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Optimization of the treatment with immunosuppressants and biologics in inflammatory bowel disease

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Abstract

Many placebo controlled trials and meta-analyses evaluated the efficacy of different drugs for the treatment of inflammatory bowel disease (IBD), including immunosuppressants and biologics. Their use is indicated in moderate to severe disease in non responders to corticosteroids and in steroid-dependent patients, as induction and maintenance treatment. Infliximab, as well as cyclosporine, is considered a second line therapy in the case of severe ulcerative colitis, or non-responders to intravenous corticosteroids. An adequate dosage and duration of therapy with thiopurines should be reached before evaluating their efficacy. Methotrexate is a valid option in patients with Crohn's disease but its use is confined to patients who are intolerant or non-responders to thiopurines. Evidence for the use of methotrexate in ulcerative colitis is insufficient. The use of thalidomide and mycophenolate mofetil is not recommended in patients with inflammatory bowel disease, these treatments could be considered in case of failure of all other therapeutic options. In patients with moderately active ulcerative colitis, refractory to thiopurines, the use of tacrolimus is considered an alternative to biologics. An increase of the dose or a decrease in the interval of administration of biological treatment could be useful in the presence of an incomplete clinical response. In the case of primary failure

of an anti-tumor necrosis factor alpha a switch to another one should be considered. Data on the efficacy of combination therapy are up to now insufficient to consider this strategy in all IBD patients. The final outcome of the treatment should be considered the clinical remission, with mucosa healing, and not the clinical response. The evaluation of serum concentration of thiopurine methyl transferase activity, thiopurine metabolites, biologic serum levels and antibiologic antibodies could be useful for the management of the treatment but it has not been routinely applied in clinical practice. The evidence of high risk development of lymphoma and cutaneous malignancies should be considered in patients treated with immunosuppressants and biologics for a long period.

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Key words: Inflammatory bowel disease; Optimization; Immunosuppressants; Biologics; Crohn's disease; Ulcerative colitis

Core tip: The clinical expression of inflammatory bowel disease (IBD) is heterogeneous with different clinical courses, so it is not easy to find the best therapy for all patients. In recent years the goals of the therapy for IBD patients have evolved from symptomatic control to altering the course of disease by achieving a "deep remission". Many trials have evaluated the efficacy of immunosuppressants and biologics in achieving clinical and endoscopic remission but the optimization of these treatments is still a debated point. We propose some recommendations about the correct use of immunosuppressants and biologics for the treatment of IBD, based on the current evidence.

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INTRODUCTION

Inflammatory bowel disease (IBD) refers to 2 chronic inflammatory disorders of the gastrointestinal tract: Crohn's disease (CD) and ulcerative colitis (UC). The clinical expression of IBD is heterogeneous, especially in CD, with a wide spectrum of patterns and different clinical courses, so it is not easy to find the best therapy for all patients. The course of IBD is characterized by phases of relapse and remission and the main goal of the therapy is to achieve and maintain disease remission. In recent years the goals of therapy for IBD patients have evolved from symptomatic control to altering the course of disease by achieving a "deep remission". This is defined as the contemporary presence of sustained clinical remission, complete mucosal healing and normalization of serological activity indexes (C-reactive protein and erythrocyte sedimentation rate). Many trials have evaluated the efficacy of different drugs for the treatment of CD and UC, including immunosuppressants and biologics. Although recent guidelines have been published to direct the clinicians on the correct management of IBD^[1-3], up to now the optimization of treatment with immunosuppressants and biologics is a debated point. However, nearly half of the IBD guideline recommendations are based on expert opinion and the guidelines are not frequently updated^[4]. We propose some recommendations about the correct use of immunosuppressants and biologics for the treatment of CD and UC, based on the current evidence.

CROHN'S DISEASE

Immunosuppressant therapies

Although the efficacy of corticosteroids in active CD is clear, their use is not indicated in maintaining treatment and the long-term therapy is associated with serious adverse consequences^[5]. To avoid the long term use of corticosteroids many studies have investigated the efficacy of immunosuppressants, including thiopurines, methotrexate (MTX), tacrolimus, thalidomide and mycophenolate mofetil (MMF) for the treatment of active and quiescent CD.

Thiopurines

6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA) are purine analogues able to reduce cell proliferation and with immune modifier properties. The efficacy of thiopurines for the treatment of active CD is controversial. In a meta-analysis^[6] evaluating 8 trials on AZA and 6-MP therapy in patients with active CD, a higher response rate was observed in patients treated with thiopurines compared with patients treated with placebo. The time of peak response in the included trials ranged from 9 wk to more than 26 wk; the minimum period for an adequate response was found to be more than 17 wk. A more recent meta-analysis^[7], including 5 trials, showed no significant efficacy of thiopurines in active CD. The discrepancy between the results of the two meta-analyses is probably due to the exclusion, in

the second one, of trials evaluating the outcome after 17 wk of follow up. This discrepancy confirms that a longer time of treatment gives a greater chance of obtaining a positive result. Based on these data the use of thiopurines as a single therapy is not recommended in active CD but a combination with corticosteroids could be useful while waiting for the slow time of action of thiopurines. Unfortunately treatment with thiopurines is sometimes associated with the occurrence of side effects that preclude their use. In these cases the discontinuation of treatment causes a complete resolution of the symptoms. Some of these side effects are severe, including suppression of white blood cells, pancreatitis and hepatitis, but other side effects could be mild, such as nausea, abdominal pain and fever. In the presence of a mild side effect during AZA use a trial of 6-MP is recommended because half of the intolerant patients tolerate a switch to 6-MP. A study was conducted to assess the long term outcomes of 6-MP treatment in patients with AZA intolerance. Fifty-two per cent of included patients tolerated 6-MP. In particular 6-MP was more tolerated in patients with hepatotoxicity and arthralgia/myalgia during AZA treatment. Less evident was the switching advantage in patients with hematologic and pancreatic toxicity^[8]. The role of thiopurines in CD is more important in the maintenance period, particularly in steroid-dependent CD, to induce early steroid sparing. A meta-analysis, including 7 placebo controlled trials, evaluated the efficacy of thiopurines in quiescent CD. AZA and 6-MP were effective in maintaining remission and inducing steroid sparing but higher doses of AZA (2.5 mg/kg daily) were more effective than lower doses^[7,9]. According to these data the dosage of 2.5 mg/kg daily is suggested to optimize the treatment with thiopurines.

The efficacy of immunosuppressants was also evaluated in fistulizing CD. Eleven placebo controlled trials on the efficacy of immunosuppressants and antibiotics in fistulizing CD have been included in a meta-analysis. The analysis showed that both immunosuppressants and antibiotics were able to significantly reduce the number of open actively draining fistulas by at least 50% from the baseline. The incidence of severe adverse events was higher in patients treated with immunosuppressants than in patients treated with placebo ($P = 0.037$)^[10]. Regarding the maintenance treatment a questionable point is how long treatment with thiopurines should be continued. A meta-analysis showed that stopping thiopurine treatment increases the risk of relapse at 6, 12 and 18 mo. A clear benefit of continuing thiopurines for at least 18 mo was observed^[11]. In a trial of Lémann *et al.*^[12] patients who discontinued AZA after more than 3 years of efficacious treatment had a higher probability of relapse compared with those who continued it. According to the ECCO guidelines^[1] in patients treated with thiopurines as maintenance treatment, discontinuation may be considered after 4 years of remission. Benefit and risks of continuing them should be considered case by case.

A question related to the long term treatment with immunosuppressants is the reported high risk of lymphoma

and cutaneous malignancies. Patients with IBD treated with thiopurines alone or in combination with anti-TNF α had an increased risk of developing lymphoproliferative disorders^[13-15]. Many lymphomas associated to immunosuppressive therapy in IBD patients seem to be related to a loss of control of Epstein-Barr virus (EBV) infection. Young males seronegative for EBV are at risk for fatal forms of primary EBV infection, with lymphoproliferation. This incidence could be limited avoiding the treatment with thiopurines in this subgroup of patients^[16,17].

Hepatosplenic T cell lymphoma (HSTCL) is another rare, lethal form of lymphoma^[15]. Patients at risk are typically young men, treated for prolonged periods with thiopurines in combination with anti-TNF- α . The risk of HSTCL can be limited by avoiding prolonged combination therapy in young males. Concerning the risk of cutaneous malignancies, an increased risk of non-melanoma skin cancers (NMSC) has been reported in patients treated with thiopurines. This risk persists in patients previously exposed to thiopurines, suggesting a definite impact on carcinogenic events^[18,20]. In a retrospective study, 26403 patients with CD and 26974 patients with UC were matched with non-IBD controls. The incidence of NMSC was higher among patients with IBD compared with controls and thiopurine use was associated with NMSC, as was biologic use among patients with CD^[18]. Another prospective cohort study evaluated the incidence of NMSC among 19486 patients with IBD. The authors showed that ongoing thiopurine treatment and past thiopurine exposure were risk factors for NMSC. These patients should be protected against UV radiation and receive lifelong dermatologic screening^[19]. In a third study^[20], 9618 IBD patients were followed up and matched with 91378 controls. At the end of the study a diagnosis of basal cell skin cancer was made in 1696 individuals and a diagnosis of squamous cell skin cancer in 341 patients. IBD patients had an increased risk for basal cell skin cancer, compared with controls. Among patients with IBD, the use of thiopurines increased the risk of squamous cell skin cancer compared with controls. In order to explain the interindividual variability in efficacy and toxicity, the importance of measuring serum concentrations of thiopurine metabolites, 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP), has been recently proposed. Furthermore thiopurine methyltransferase (TPMT), that is one of the enzymes involved in the thiopurine metabolism, has been measured to predict the tolerability of thiopurines. A decreased TPMT activity has been related with myelotoxicity, whereas a high activity of TPMT has been related with thiopurine ineffectiveness. Low TPMT activity and high 6-TGN concentrations have been related to therapeutic success.

