyme activity testing Reduce dose in renal impairment Reduce dose if concomitant allopurinol
Tacrolimus	OD, oral, 0,1 mg/kg	Liver insufficiency	ECG, CBC, LF, RF	CBC, LF, RF, TL	Aim for trough level 4-8 ng/mL
Mycophenolate mofetil	BD, oral, 500-1000mg	Pregnancy	CBC, LF, RF	CBC, LF, RF	Adjust dose based on CBC
Methotrexate	QWK, SC, 25 mg Reduce to QWK 15 mg after 12 weeks	Renal impairment (GFR <20 mL/min) Pregnancy	CBC, LF, RF	CBC, LF, RF	Also prescribe QWK 5 mg folic acid Adjust dose based on CBC

OD: once daily; BD: twice daily; QWK: once weekly; SC: subcutaneous; GFR: glomeruler filtration rate; CBC: complete blood count; LF: liver function; RF: renal function; TL: trough level; TPMT: thiopurine methyltransferase.

We strongly recommend that all the above drug treatments should be accompanied by close follow-up in order to detect treatment failure in a timely fashion. Laboratory markers such as faecal calprotectin, reflecting intestinal inflammation,[78,79] may aid in the follow-up process. In case of treatment failure or clinical deterioration, re-assessment should ensue, after which optimising therapy, switching therapy or, if necessary, colectomy should follow.

FUTURE THERAPIES

A search in the U.S. National Institutes of Health clinical trial database (http://clinicaltrials.gov) using the term 'ulcerative colitis' yields 169 planned or active studies. 29 of these studies involve new compounds, which reflect the continuing interest of many pharmaceutical companies regarding treatment for UC. These compounds are still only known by their study names and mostly involve Phase I and Phase II studies, with no results currently available on the website. Amongst these drug candidates are OKT-3 (an oral anti CD-3 agent), ASP3291 (a melanocortin receptor agonist), KRP203 (a sphingosine-1-phospate receptor modulator), GWP42003 (a cannabinoid), AMG181 (an α4β7 integrin antibody), HE3286 (a synthetic steroid derivative), GL1001 (an ACE-2 inhibitor), and MDX1100 (an CLCL10 antibody). It is anticipated that their role in UC will become clear in the near future.

Not all new and promising therapies live up to our expectations. For instance, basiliximab, daclizumab and visilizumab were promising in uncontrolled pilot studies,[80-84] but eventually showed identical remission rates to placebo in randomised controlled trials.[85-87]

Golimumab

Golimumab is a fully human antibody against TNFα. At the Digestive Disease Week, 2012 (DDW 2012), the initial results of the PURSUIT-SC trial regarding golimumab in UC were presented. Recently the complete article on this two-part, randomised, double-blind, placebo controlled Phase II-III study has been published.[88] A total of 1,064 patients were included, 291 in the Phase II dose-ranging study, 774 in the Phase III, efficacy study. All patients had moderate-to-severe UC and an inadequate or failed response to at least one conventional therapy. The efficacy study evaluated clinical response after 6 weeks of treatment which was achieved in 53% (275 out of 515) of the golimumab groups versus 30% (76 out of 256) of the placebo group. Clinical remission at 6 weeks was 18% (94 out of 515) for the golimumab groups versus 6% (16 out of 256) for the placebo group.

At least one study is planned to examine the efficacy in paediatric patients, whilst another study in Japan is recruiting patients. These studies will address the reproducibility of the results found in the PURSUIT-SC study, though its results have already led to FDA approval for golimumab in moderate-to-severe UC in May 2013.

Vedolizumab

Vedolizumab is an antibody to the α4β7 integrin heterodimer complex. Three studies have been published on its efficacy in UC. The first study[89] reported results of a randomised controlled trial performed in 181 patients. Patients were either untreated or had only received 5-ASA therapy. Vedolizumab or placebo was administered on day 1 and day 29. Clinical response rates were 66% and clinical remission was achieved in 33% at 6 weeks of follow-up.