A prospective study was conducted to compare the 6-TGN levels in active IBD patients with those in patients in clinical remission. One hundred patients were included (41 with an exacerbation, 59 in remission). Twenty-six of the 41 patients (63%) with active disease and 24 of the 59 patients (41%) in clinical remission had

a 6-TGN level below the therapeutic cut-off level of 235 pmol/ 8×10^8 erythrocytes ($P = 0.04$)^[21]. Recent studies suggest that too low 6-TGN and too high 6-MMP nucleotide concentrations can be reversed by a combination therapy of allopurinol and thiopurines. In a study a dose-escalation of allopurinol was performed in 11 IBD patients with low 6-TGN and/or elevated 6-MMP concentrations, treated with AZA. Adequate 6-TGN concentrations were achieved with a combination of 25 mg allopurinol and 50 mg AZA in one patient and with 50 mg allopurinol and 50 mg AZA in nine patients. The 6-MMP concentrations were normalized immediately in all patients. The authors concluded that combination therapy with 50 mg allopurinol and 50 mg AZA daily is efficacious in IBD patients with inadequate thiopurine metabolite concentrations to optimize AZA therapy^[22].

The results of a recent prospective study do not support the capability of TPMT activity or 6-TGN to predict treatment outcome and no serum threshold value was identified to adjust the thiopurine dose. A total of 113 IBD patients treated with thiopurines were included. The TPMT activity was determined at inclusion (> 5 U/mL required) and thiopurine metabolites were periodically monitored. At the end of the study no cut-off point with worthwhile sensitivity/specificity was found. Eight patients showed thiopurine-related toxicity that could not be linked to TPMT activity or 6-TGN levels^[23].

Up to now the use of thiopurine metabolites has not been applied in clinical practice. A survey performed to evaluate the extent to which IBD gastroenterologists are utilizing thiopurine metabolism in practice showed that TPMT evaluation was performed by only 30% of gastroenterologists before AZA initiation. In patients on thiopurine therapy, 6-TGN and 6-MMP levels were determined by 54% and 44% of gastroenterologists respectively and 81% did not recheck metabolite levels after dose escalation or reduction^[24].

Methotrexate

Despite the wide use of thiopurines in the management of both CD and UC, approximately 20% of patients are intolerant and 30% are refractory to AZA/6-MP. An alternative immunosuppressant in these cases is MTX, an inhibitor of dihydrofolate reductase. Based on the results of 3 small studies^[25-27], where the efficacy of oral MTX was compared with placebo or 6-MP, MTX was considered ineffective in the treatment of active CD. A placebo-controlled trial^[28] compared the efficacy of intramuscular MTX (25 mg once weekly) with placebo. After 16 wk of therapy, 39% of patients were in clinical remission in the MTX group compared with 19% of patients in the placebo group. The authors supported the efficacy of intramuscular MTX in active CD, although a higher rate of adverse events was reported with respect to placebo, including dyspepsia, alopecia, myelosuppression, increase in transaminase levels, abdominal pain, headache and arthralgia. To avoid some of these adverse events folic acid given routinely the day after MTX injection is recom-

mended. Furthermore, the teratogenic effect of this drug must be considered when it is started.

The efficacy of MTX in quiescent CD was observed in a trial^[23] in which MTX (15 mg weekly) intramuscularly was compared with placebo. After 40 wk of treatment, relapse occurred in 35% of patients treated with MTX and in 61% of patients treated with placebo. However in another two studies^[25,26] the superiority of MTX with respect to placebo, 5-ASA or 6-MP was not confirmed. Up to now the use of MTX in CD is confined to patients who are intolerant or non-responders to thiopurines.

Tacrolimus

Several studies, but not randomized controlled trials, evaluated the efficacy of oral or intravenous tacrolimus in the treatment of active luminal CD. Six of these studies, including a total of 70 patients, have been systematically reviewed^[30]. The duration of treatment varied from weeks to years. A total of 31 treated patients (44.3%) achieved a complete remission at the end of the studies. Eight studies evaluated the efficacy of tacrolimus in patients with perianal CD^[31-38]. Data were available for 49 patients with perianal disease who were treated with oral or intravenous tacrolimus and for 8 patients treated with topical tacrolimus. Among the patients treated with oral or intravenous tacrolimus 14 patients (28.6%) achieved remission and 19 patients (38.8%) achieved a partial response. Regarding the topical treatment, in a placebo controlled trial 8 patients with perianal CD were stratified according to ulcerating or fistulizing disease. A benefit in the ulcerating group was observed. No benefit was reported in the fistulizing group^[36].

Thalidomide

Thalidomide, originally used to treat morning sickness, had been withdrawn from the market because of its teratogenic effect. Subsequently immunomodulatory properties of thalidomide have been discovered as inhibitors of TNF- α synthesis. Thus in recent years its use was proposed for a few diseases including CD. No published randomized controlled trials on thalidomide efficacy in adult CD patients are available. In one trial^[39] the efficacy of its analogue lenalidomide was evaluated. In this study, 89 patients were included and randomized to receive 25 mg of lenalidomide daily, 5 mg of lenalidomide daily or placebo. At the end of the study the rate of clinical remission in both treatment groups was not significantly different from the placebo group. Other data come from uncontrolled studies. In a study^[40] 25 patients with luminal and fistulizing CD were treated with thalidomide. At the end of the study 6 out of 8 patients treated for luminal disease and 9 out of 11 patients treated for fistulizing disease achieved clinical response after a median follow-up of 12 mo. The 4 patients treated for both luminal and fistulizing disease had a fistula response and 3 of them had also a luminal response. The authors concluded that thalidomide was an effective treatment in patients with refractory luminal and fistulizing CD. Other encouraging

results come from the pediatric population. In a study^[41] 28 patients (young adults and children) with refractory moderate to severe IBD (19 CD, 9 UC) received thalidomide (1.5-2.5 mg/kg daily). Remission was achieved in 21 out of 28 (75%) patients (17 with CD, 4 with UC). In a recent small study^[42] 12 children, non-responders to previous drugs including AZA/6-MP, MTX and biologics, received thalidomide as rescue therapy. After 6 mo a significant improvement was observed in terms of symptoms, corticosteroid use, hospitalizations, laboratory values, fistula closure and surgery. Unfortunately a high rate of adverse reactions was reported during treatment with thalidomide, including peripheral neuropathy, dizziness and allergic reaction.

Based on these data the use of thalidomide can be proposed only in patients with active CD, refractory to conventional immunosuppressants and biologics, as rescue therapy. However given its teratogenic nature and the high probability of side effects, its use for maintenance therapy is difficult to justify. However contraception should be recommended in woman with CD during thalidomide treatment. Up to now there are no recommendations for the use of thalidomide in CD. However it could have a role in the treatment of children with active CD despite immunosuppressive treatment.

Mycophenolate mofetil

MMF is an immunosuppressant largely used for the prevention of solid organ transplantation rejection. It is an antimetabolite similar to AZA and its use has been proposed in the management of autoimmune diseases, including psoriasis^[43], rheumatoid arthritis^[44] and IBD^[45,46].

A retrospective study^[47] assessed the efficacy and tolerance of MMF in 20 patients with CD who were intolerant or non-responders to AZA and/or MTX. The authors reported only 20% success with MMF and 25% intolerance. A study^[48] compared the efficacy of MMF with AZA in 45 patients with active CD, 15 treated with MMF and 30 with AZA over a period of 1 year. All patients who completed the 12 mo of treatment (77% AZA, 60% MMF) achieved remission but MMF patients had almost twice as many flare-ups (80% vs 47%) with respect to AZA patients. The authors concluded that both drugs were effective in inducing remission, AZA was more effective in maintaining remission but the onset of therapeutic effect was delayed less under MMF than under AZA. A randomized trial^[49] compared the efficacy of AZA plus corticosteroids with MMF plus corticosteroids in 70 patients with active CD. The authors observed a significant reduction in clinical activity with MMF plus corticosteroids compared to AZA plus corticosteroids. In patients with more severe CD, MMF plus corticosteroids caused a significant suppression of clinical activity earlier than AZA plus corticosteroids with few adverse effects.

Based on these data, although AZA is still the immunosuppressant of choice in the treatment of IBD, MMF may have a role for steroid-dependent patients refractory to other immunosuppressive therapies. Up to now there

are no recommendations for the use of MMF in CD.

biological therapies

In recent years the use of biologics has changed the management of IBD. The efficacy of anti-TNF α molecules (infliximab, adalimumab and certolizumab pegol) has been largely investigated in the treatment of active and quiescent CD, with good results^[50,51]. Up to now infliximab and adalimumab have been approved for the use in CD in many countries. These two anti-TNF α are both equal options in patients with moderate to severe steroid-refractory or steroid-dependent disease and in patients who are non responders or intolerant to immunosuppressants. Their use is also indicated in the case of complex perianal disease, in combination with surgical therapy. Furthermore, in presence of axial arthropathy (sacroileitis and ankylosing spondylitis) the efficacy of anti-TNF α treatment has been well established, as well as in the case of peripheral arthritis non-responder to sulfasalazine^[1,2]. Certolizumab pegol is not approved in the European Union but in the United States and Switzerland it has the same indications as infliximab and adalimumab.

Two meta-analyses^[50,51] confirmed the efficacy of anti-TNF α antibodies in inducing and maintaining remission of luminal CD. Some studies evaluated the efficacy of these drugs in a subgroup of patients with steroid-dependent CD. Regarding infliximab, the study by Lémann *et al.*^[52] was planned to treat patients with steroid-dependent CD. These patients received infliximab 5 mg/kg or placebo at weeks 0, 2, and 6. All patients were treated also with AZA/6-MP for 52 wk. Among the 113 enrolled patients, the steroid-free remission rate was higher in the infliximab group than in the placebo group (75% *vs* 38%, $P < 0.001$ at week 12 and 40% *vs* 22%, $P = 0.04$ at week 52). Regarding adalimumab, data on steroid-dependent patients could be taken from a subgroup analysis of the CHARM study^[53]. At week 26, 19% of patients treated with adalimumab (40 mg every other week) achieved a sustained corticosteroid-free remission compared with 3% of patients treated with placebo ($P = 0.006$). At week 56, 29% of patients treated with adalimumab achieved a sustained corticosteroid-free remission compared with 5% of patients treated with placebo ($P = 0.001$). Recently the long term efficacy of adalimumab in steroid-dependent CD patients has been evaluated in a long-term open label extension of the CHARM study. After 4 years of follow up 16% of patients taking corticosteroids at baseline were in corticosteroid-free remission^[54]. A prospective observational study including 110 steroid-dependent CD patients reported clinical data on the efficacy and prognostic factors of response to adalimumab in corticosteroid-dependent CD patients. At week 6, 100 patients had a clinical benefit (91%), 50 of these (45.5%) were in steroid-free clinical remission, the other 50 (45.5%) achieved a clinical response. Nine patients (8.1%) did not achieve a clinical benefit and only one patient discontinued adalimumab due to intolerance. At the end of the follow-up (mean 14.6 \pm 10 mo, range

2-47 mo) 89 patients (80.9%) had a clinical benefit, 18 of these achieved a clinical response (16.4%), 71 were in complete remission (64.5%) and 11 discontinued adalimumab (10%) due to lack of efficacy or severe side effects. At multivariable analysis only a higher induction regimen was related to remission at week 6. At the end of the follow-up, none of the variables were associated with remission^[55]. All the 110 patients treated in this study have been followed up for a further 24 mo. At the end of the follow up (mean 38.6 \pm 8.6 mo) 54 patients (49%) were still on maintenance treatment with adalimumab with significant clinical benefit; 56 patients stopped treatment because of ineffectiveness (35), side effects (15) or mucosal healing (6). Mucosal healing was reported in 15 out of 60 patients who underwent colonoscopy (25%). At univariable analysis a lower induction regimen (80/40 mg) was associated with a best response to infliximab ($P < 0.001$, OR = 6, 95%CI: 1.01-35.91) while 160/80 mg induction regimen was associated with a lower risk of surgery with respect to 80/40 mg ($P = 0.04$, OR = 0.311, 95%CI: 0.069-0.998)^[56].

The advantage of biologics with respect to thiopurines is the more rapid effect. After 4 wk of treatment most of the treated patients show a clinical benefit^[57,58]. However from 17% to 21% of patients treated with infliximab develop antibodies directed against the murine sequences of infliximab molecule during the treatment, with immediate-type hypersensitivity reactions. Intravenous hydrocortisone premedication reduces antibodies to infliximab but some patients discontinue the treatment because of side effects, despite premedication and schedule treatment. Adalimumab, that is a recombinant human monoclonal antibody containing only human peptide sequences, has been proposed as an effective option in patients who had showed a previous allergic reaction to infliximab^[59]. Furthermore some patients treated with infliximab experience a loss of efficacy over time. In the Gain study^[60] 22% of CD patients with loss of response or previous intolerance to infliximab achieved remission with adalimumab. Based on these data, in the case of primary failures, loss of response or intolerance to infliximab, adalimumab can be used as a second line treatment. On the other hand the effectiveness of infliximab as a second line therapy after adalimumab failure has also been evaluated in CD patients. In a recent study 15 patients who discontinued adalimumab for loss of response (5), adverse events (3) or partial response (7), were treated with infliximab. After infliximab therapy all the patients who had discontinued adalimumab due to loss of efficacy or adverse events obtained a clinical response, but 2 of them developed adverse events. None of the patients who discontinued adalimumab due to partial response reached remission with infliximab^[61]. Up to now no trial has compared the efficacy and safety of infliximab and adalimumab in CD patients, thus the only factor that can guide the choice of one of the two biologics as first line therapy is the route of administration (subcutaneous for adalimumab and intravenous for infliximab). This should

be discussed with the patient and the choice of treatment should be made case by case. In the case of patients with primary failure to one anti-TNF α , a switch to the other one should be considered. However, in the case of failure of one anti-TNF- α , before switching to the other one, an increase in dose or a decrease in the interval between infusions has been proposed. In a study, 54 out of 108 CD patients treated with infliximab received a dose intensification, defined as an increase in infliximab dose, a decrease in interval, or both, at 30 mo from initial infusion. At 30 mo 69.1% of patients were event-free from an interval decrease, 48.5% from a dose increase, and 45.7% from any dose intensification. Of the 54 patients who received a dose intensification, 75.9% were able to obtain and maintain a clinical response^[62]. In another prospective study 14 CD patients, initially responders to adalimumab, experienced a relapse. All patients were then treated with adalimumab 40 mg weekly for 12 wk before returning to adalimumab 40 mg every other week. Nine out of the 14 CD patients achieved a clinical response (1) or remission (8) 3 mo after reinstating the standard dosage^[63]. Also, in the CHARM study^[53] the dosage of adalimumab could be escalated to open-label treatment with 40 mg weekly in patients with continued non response or recurrent flare. A total of 140 out of 854 enrolled patients completed the study on open-label adalimumab 40 mg weekly.

Two questionable points regarding biological therapy are: when to start and when to stop the treatment?

Some studies supported an early use of biologics in CD. In a randomized, controlled trial^[64] early combined infliximab and thiopurines treatment was more effective than a conventional step-up approach at 6 and 12 mo. Furthermore a subgroup analysis of the CHARM study^[53] showed a higher remission rate at 26 and 56 wk in patients with disease duration < 2 years with respect to patients with disease duration > 5 years. These data are not enough to confirm that an early treatment with biologics can improve patient outcomes. Therefore, a widespread early use of biologics in all CD patients cannot be recommended^[1,2] but in patient subgroups with a predicted disabling course^[66] (extensive disease, severe rectal disease, young age, severe perianal disease, steroid need at diagnosis) early introduction of biologics can be considered.

Regarding long term treatment, adalimumab was able to maintain remission for up to 4 years in patients who responded to induction therapy^[54] and long-term treatment with infliximab seems to have a safe maintenance efficacy^[67]. Despite these promising results the duration of biological therapy over 1 year is recommended only after a careful evaluation on a case-by-case basis and should be discussed with each patient^[1,2]. Some prospective studies^[68,69] showed that mucosal healing after biological therapy predicts a prolonged remission. Based on this observation a colonoscopy evaluation in patients receiving long-term anti-TNF- α therapy could guide the choice of treatment duration.

Recently pharmacokinetics and inter-individual variability of clearance and immunogenicity of biologics have

been evaluated to explain their efficacy and tolerability. Antidrug antibodies (ADA) impacted the clearance of infliximab and trough levels have been shown to correlate with clinical remission. In CD patients high trough levels of infliximab were associated positively with sustained clinical response, low C-reactive protein (CRP) levels and endoscopic improvement^[70]. In the SONIC trial, steroid-free remission at weeks 30 and 46 was more frequent in patients with high infliximab trough levels. Furthermore concomitant immunosuppressive therapy was shown to increase the trough levels of infliximab^[71]. In the AC-CENT trial a complete fistula healing was achieved in 64% of CD patients with high infliximab trough levels and in 25% of patients without detectable trough levels^[72]. In another study, in patients with infliximab levels below 12 mg/mL at mid infusion, a dose increase produced a response in 25 out of 29 patients and was more effective than changing to another anti-TNF- α agent^[73]. However the definition of therapeutic thresholds is still unclear. In a large series of 532 CD patients treated with infliximab from various trials a trough level of 3 mg/mL discriminated inflammatory activity^[74]. A cut-off of 3 mg/mL was associated with steroid-free remission in the SONIC trial^[71].

For adalimumab, pharmacokinetic-efficacy relations are less clear. In the CLASSIC trials correlations between adalimumab serum levels and remission rates were weak during induction and absent during maintenance therapy^[75]. In an observational cohort study^[76] a relationship between adalimumab serum trough levels and remission or response rates was not demonstrated.

Regarding the ADA evaluation, it seems to be the most important variable associated with low infliximab trough levels and low efficacy. The appearance of antibodies to infliximab (ATI) has been associated with loss of response and infusion reactions. In a study^[77], 73% of patients with loss of response to infliximab and all patients who developed infusion reactions showed ATI positive.

The occurrence of human antichimeric antibodies (HACA) was also inversely correlated with clinical response and positively correlated with infusion reactions^[78,79]. Premedication with glucocorticoids seems to reduce significantly the HACA levels^[77]. In a study it was observed that in 65% (11 out of 17) of patients initially positive for HACA, antibodies disappeared during maintenance treatment with infliximab but only in those with a clinical response^[80]. Furthermore the addition of immunosuppressants to infliximab therapy seems to restore the efficacy in patients positive for HACA^[81]. As for thiopurine metabolites up to now the utilization of biologic serum levels or ADA have not been routinely applied in clinical practice.

ULCERATIVE COLITIS

Immunosuppressant therapies

According to the ECCO guidelines^[3] patients with steroid-dependent UC should be treated with thiopurines

The evidence to support the use of MTX in UC is insufficient. In patients with severely active UC, non-responder to intravenous steroids, the use of cyclosporine or infliximab is recommended.

Thiopurines

The efficacy of AZA in active UC was evaluated in two controlled trials at the dosage of 2-2.5 mg/kg daily^[82,83]. A meta-analysis^[7] of these trials was conducted and a trend towards the benefit of AZA compared with placebo was observed but this did not achieve any statistical significance (RR = 0.85, 95%CI: 0.71-1.01, $P = 0.07$). In these two trials the efficacy of AZA was also investigated in quiescent UC. The meta-analysis of these trials showed a statistically significant benefit of AZA compared with placebo in preventing relapse (RR = 0.60, 95%CI: 0.37-0.95, $P = 0.03$)^[7]. In a study^[84] the efficacy of AZA was investigated in a subgroup of patients with steroid-dependent UC, comparing it to mesalamine. Seventy-two patients were randomised to receive AZA (2 mg/kg daily) or mesalamine (3.2 g daily), in addition to prednisolone (40 mg daily) for 6 mo. At the end of the follow up AZA was significantly more effective than mesalamine at achieving clinical and endoscopic remission with steroid sparing. More recently an observational cohort study was conducted in 42 patients with steroid-dependent UC treated with AZA (2-3 mg/kg daily) over a 3-year period. In this study AZA showed sustained efficacy for maintenance of clinical remission off steroids. Furthermore patients with earlier UC were those who most probably had sustained steroid-free remission at the end of 12 mo while on AZA^[85]. Considerations regarding the best dosage and the best duration of therapy with thiopurines are similar to the treatment for CD.