Two other studies[90,91] on vedolizumab were a randomised, controlled dose-ranging study, and an open-label extension of the first, with additional enrollment of treatment-naïve patients. In the controlled trial 47 patients with moderate, but not steroid-resistant, UC participated and medication or placebo was administered on day 1, 15, 29, and 85. Clinical response at 16 weeks was 60% to 80% (depending on dose). Clinical remission is reported as varying from 53% to 79% between day 29 and 253, compared with 25% to 50% in the placebo group. The study was underpowered for assessment of clinical outcome. The open-label extension study involved 72 patients with UC who were administered vedolizumab on day 1, 15, 43, followed by maintenance dose every 8 weeks. After 70 weeks of follow-up, clinical response was achieved in 92% and remission in 77% of patients with moderate-to-severe UC.

Recently the results of the GEMINI study, a multi-centre, randomised, double-blind, placebo-controlled trial were published.[92] This study involved two phases, with 895 patients in the induction and maintenance phase combined. Notably, patients had active disease and had

failed previous glucocorticoid, immunosuppressive or anti-TNFα therapy, though disease limited to the rectum was an exclusion criterion. After 6 weeks, coinciding with the end of the induction phase, vedolizumab showed a statistically significant 47% clinical response rate compared with 26% for placebo. The maintenance phase ended after 52 weeks, again showing a significant difference in clinical remission rates with 42% and 45% for vedolizumab in different doses, compared with 16% for placebo.

No current trials on vedolizumab were identified, but a request for FDA approval was filed in June 2013, most likely based on the results of the abovementioned studies.

Tofacitinib

Tofacitinib is an oral inhibitor of Janus kinase (JAK) 1, 2 and 3, and its effect should result in reduction of interleukin 2, 4, 7, 9, 15, and 21. The results of a large, multicentre, randomised, double-blind, placebo-controlled trial were published in 2012,[93] examining the efficacy of tofacitinib in patients with active UC. A total of 194 patients were randomised between five groups, one placebo group and four groups with different tofacitinib dosage (0.5 mg, 3 mg, 10 mg, and 15 mg twice daily). 34% of patients were using concomitant steroids, whilst 27% were steroid-resistant and 19% had failed anti-TNF therapy.

Significant difference in clinical remission was seen in the 3 mg, 10 mg, and 15 mg groups compared with placebo, with remission rates of 33%, 48%, 41% compared with 10%, respectively. Endoscopic remission showed similar significant differences, with 18%, 30%, 27% compared with 2% in the placebo group.

Regarding clinical and endoscopic response, only the highest tofacitinib dose showed a significant difference compared with placebo. Clinical response was 78% compared with 42%, whilst endoscopic response was 78% versus 46%.

Currently, the OCTAVE study is recruiting UC patients to analyse the efficacy in moderate-to-severely acute UC, resistant to at least corticosteroids, azathioprine or anti-TNF therapy. It consists of a remission induction phase, examining efficacy at 8 weeks, and is followed by a long-term follow-up study of 52 weeks.

CONCLUSION

In this paper we have reviewed the most recent guidelines by the ECCO on the treatment of UC. The proper evidence-based approach is described extensively in the guidelines, and we underscore its usefulness in clinical practice. Nevertheless, it remains challenging for clinicians to extrapolate the results obtained in clinical trials to individual patients.

When patients become resistant to conventional therapies, the situation moves beyond the guidelines, and it is for these situations that we offer the treatment algorithm described above. Of utmost importance remains the individualised and tailored approach, based on the patient's preference, the clinician's preference, and the availability of therapies. The choice of these unconventional therapies should be made in conjunction with the patient, underscoring the need for clear communication between clinician and patient, regarding the pros and cons of each treatment modality.

Finally, though the primary aim of these therapies is the induction and maintenance of remission, and subsequently the avoidance of surgery, one could also consider these agents as a bridge to novel treatments, either those substances currently awaiting regulatory approval or those in the last stage of their development.

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