Methotrexate

Data on the efficacy of MTX in UC comes from small prospective studies where different doses and routes of administration have been used, with inconsistent results^[23,83,87]. A placebo-controlled trial showed no benefit of oral MTX at the dosage of 12.5 mg per week in UC patients^[88]. A study^[26] compared the efficacy of oral MTX at the dosage of 15 mg weekly with 6-MP (1.5 mg/kg daily) and mesalamine (3 g daily) in 72 steroid-dependent patients (34 UC and 38 CD). After 30 wk a significantly higher remission rate was observed in UC patients treated with 6-MP (78.6%) with respect to patients treated with mesalamine (25%) but no statistical differences were observed between patients treated with MTX (58.3%) with respect to patients treated with mesalamine. With regard to maintaining remission, after 76 wk UC patients treated with 6-MP presented significantly higher remission rates with respect to the other 2 groups. More recently a retrospective study^[88] evaluated the efficacy and safety of MTX in 131 patients with IBD (99 CD, 32 UC) intolerant or non-responsive to thiopurines. In UC patients clinical response occurred in 78% of patients refractory to AZA/MP and in 65% of pa-

tients intolerant to thiopurines. MTX was well tolerated in a majority of individuals. Based on these data there is insufficient evidence to support the use of MTX in UC as an alternative to thiopurines.

Tacrolimus

In patients with severely active UC not responding to intravenous corticosteroids a second line therapy with tacrolimus, as well as with cyclosporin or infliximab may be appropriate^[3]. A placebo controlled trial evaluated the efficacy of tacrolimus in 60 patients with moderate or severe UC. Patients were treated with a high concentration (10-15 ng/mL) of tacrolimus, a low concentration (5-10 ng/mL) of tacrolimus or placebo. At week 2, a clinical improvement was observed in 68.4% of patients treated with high concentration of tacrolimus and in 10% of patients treated with placebo ($P < 0.001$). Clinical remission was observed in 20% of patients treated with a high concentration. In the open label extension, 55.2% of all patients had a clinical improvement at week 10. The optimal target range appears to be 10-15 ng/mL. The incidence of side effects in the tacrolimus group was significantly higher than in the placebo group ($P = 0.043$). The most common event was finger tremor^[89]. A more recent placebo controlled trial was conducted on 62 patients with steroid-refractory UC. A response rate of 50% was reported in patients treated with oral tacrolimus compared to 13.3% in patients treated with placebo ($P = 0.003$) after 2 wk of treatment. Rates of mucosal healing were higher in the treatment group respect to the placebo group (43.8% vs 13.3%, $P = 0.012$), but the rates of clinical remission were not significantly different (3 out of 30 vs 0 out of 30, $P = 0.238$)^[90]. A retrospective review of 130 steroid refractory patients with moderate to severe UC showed that 94 patients (72%) had achieved remission after 3 mo of follow up and that the addition of thiopurines correlated significantly with remission rates^[91]. However another retrospective study on 32 refractory UC patients revealed that only 4 out of 30 steroid-dependent patients were able to discontinue steroids after a median follow-up of 29 wk and 12 out of 32 patients underwent colectomy^[92]. The efficacy of rectal tacrolimus ointment has been analysed in a small study on 8 patients with steroid dependent proctitis refractory to immunosuppressive and infliximab treatment. After 8 wk of therapy 6 out of 8 patients had achieved remission^[93].

A recent prospective study investigated the efficacy of topical tacrolimus in the treatment of refractory pouchitis. Ten patients with antibiotic-refractory pouchitis were treated for 8 wk with a tacrolimus enema. The mean pouchitis disease activity index score decreased from 15.9 ± 0.8 to 7.8 ± 0.8 during 8 wk of treatment ($P < 0.01$) but endoscopic healing was not achieved^[94].

Cyclosporine

A second line therapy with cyclosporine is indicated in the case of severe UC, which does not respond to 3-5 d of intravenous steroids. If no improvement is observed

within 4-7 d a colectomy is recommended. Two placebo controlled trials investigated the efficacy of cyclosporine in the treatment of severe UC^[95,96]. In the first study^[95] 30 patients with severe UC were randomized to intravenous cyclosporine at the dosage of 4 mg/kg daily or methylprednisolone at the dosage of 40 mg daily. After 8 d responders were treated with the same medication orally, in combination with AZA. After 8 d, 8 out of 15 patients (53%) who received methylprednisolone had a response compared with 9 out of 14 (64%) receiving cyclosporine. In non-responders, 3 out of 7 methylprednisolone patients and 1 out of 3 cyclosporine patients improved when both treatments were combined. At 12 mo, 7 out of 9 patients (78%) initially controlled with cyclosporine maintained their remission compared with 3 out of 8 (37%) initially treated with methylprednisolone.

In the second study^[96] 20 patients with severe UC, non-responders to 7 d of intravenous corticosteroids, were treated with intravenous cyclosporine (4 mg/kg daily) or placebo. Nine out of 11 patients (82%) treated with cyclosporine had a response within a mean of 7 d compared with 0 out of 9 patients who received placebo ($P < 0.001$).

Unfortunately the use of cyclosporine is associated with important adverse effects that are mainly dose dependent. A controlled trial investigated the additional clinical benefit of 4 mg/kg over 2 mg/kg intravenous cyclosporine in the treatment of severe UC. Seventy-three patients were included. After 8 d response rates were 84% in patients treated with 4 mg/kg and 86% in patients treated with 2 mg/kg. Furthermore short-term colectomy rates were 13% in patients treated with 4 mg/kg and 9% in patients treated with 2 mg/kg. The authors concluded that high-dose cyclosporine has no additional clinical benefit over low dose in the treatment of severe UC^[97]. Up to now 2 mg/kg daily has become the standard dose used in current clinical practice.

A study assessed the long-term colectomy-sparing effects and safety of cyclosporine in 71 patients with severe UC. Sixty out of 71 patients (85%) responded to intravenous cyclosporine and were discharged on oral cyclosporine. Of these 60 patients, 26 were transitioned from cyclosporine to 6-MP. Cumulative colectomy rates for the entire cohort were 39% at 1 year, 42% at 2 years, and 46% at 5 years. In the sub-group of patients maintained with 6-MP only one patient required a colectomy, whereas colectomy was carried out in 76% of patients who were not transitioned from cyclosporine to 6-MP. In conclusion concomitant 6-MP therapy was associated with a reduced risk of colectomy (OR = 0.01, 95%CI: 0.001-0.09, $P < 0.0001$) on long-term follow-up. Side effects were noted in two-thirds of the patients, the majority of which were mild. The authors concluded that transition to oral thiopurines after intravenous cyclosporine was useful in preventing a future colectomy^[98].

Mycophenolate mofetil

As for CD, also for UC - data on the efficacy of MMF

come from small, uncontrolled, retrospective studies, in which patients with IBD and not only UC were included. A retrospective study^[99] evaluated the efficacy of MMF (1-2 g daily) in patients with IBD, only 7 of them with UC, treated over a 3-year period. Thirty-nine patients (32 CD and 7 UC), intolerant or non-responders to AZA, were identified. During the study period 40% of patients (a total of 16 patients, only 4 with UC) achieved remission and complete steroid withdrawal, 30% could not tolerate the drug and 30% did not respond. An open-label prospective and uncontrolled 6 mo trial^[100] on the efficacy of MMF (2 g daily) in combination with steroids was conducted in 24 IBD patients (11 CD, 13 UC). Only 10 out of 24 patients achieved remission after 3 mo. All but one CD patient had relapsed by the end of the study. The authors concluded that MMF at the dosage of 2 g daily was unable to induce and maintain remission for a period of 6 mo in 23 out of 24 chronic active IBD patients. A retrospective study^[101] reported the results on the efficacy of MMF in 70 patients with IBD (51 CD, 19 UC) over a 5-year period. Seventeen of the 70 patients (24.3%) had a sustained steroid-free remission for 33 mo. Treatment with MMF was discontinued in 53 patients, 17 because of side effects and 36 because of non response to the treatment. A more recent study^[102] was conducted in 14 patients with IBD (9 CD, 5 UC) intolerant or refractory to conventional medical therapy who received MMF (500-2000 mg bid). Of the 11 patients who were not in remission at baseline, 7 out of 11 (63.6%) achieved remission after 8 wk. All 3 patients in remission at baseline maintained their remission. At 6 mo 64.3% patients were in remission. Of 12 patients followed for 12 mo, 8 were in remission (66.7%).

As for CD patients, MMF may be considered an alternative immunosuppressant therapy in steroid-dependent patients with UC, refractory to AZA/6-MP. Up to now there are no recommendations for the use of MMF in UC.

Biologic therapies

The use of anti-TNF α in UC patients is recommended in the case of severe UC that is refractory to steroids^[103,104] after exclusion of other causes of persistent symptoms such as coexistent cytomegalovirus or *Clostridium difficile* infection. Furthermore steroid-dependent UC patients, refractory or intolerant to thiopurines, can be treated with biologics. Also in patients with UC, as well as in CD patients, in the presence of axial arthropathy the efficacy of anti-TNF α treatment has been well established, as well as in the case of peripheral arthritis, not responding to sulfasalazine^[3].

A Cochrane meta-analysis on infliximab in moderate to severe UC, refractory to corticosteroids and/or immunomodulators, showed that infliximab was more effective than placebo in inducing clinical remission^[105]. Two placebo-controlled trials evaluated the efficacy of adalimumab in patients with moderately active UC despite conventional therapy^[104,106]. In one of these studies^[104]

adalimumab was compared with placebo in patients naïve to biologics. At week 8, clinical remission was observed in 18.5% of patients in the adalimumab group compared with 9.2% in the placebo group ($P = 0.031$). In the second study^[106] 40.3% of the included patients had been previously treated with infliximab. Clinical remission was achieved in significantly more patients receiving adalimumab than placebo at week 8 (16.5% and 9.3%, $P = 0.02$) and week 52 (17.3% and 8.5%, $P = 0.01$). The authors observed that the clinical remission rates in the adalimumab group were higher in patients who were naïve to anti-TNF α therapy at baseline. Other studies reported a benefit of adalimumab in patients with active UC previously exposed to infliximab with up to 27% of clinical remission in the short term^[107-109].

An Italian multicentre study reported data on the effectiveness of adalimumab in a cohort of 88 UC patients, retrospectively reviewed. Clinical remission rates were reported in 17%, 28.4%, 36.4% and 43.2% of the patients at 4, 12, 24 and 54 wk respectively. Twenty-two patients required colectomy. Clinical remission and low C-reactive protein at week 12 predicted clinical remission at week 54. Previous immunosuppressant use was associated with a lower probability of clinical remission at week 54 and with a higher rate of colectomy^[110].

Golimumab, a fully human monoclonal anti-TNF- α antibody, has been recently approved by the United States Food and Drug Administration for inducing and maintaining clinical remission in patients with moderate to severe UC. The efficacy of golimumab induction therapy has been evaluated in a trial on 1064 patients with UC. Patients were treated with golimumab at the dosage of 100 mg and then 50 mg, 200 mg and then 100 mg, 400 mg and then 200 mg, or placebo. The rates of clinical response at week 6 were 51% and 54.9% among patients treated with 200 mg/100 mg and 400 mg/200 mg golimumab, respectively, *vs* 30.3% among patients treated with placebo ($P \leq 0.0001$). The rates of clinical remission and mucosal healing were significantly greater in both golimumab groups than in the placebo group ($P \leq 0.0014$). The rates of serious adverse events were 6.1% and 3.0% in the placebo and golimumab groups, respectively^[111].

In a subsequent trial the efficacy of golimumab as maintenance therapy was evaluated. Patients who responded to induction therapy with golimumab ($n = 464$) were treated with placebo or golimumab (50 or 100 mg) every 4 wk through week 52. Patients who responded to placebo in the induction study continued to receive placebo. Non responders in the induction study received 100 mg of golimumab. At weeks 30 and 54, a higher percentage of patients who received 100 mg of golimumab were in clinical remission and had mucosal healing (27.8% and 42.4%) compared with patients who received placebo (15.6% and 26.6%; $P = 0.004$ and $P = 0.002$, respectively) or 50 mg of golimumab (23.2% and 41.7%, respectively)^[112].

Regarding the maintenance treatment, according to the ECCO guidelines^[3] in patients responding to anti-

TNF α both maintaining remission with thiopurines and anti-TNF α are considered appropriate. In patients with severe UC, responding to intravenous steroids, ciclosporin or infliximab, thiopurines should be considered to maintain remission. However, in patients responding to infliximab, continuing infliximab is also considered appropriate. The prior failure of thiopurines favours maintenance with anti-TNF- α therapy. According to the Italian guidelines^[2] 1 year scheduled treatment with infliximab is indicated in patients who have responded to infliximab induction. In patients who are thiopurine naïve, maintenance therapy with thiopurines may be a valuable option as maintenance treatment. The duration of therapy over 1 year should be evaluated case-by-case.

In severe UC infliximab is considered a second line salvage therapy before colectomy, such as ciclosporine^[2,3]. A small randomised controlled study showed that a single dose (5 mg/kg) of infliximab was an effective salvage therapy in patients with severe UC refractory to intravenous corticosteroids. Colectomy rates at 3 mo were significantly lower in patients receiving infliximab than placebo (7 out of 24 *vs* 14 out of 21, $P = 0.017$)^[113]. The authors observed that patients with a less active disease who were randomised after 5-7 d of intravenous corticosteroids seemed to benefit more than patients with more severe disease randomised at day 3. A retrospective Italian study^[114] then suggested that patients receiving a single infusion were more likely to require a colectomy at 2 mo than those who receive more infusions.

Other studies reported variable results^[115,116]. A placebo controlled trial showed a colectomy rate at 3 years of 50% in patients with severe UC treated with infliximab with respect to 76% in patients treated with placebo ($P = 0.012$)^[117].

The impact of preoperative infliximab use on the rate of surgical interventions and on post-surgical complications in patients with IBD was investigated in a meta-analysis. Twelve studies (8 on UC, 3 on CD and 1 on both UC and CD) were included in the analysis. In comparison with control groups, infliximab neither decreases the rate of colectomy nor increases the rate of infectious complications. However thrombotic events, ileal pouch complications, sepsis and anastomotic leaks were increased in patients treated with infliximab. On the other hand patients treated with biological therapies have a more severe disease and most of the time are refractory to other therapies. Thus it is possible that the postsurgical complications in these studies were associated with the severity of the disease and not with the treatment^[118].

A questionable point is what is the best second line rescue therapy in severe UC: infliximab or ciclosporine? Up to now no randomised trial showed clear advantages of one strategy over the other. A retrospective study compared 2 cohorts of patients receiving infliximab or ciclosporine as a rescue therapy. A lower immediate colectomy rate was reported in the ciclosporine group^[119]. At the end of the study the risk of colectomy was 11.2

(95%CI: 2.4-53.1, $P = 0.002$) at 3 mo and was 3.0 (95%CI: 1.1-8.2, $P = 0.030$) at 12 mo in infliximab treated patients, in comparison with cyclosporine treated patients

Another retrospective study^[120] compared 2 historical cohorts of severe UC patients treated with cyclosporine (35 patients) or infliximab (30 patients). At 3 mo the colectomy rate was 28.5% in the cyclosporine group and 17% in the infliximab group ($P = 0.25$), at 12 mo the colectomy rate was 48% vs 17% ($P = 0.007$). At the end of the follow-up the colectomy rate was 60% vs 30% ($P = 0.04$). A high level of C reactive protein ($P = 0.04$), an extensive disease ($P = 0.01$) and no AZA treatment ($P = 0.001$) were related to the risk of colectomy.

In the CYSIF trial^[121] 111 patients with severe UC despite 5 d of intravenous corticosteroids were randomized to receive intravenous cyclosporine (2 mg/kg daily for 8 d) followed by oral cyclosporine (4 mg/kg daily) or infliximab (5 mg/kg at weeks 0, 2 and 6), followed by oral AZA. At day 7, 85% of patients responded to treatment in both groups. At day 98 treatment failure was reported in 60% of patients treated with cyclosporine compared with 54% of patients treated with infliximab ($P = 0.49$), with a colectomy rate of 18% in the cyclosporine group respect to 21% in the infliximab group ($P = 0.66$).

Regarding the evaluation of biologics serum levels or ADA in UC, in patients with UC infliximab serum levels were correlated with albumin serum levels^[122]. Patients with high serum albumin have a prolonged infliximab half-life and increased efficacy. Furthermore in UC patients the colectomy rate was significantly higher in the case of undetectable infliximab trough levels^[123]. In a post hoc analysis from the ACT I and ACT II studies higher infliximab concentrations were associated with an increased clinical remission and mucosal healing. The highest proportion of patients in clinical remission was observed in patients with serum levels of infliximab between 2.4 and 6.8 mg/mL at week 30^[124].

As for CD also in UC - biologics serum levels or ADA have not been routinely applied in clinical practice.

COMBINATION THERAPY IN IBD

Some studies supported the efficacy of combination therapy with biologics and thiopurines both in CD and UC. A trial compared the efficacy of induction treatment with infliximab plus AZA/6-MP to AZA/6-MP alone in steroid-dependent CD patients^[52]. At the end of the study, combination therapy was more effective than thiopurines alone. Furthermore a higher remission rate was observed in the subgroup of patients naive to AZA/6MP. In patients with previous thiopurines failure the difference between infliximab and placebo was not statistically significant. In another study^[70] combined immunosuppressive therapy with infliximab and AZA was able to obtain a higher steroid-free remission rate with respect to monotherapy with infliximab or AZA. Patients with moderate to severe CD were treated with infliximab, AZA or a combination therapy with the 2 drugs. After

26 wk 57% of patients assigned to combination therapy achieved a steroid-free remission, compared with 44% of patients assigned to infliximab alone and 30% of patients assigned to AZA alone. However the greater efficacy of combination therapy was observed mainly in patients with normal value of CRP and absence of endoscopic lesions at baseline.

Regarding UC, a recent trial^[125] suggested that in steroid-refractory patients with active UC a combination therapy with AZA and infliximab was more effective than either monotherapy. At week 16 clinical remission was achieved in 24% of patients receiving AZA, in 22% of patients received infliximab and in 40% of patients receiving combination therapy ($P = 0.032$ for combination therapy vs AZA monotherapy and $P = 0.017$ for combination therapy vs infliximab monotherapy).

These data are up to now insufficient to consider combination therapy efficient in all IBD patients. Furthermore, it is still being debated whether combined immunosuppressive therapy increases the long term toxicity. In clinical practice the use of combination therapy should be reserved for patients who do not respond to monotherapy.

The evidence of higher incidence of hepatosplenic T cell lymphoma in young men treated with combined immunosuppressive therapy^[126,127] should avoid prolonged combination therapy in young males. The recent observation that most of the lymphomas associated with immunosuppressive therapies in IBD patients were due to a loss of control of EBV infection leads to a recommendation of avoiding the use of thiopurines in patients seronegative for EBV^[128].

CONCLUSION

The use of immunosuppressive therapy, with conventional immunosuppressants or biologics, is indicated in the case of moderate to severe disease not responding to corticosteroids and in steroid-dependent IBD patients, as induction and maintenance treatment. Cyclosporine, infliximab and tacrolimus are considered a second line therapy in patients with severe UC not responding to 3-5 d of intravenous corticosteroids. The choice of biologics instead of immunosuppressants in the case of steroid-dependent IBD patients is guided by the severity of the disease, the presence of complex perianal disease in patients with CD or the concomitant extra-intestinal manifestations. Furthermore the recent observation that patients seronegative for EBV and treated with immunosuppressants have a higher risk of lymphomas, should lead to avoiding treatment with thiopurines in this subgroup of patients. The slow onset of action of thiopurines precludes their use as a single therapy in active IBD patients but they can be used in combination with corticosteroids. When treatment with thiopurines is chosen, adequate dosage and duration of therapy should be reached before evaluating their efficacy. The evaluation of serum concentration of thiopurine methyl transferase

activity and thiopurine metabolites could be useful for the management of the treatment but up to now it has not been routinely applied in clinical practice. The use of thalidomide and MMF is not recommended in IBD patients, the decision to use them might only be made on a case by case basis after failure of all other options including optimization of anti-TNF α therapies and surgical strategies

Regarding biological treatment, dose intensification could be useful in the presence of incomplete response. In the case of primary failures to one anti-TNF α , a switch to the other one should be considered. In cases of intolerance to infliximab, the use of adalimumab as a second line treatment is recommended. Data on the efficacy of combination therapy are up to now insufficient to consider this strategy in all IBD patients. Furthermore the evidence of higher incidence of hepatosplenic T cell lymphoma in young men treated with combined immunosuppressive therapy means prolonged combination therapy should be avoided in these patients. As for immunosuppressants also for biologics - the evaluation of biologic serum levels and antibiologic antibodies could be useful for the management of the treatment but it is not routinely applied in clinical practice.

The final outcome of the treatment should be considered the clinical remission, with mucosa healing and not the clinical response.

Considering the evidence of high risk of cutaneous malignancies in patients treated with immunosuppressants and biologics for a long term period, lifelong sun protection and periodical dermatological screening should be recommended for these patients.

REFERENCES

- Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gommollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62 [PMID: 21122489 DOI: 10.1016/j.crohns.2009.12.002]
- Orlando A**, Armuzzi A, Papi C, Annese V, Ardizzone S, Biancone L, Bortoli A, Castiglione F, D'Inca R, Gionchetti P, Kohn A, Poggioli G, Rizzello F, Vecchi M, Cottone M. The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: The use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease. *Dig Liver Dis* 2011; **43**: 1-20 [PMID: 20843756 DOI: 10.1016/j.dld.2010.07.010]
- Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]
- Feuerstein JD**, Akbari M, Gifford AE, Cullen G, Leffler DA, Sheth SG, Cheifetz AS. Systematic review: the quality of the scientific evidence and conflicts of interest in international inflammatory bowel disease practice guidelines. *Aliment Pharmacol Ther* 2013; **37**: 937-946 [PMID: 23550536 DOI: 10.1111/apt.12290]
- Munkholm P**, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994; **35**: 360-362 [PMID: 8150347]
- Prefontaine E**, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2010; **(6)**: CD000545 [PMID: 20556747 DOI: 10.1002/14651858.CD000545]
- Khan KJ**, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 630-642 [PMID: 21407186 DOI: 10.1038/ajg.2011.64]
- Hindorf U**, Johansson M, Eriksson A, Kvifors E, Almer SH. Mercaptopurine treatment should be considered in azathioprine intolerant patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2009; **29**: 654-661 [PMID: 19183142 DOI: 10.1111/j.1365-2036.2008.03925.x]
- Prefontaine E**, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009; **(1)**: CD000067 [PMID: 19160175 DOI: 10.1002/14651858.CD000067]
- Nikfar S**, Mirfazaelian H, Abdollahi M. Efficacy and tolerability of immunoregulators and antibiotics in fistulizing Crohn's disease: a systematic review and meta-analysis of placebo-controlled trials. *Curr Pharm Des* 2010; **16**: 3684-3698 [PMID: 21143147]
- French H**, Mark Dalzell A, Srinivasan R, El-Matary W. Relapse rate following azathioprine withdrawal in maintaining remission for Crohn's disease: a meta-analysis. *Dig Dis Sci* 2011; **56**: 1929-1936 [PMID: 21476031 DOI: 10.1007/s10620-011-1671-5]
- Lémann M**, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Modigliani R, Bouhnik Y. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128**: 1812-1818 [PMID: 15940616]
- Beaugerie L**, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, Hébuterne X, Cortot A, Bouhnik Y, Gendre JP, Simon T, Maynadié M, Hermine O, Faivre J, Carrat F. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; **374**: 1617-1625 [PMID: 19837455 DOI: 10.1016/S0140-6736(09)61302-7]
- Kandiel A**, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54**: 1121-1125 [PMID: 16009685]
- Siegel CA**, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009; **7**: 874-881 [PMID: 19558997 DOI: 10.1016/j.cgh.2009.01.004]
- Reijasse D**, Le Pendevan C, Cosnes J, Dehee A, Gendre JP, Nicolas JC, Beaugerie L. Epstein-Barr virus viral load in Crohn's disease: effect of immunosuppressive therapy. *Inflamm Bowel Dis* 2004; **10**: 85-90 [PMID: 15168806]
- Serrate C**, Silva-Moreno M, Dartigues P, Poujol-Robert A, Sokol H, Gorin NC, Coppo P. Epstein-Barr virus-associated lymphoproliferation awareness in hemophagocytic syndrome complicating thiopurine treatment for Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1449-1451 [PMID: 19177429 DOI: 10.1002/ibd.20823]
- Long MD**, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2010; **8**: 268-274 [PMID: 20005977 DOI: 10.1016/j.cgh.2009.11.024]

- 19 **Peyrin-Biroulet L**, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, Carbonnel F, Colombel JF, Dupas JL, Godeberge P, Hugot JP, Lémann M, Nahon S, Sabaté JM, Tucut G, Beaugerie L. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011; **141**: 1621-1628.e1-5 [PMID: 21708105 DOI: 10.1053/j.gastro.2011.06.050]
- 20 **Singh H**, Nugent Z, Demers AA, Bernstein CN. Increased risk of nonmelanoma skin cancers among individuals with inflammatory bowel disease. *Gastroenterology* 2011; **141**: 1612-1620 [PMID: 21806945 DOI: 10.1053/j.gastro.2011.07.039]
- 21 **Gilissen LP**, Wong DR, Engels LG, Bierau J, Bakker JA, Paulussen AD, Romberg-Camps MJ, Stronkhorst A, Bus P, Bos LP, Hooymans PM, Stockbrügger RW, Neef C, Masclee AA. Therapeutic drug monitoring of thiopurine metabolites in adult thiopurine tolerant IBD patients on maintenance therapy. *J Crohns Colitis* 2012; **6**: 698-707 [PMID: 22398098 DOI: 10.1016/j.crohns.2011.12.003]
- 22 **Curkovic I**, Rentsch KM, Frei P, Fried M, Rogler G, Kullak-Ublick GA, Jetter A. Low allopurinol doses are sufficient to optimize azathioprine therapy in inflammatory bowel disease patients with inadequate thiopurine metabolite concentrations. *Eur J Clin Pharmacol* 2013; **69**: 1521-1531 [PMID: 23588559 DOI: 10.1007/s00228-013-1500-1]
- 23 **González-Lama Y**, Bermejo F, López-Sanromán A, García-Sánchez V, Esteve M, Cabriada JL, McNicholl AG, Pajares R, Casellas F, Merino O, Carpio D, Vera MI, Muñoz C, Calvo M, Benito LM, Bujanda L, García-Fernández FJ, Ricart E, Ginard D, Velasco M, Carneros JA, Mancañido N, Calvo M, Algaba A, Froilan C, Cara C, Maté J, Abreu L, Gisbert JP; "Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU)". Thiopurine methyl-transferase activity and azathioprine metabolite concentrations do not predict clinical outcome in thiopurine-treated inflammatory bowel disease patients. *Aliment Pharmacol Ther* 2011; **34**: 544-554 [PMID: 21722149 DOI: 10.1111/j.1365-2036.2011.04756.x]
- 24 **Roblin X**, Oussalah A, Chevaux JB, Sparrow M, Peyrin-Biroulet L. Use of thiopurine testing in the management of inflammatory bowel diseases in clinical practice: a worldwide survey of experts. *Inflamm Bowel Dis* 2011; **17**: 2480-2487 [PMID: 21351210 DOI: 10.1002/ibd.21662]
- 25 **Arora S**, Katkov W, Cooley J, Kemp JA, Johnston DE, Schapiro RH, Podolsky D. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; **46**: 1724-1729 [PMID: 10430331]
- 26 **Maté-Jiménez J**, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2000; **12**: 1227-1233 [PMID: 11111780]
- 27 **Oren R**, Moshkowitz M, Odes S, Becker S, Keter D, Pomeranz I, Shirin C, Reisfeld I, Broide E, Lavy A, Fich A, Eliakim R, Patz J, Villa Y, Arber N, Gilat T. Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997; **92**: 2203-2209 [PMID: 9399753]
- 28 **Feagan BG**, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995; **332**: 292-297 [PMID: 7816064]
- 29 **Feagan BG**, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000; **342**: 1627-1632 [PMID: 10833208]
- 30 **McSharry K**, Dalzell AM, Leiper K, El-Matary W. Systematic review: the role of tacrolimus in the management of Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 1282-1294 [PMID: 21999607 DOI: 10.1111/j.1365-2036.2011.04873.x]
- 31 **Sandborn WJ**, Present DH, Isaacs KL, Wolf DC, Greenberg E, Hanauer SB, Feagan BG, Mayer L, Johnson T, Galanko J, Martin C, Sandler RS. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. *Gastroenterology* 2003; **125**: 380-388 [PMID: 12891539]
- 32 **González-Lama Y**, Abreu L, Vera MI, Pastrana M, Tabernero S, Revilla J, Durán JG, Escartin P. Long-term oral tacrolimus therapy in refractory to infliximab fistulizing Crohn's disease: a pilot study. *Inflamm Bowel Dis* 2005; **11**: 8-15 [PMID: 15674108]
- 33 **Lowry PW**, Weaver AL, Tremaine WJ, Sandborn WJ. Combination therapy with oral tacrolimus (FK506) and azathioprine or 6-mercaptopurine for treatment-refractory Crohn's disease perianal fistulae. *Inflamm Bowel Dis* 1999; **5**: 239-245 [PMID: 10579116]
- 34 **Casson DH**, Eltumi M, Tomlin S, Walker-Smith JA, Murch SH. Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; **47**: 436-440 [PMID: 10940284]
- 35 **Ng SC**, Arebi N, Kamm MA. Medium-term results of oral tacrolimus treatment in refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 129-134 [PMID: 17206694]
- 36 **Hart AL**, Plamondon S, Kamm MA. Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007; **13**: 245-253 [PMID: 17206671]
- 37 **Benson A**, Barrett T, Sparberg M, Buchman AL. Efficacy and safety of tacrolimus in refractory ulcerative colitis and Crohn's disease: a single-center experience. *Inflamm Bowel Dis* 2008; **14**: 7-12 [PMID: 17879277]
- 38 **Tamaki H**, Nakase H, Matsuura M, Inoue S, Mikami S, Ueno S, Uza N, Kitamura H, Kasahara K, Chiba T. The effect of tacrolimus (FK-506) on Japanese patients with refractory Crohn's disease. *J Gastroenterol* 2008; **43**: 774-779 [PMID: 18958546 DOI: 10.1007/s00535-008-2229-y]
- 39 **Mansfield JC**, Parkes M, Hawthorne AB, Forbes A, Probert CS, Perowne RC, Cooper A, Zeldis JB, Manning DC, Hawkey CJ. A randomized, double-blind, placebo-controlled trial of lenalidomide in the treatment of moderately severe active Crohn's disease. *Aliment Pharmacol Ther* 2007; **26**: 421-430 [PMID: 17635377]
- 40 **Plamondon S**, Ng SC, Kamm MA. Thalidomide in luminal and fistulizing Crohn's disease resistant to standard therapies. *Aliment Pharmacol Ther* 2007; **25**: 557-567 [PMID: 17305756]
- 41 **Lazzerini M**, Martelossi S, Marchetti F, Scabar A, Bradascchia F, Ronfani L, Ventura A. Efficacy and safety of thalidomide in children and young adults with intractable inflammatory bowel disease: long-term results. *Aliment Pharmacol Ther* 2007; **25**: 419-427 [PMID: 17269997]
- 42 **Felipez LM**, Gokhale R, Tierney MP, Kirschner BS. Thalidomide use and outcomes in pediatric patients with Crohn disease refractory to infliximab and adalimumab. *J Pediatr Gastroenterol Nutr* 2012; **54**: 28-33 [PMID: 21681114 DOI: 10.1097/MPG.0b013e318228349e]
- 43 **Epinete WW**, Parker CM, Jones EL, Greist MC. Mycophenolic acid for psoriasis. A review of pharmacology, long-term efficacy, and safety. *J Am Acad Dermatol* 1987; **17**: 962-971 [PMID: 3429723]
- 44 **Goldblum R**. Therapy of rheumatoid arthritis with mycophenolate mofetil. *Clin Exp Rheumatol* 1993; **11** Suppl 8: S117-S119 [PMID: 8324935]
- 45 **Hassard PV**, Vasiliauskas EA, Kam LY, Targan SR, Abreu MT. Efficacy of mycophenolate mofetil in patients failing 6-mercaptopurine or azathioprine therapy for Crohn's disease. *Inflamm Bowel Dis* 2000; **6**: 16-20 [PMID: 10701145]
- 46 **Wenzl HH**, Hinterleitner TA, Aichbichler BW, Fickert P, Petritsch W. Mycophenolate mofetil for Crohn's disease: short-

- term efficacy and long-term outcome. *Aliment Pharmacol Ther* 2004; **19**: 427-434 [PMID: 14871282]
- 47 **Hafraoui S**, Dewit O, Marteau P, Cosnes J, Colombel JF, Modigliani R, Cortot A, Lémann M. [Mycophenolate mofetil in refractory Crohn's disease after failure of treatments by azathioprine or methotrexate]. *Gastroenterol Clin Biol* 2002; **26**: 17-22 [PMID: 11938035]
- 48 **Miehsler W**, Reinisch W, Moser G, Gangl A, Vogelsang H. Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? *Am J Gastroenterol* 2001; **96**: 782-787 [PMID: 11280551]
- 49 **Neurath MF**, Wanitschke R, Peters M, Krummenauer F, Meyer zum Büschenfelde KH, Schlaak JF. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. *Gut* 1999; **44**: 625-628 [PMID: 10205197]
- 50 **Peyrin-Biroulet L**, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2008; **6**: 644-653 [PMID: 18550004 DOI: 10.1016/j.cgh.2008.03.014]
- 51 **Ford AC**, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 644-659, quiz 660 [PMID: 21407183 DOI: 10.1038/ajg.2011.73]
- 52 **Lémann M**, Mary JY, Duclos B, Veyrac M, Dupas JL, Delchier JC, Laharie D, Moreau J, Cadot G, Picon L, Bourreille A, Sobahni I, Colombel JF. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006; **130**: 1054-1061 [PMID: 16618399]
- 53 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859]
- 54 **Panaccione R**, Colombel JF, Sandborn WJ, D'Haens G, Zhou Q, Pollack PF, Thakkar RB, Robinson AM. Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther* 2013; **38**: 1236-1247 [PMID: 24134498 DOI: 10.1111/apt.12499]
- 55 **Orlando A**, Renna S, Mocciano F, Cappello M, Di Mitri R, Randazzo C, Cottone M. Adalimumab in steroid-dependent Crohn's disease patients: prognostic factors for clinical benefit. *Inflamm Bowel Dis* 2012; **18**: 826-831 [PMID: 21837774 DOI: 10.1002/ibd.21835]
- 56 **Orlando A**, Renna S, Mocciano F, Cappello M, Di Mitri R, Orlando R, Modesto I, Randazzo C, Marino A, Craxi A, Cottone M. Long Term Adalimumab Efficacy In Steroid-dependent Crohn's Disease Patients. *Gastroenterol J* 2013; **1** Supp 1: P1434
- 57 **Targan SR**, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035 [PMID: 9321530]
- 58 **Hanauer SB**, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130**: 323-333; quiz 591 [PMID: 16472588]
- 59 **Youdim A**, Vasilias EA, Targan SR, Papadakis KA, Ippoliti A, Dubinsky MC, Lechago J, Paavola J, Loane J, Lee SK, Gaiennie J, Smith K, Do J, Abreu MT. A pilot study of adalimumab in infliximab-allergic patients. *Inflamm Bowel Dis* 2004; **10**: 333-338 [PMID: 15475739]
- 60 **Sandborn WJ**, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, D'Haens G, Li J, Rosenfeld MR, Kent JD, Pollack PF. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007; **146**: 829-838 [PMID: 17470824]
- 61 **Chaparro M**, Andreu M, Barreiro-de Acosta M, García-Planella E, Ricart E, Domènech E, Esteve M, Merino O, Nos P, Peñalva M, Gisbert JP. Effectiveness of infliximab after adalimumab failure in Crohn's disease. *World J Gastroenterol* 2012; **18**: 5219-5224 [PMID: 23066316 DOI: 10.3748/wjg.v18.i37.5219]
- 62 **Regueiro M**, Siemanowski B, Kip KE, Plevy S. Infliximab dose intensification in Crohn's disease. *Inflamm Bowel Dis* 2007; **13**: 1093-1099 [PMID: 17480021]
- 63 **Sutharshan K**, Geary RB. Temporary adalimumab dose escalation is effective in Crohn's disease patients with secondary non-response. *J Crohns Colitis* 2013; **7**: e277-e278 [PMID: 23434316 DOI: 10.1016/j.crohns.2013.01.002]
- 64 **D'Haens G**, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkühn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; **371**: 660-667 [PMID: 18295023 DOI: 10.1016/S0140-6736(08)60304-9]
- 65 **Schreiber S**, Reinisch W, Colombel JF. Early Crohn's disease shows high levels of remission to therapy with adalimumab: sub-analysis of CHARM. *Gastroenterology* 2007; **132** (Suppl 2): A985
- 66 **Beaugerie L**, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006; **130**: 650-656 [PMID: 16530505]
- 67 **Fidder H**, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segart S, Henckaerts L, Van Assche G, Vermeire S, Rutgeerts P. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009; **58**: 501-508 [PMID: 18832524 DOI: 10.1136/gut.2008.163642]
- 68 **Schnitzler F**, Fidder H, Ferrante M, Noman M, Arijis I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1295-1301 [PMID: 19340881 DOI: 10.1002/ibd.20927]
- 69 **Rutgeerts P**, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, Reinisch W, Kumar A, Lazar A, Camez A, Lomax KG, Pollack PF, D'Haens G. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012; **142**: 1102-1111.e2 [PMID: 22326435 DOI: 10.1053/j.gastro.2012.01.035]
- 70 **Maser EA**, Vilella R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1248-1254 [PMID: 16931170]
- 71 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
- 72 **Fasanmade A**, Olson A, Bao W, Pendley C, Davis H, Mayer L. Relationship between infliximab pharmacokinetics and improvement in Crohn's disease. *Gastroenterology* 2002; **122**: A617-618
- 73 **Afif W**, Loftus EV, Faubion WA, Kane SV, Bruining DH, Hanson KA, Sandborn WJ. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations

- in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**: 1133-1139 [PMID: 20145610 DOI: 10.1038/ajg.2010.9]
- 74 **Feagan BG**, Singh S, Lockton S, Hauenstein S, Ohrmund L, Croner LJ, Greenberg GR, Sandborn WJ, Rutgeerts PJ, Vermeire S. 565 novel infliximab (IFX) and antibody-to-infliximab (ATI) assays are predictive of disease activity in patients with Crohn's disease (CD). *Gastroenterology* 2012; **142**: S114
- 75 **Li J**, Chiu Y, Robinson A. Evaluation of potential correlations between serum adalimumab concentration and remission in patients with Crohn's disease in CLASSIC I and II. *J Crohn's Colitis* 2010; **4**: 73
- 76 **Karmiris K**, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, Claes K, Coopman T, Van Schuerbeek N, Van Assche G, Vermeire S, Rutgeerts P. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009; **137**: 1628-1640 [PMID: 19664627 DOI: 10.1053/j.gastro.2009.07.062]
- 77 **Farrell RJ**, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003; **124**: 917-924 [PMID: 12671888]
- 78 **Ainsworth MA**, Bendtzen K, Brynskov J. Tumor necrosis factor-alpha binding capacity and anti-infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of infliximab in Crohn's disease. *Am J Gastroenterol* 2008; **103**: 944-948 [PMID: 18028512]
- 79 **Steenholdt C**, Bendtzen K, Brynskov J, Thomsen OØ, Ainsworth MA. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. *Scand J Gastroenterol* 2011; **46**: 310-318 [PMID: 21087119 DOI: 10.3109/00365521.2010.536254]
- 80 **Steenholdt C**, Al-khalaf M, Brynskov J, Bendtzen K, Thomsen OØ, Ainsworth MA. Clinical implications of variations in anti-infliximab antibody levels in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2209-2217 [PMID: 22344964 DOI: 10.1002/ibd.22910]
- 81 **Ben-Horin S**, Waterman M, Kopylov U, Yavzori M, Picard O, Fudim E, Awadie H, Weiss B, Chowers Y. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 444-447 [PMID: 23103905 DOI: 10.1016/j.cgh.2012.10.020]
- 82 **Sood A**, Midha V, Sood N, Kaushal V. Role of azathioprine in severe ulcerative colitis: one-year, placebo-controlled, randomized trial. *Indian J Gastroenterol* 2000; **19**: 14-16 [PMID: 10659481]
- 83 **Sood A**, Kaushal V, Midha V, Bhatia KL, Sood N, Malhotra V. The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis. *J Gastroenterol* 2002; **37**: 270-274 [PMID: 11993510]
- 84 **Ardizzone S**, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47-53 [PMID: 15972298]
- 85 **Chebli LA**, Chaves LD, Pimentel FF, Guerra DM, Barros RM, Gaburri PD, Zanini A, Chebli JM. Azathioprine maintains long-term steroid-free remission through 3 years in patients with steroid-dependent ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 613-619 [PMID: 19705415 DOI: 10.1002/ibd.21083]
- 86 **Oren R**, Arber N, Odes S, Moshkowitz M, Keter D, Pomeranz I, Ron Y, Reifeld I, Broide E, Lavy A, Fich A, Eliakim R, Patz J, Bardan E, Villa Y, Gilat T. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996; **110**: 1416-1421 [PMID: 8613046]
- 87 **Kozarek RA**, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989; **110**: 353-356 [PMID: 2492786]
- 88 **Wahed M**, Louis-Auguste JR, Baxter LM, Limdi JK, McCartney SA, Lindsay JO, Bloom SL. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine / mercaptopurine. *Aliment Pharmacol Ther* 2009; **30**: 614-620 [PMID: 19552632 DOI: 10.1111/j.1365-2036.2009.04073.x]
- 89 **Ogata H**, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y, Hibi T. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55**: 1255-1262 [PMID: 16484504]
- 90 **Ogata H**, Kato J, Hirai F, Hida N, Matsui T, Matsumoto T, Koyanagi K, Hibi T. Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. *Inflamm Bowel Dis* 2012; **18**: 803-808 [PMID: 21887732 DOI: 10.1002/ibd.21853]
- 91 **Schmidt KJ**, Herrlinger KR, Emmrich J, Barthel D, Koc H, Lehnert H, Stange EF, Fellermann K, Büning J. Short-term efficacy of tacrolimus in steroid-refractory ulcerative colitis - experience in 130 patients. *Aliment Pharmacol Ther* 2013; **37**: 129-136 [PMID: 23121200 DOI: 10.1111/apt.12118]
- 92 **Yamamoto S**, Nakase H, Mikami S, Inoue S, Yoshino T, Takeda Y, Kasahara K, Ueno S, Uza N, Kitamura H, Tamaki H, Matsuura M, Inui K, Chiba T. Long-term effect of tacrolimus therapy in patients with refractory ulcerative colitis. *Aliment Pharmacol Ther* 2008; **28**: 589-597 [PMID: 18549460 DOI: 10.1111/j.1365-2036.2008.03764.x]
- 93 **Lawrance IC**, Copeland TS. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. *Aliment Pharmacol Ther* 2008; **28**: 1214-1220 [PMID: 18761706 DOI: 10.1111/j.1365-2036.2008.03841.x]
- 94 **Uchino M**, Ikeuchi H, Matsuoka H, Bando T, Hida N, Nakamura S, Takesue Y, Tomita N. Topical tacrolimus therapy for antibiotic-refractory pouchitis. *Dis Colon Rectum* 2013; **56**: 1166-1173 [PMID: 24022534 DOI: 10.1097/DCR.0b013e31829ebd83]
- 95 **D'Haens G**, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortelmans L, Peeters M, Vermeire S, Penninckx F, Nevens F, Hiele M, Rutgeerts P. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001; **120**: 1323-1329 [PMID: 11313301]
- 96 **Lichtiger S**, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841-1845 [PMID: 8196726]
- 97 **Van Assche G**, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'Hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003; **125**: 1025-1031 [PMID: 14517785]
- 98 **Cheifetz AS**, Stern J, Garud S, Goldstein E, Malter L, Moss AC, Present DH. Cyclosporine is safe and effective in patients with severe ulcerative colitis. *J Clin Gastroenterol* 2011; **45**: 107-112 [PMID: 20679905 DOI: 10.1097/MCG.0b013e3181e883dd]
- 99 **Ford AC**, Towler RJ, Moayyedi P, Chalmers DM, Axon AT. Mycophenolate mofetil in refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **17**: 1365-1369 [PMID: 12786630]
- 100 **Fellermann K**, Steffen M, Stein J, Raedler A, Hämling J, Ludwig D, Loeschke K, Stange EF. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; **14**: 171-176 [PMID: 10651657]
- 101 **Palaniappan S**, Ford AC, Greer D, Everett SM, Chalmers DM, Axon AT, Hamlin PJ. Mycophenolate mofetil therapy for refractory inflammatory bowel disease. *Inflamm Bowel Dis*

- 2007; **13**: 1488-1492 [PMID: 17924566]
- 102 **Tan T**, Lawrance IC. Use of mycophenolate mofetil in inflammatory bowel disease. *World J Gastroenterol* 2009; **15**: 1594-1599 [PMID: 19340901]
- 103 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095]
- 104 **Reinisch W**, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; **60**: 780-787 [PMID: 21209123 DOI: 10.1136/gut.2010.221127]
- 105 **Lawson MM**, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; **(3)**: CD005112 [PMID: 16856078]
- 106 **Sandborn WJ**, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257-265.e1-3 [PMID: 22062358 DOI: 10.1053/j.gastro.2011.10.032]
- 107 **Peyrin-Biroulet L**, Laclotte C, Roblin X, Bigard MA. Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an open-label study. *World J Gastroenterol* 2007; **13**: 2328-2332 [PMID: 17511032]
- 108 **Oussalah A**, Laclotte C, Chevaux JB, Bensenane M, Babouri A, Serre AA, Boucekkine T, Roblin X, Bigard MA, Peyrin-Biroulet L. Long-term outcome of adalimumab therapy for ulcerative colitis with intolerance or lost response to infliximab: a single-centre experience. *Aliment Pharmacol Ther* 2008; **28**: 966-972 [PMID: 18652603 DOI: 10.1111/j.1365-2036.2008.03811.x]
- 109 **Taxonera C**, Estellés J, Fernández-Blanco I, Merino O, Marín-Jiménez I, Barreiro-de Acosta M, Saro C, García-Sánchez V, Gento E, Bastida G, Gisbert JP, Vera I, Martínez-Montiel P, García-Morán S, Sánchez MC, Mendoza JL. Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. *Aliment Pharmacol Ther* 2011; **33**: 340-348 [PMID: 21133961 DOI: 10.1111/j.1365-2036.2010.04531.x]
- 110 **Armuzzi A**, Biancone L, Daperno M, Coli A, Pugliese D, Annesse V, Aratari A, Ardizzone S, Balestrieri P, Bossa F, Cappello M, Castiglione F, Cicala M, Danese S, D'Inca R, Dulbecco P, Feliciani G, Fries W, Genise S, Gionchetti P, Gozzi S, Kohn A, Lorenzetti R, Milla M, Onali S, Orlando A, Papparella LG, Renna S, Ricci C, Rizzello F, Sostegni R, Guidi L, Papi C. Adalimumab in active ulcerative colitis: a "real-life" observational study. *Dig Liver Dis* 2013; **45**: 738-743 [PMID: 23683530 DOI: 10.1016/j.dld.2013.03.018]
- 111 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Hibi T, Rutgeerts P. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 85-95; quiz e14-15 [PMID: 23735746 DOI: 10.1053/j.gastro.2013.05.048]
- 112 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Rutgeerts P. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 96-109.e1 [PMID: 23770005 DOI: 10.1053/j.gastro.2013.06.010]
- 113 **Järnerot G**, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilien M, Ström M, Danielsson A, Verbaan H, Hellström PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005; **128**: 1805-1811 [PMID: 15940615]
- 114 **Kohn A**, Daperno M, Armuzzi A, Cappello M, Biancone L, Orlando A, Viscido A, Annesse V, Riegler G, Meucci G, Marrollo M, Sostegni R, Gasbarrini A, Peralta S, Prantera C. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther* 2007; **26**: 747-756 [PMID: 17697208]
- 115 **Sands BE**, Tremaine WJ, Sandborn WJ, Rutgeerts PJ, Hanauer SB, Mayer L, Targan SR, Podolsky DK. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. *Inflamm Bowel Dis* 2001; **7**: 83-88 [PMID: 11383595]
- 116 **Lees CW**, Heys D, Ho GT, Noble CL, Shand AG, Mowat C, Boulton-Jones R, Williams A, Church N, Satsangi J, Arnott ID. A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2007; **26**: 411-419 [PMID: 17635376]
- 117 **Gustavsson A**, Järnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilien M, Ström M, Verbaan H, Hellström PM, Magnuson A, Halfvarson J, Tysk C. Clinical trial: colectomy after rescue therapy in ulcerative colitis - 3-year follow-up of the Swedish-Danish controlled infliximab study. *Aliment Pharmacol Ther* 2010; **32**: 984-989 [PMID: 20937043 DOI: 10.1111/j.1365-2036.2010.04435.x]
- 118 **Ehteshami-Afshar S**, Nikfar S, Rezaie A, Abdollahi M. A systematic review and meta-analysis of the effects of infliximab on the rate of colectomy and post-operative complications in patients with inflammatory bowel disease. *Arch Med Sci* 2011; **7**: 1000-1012 [PMID: 22328883 DOI: 10.5114/aoms.2011.26612]
- 119 **Sjöberg M**, Walch A, Meshkat M, Gustavsson A, Järnerot G, Vogelsang H, Hertervig E, Novacek G, Friis-Liby I, Blomquist L, Angelberger S, Karlen P, Grännö C, Vilien M, Ström M, Verbaan H, Hellström PM, Dejacó C, Magnuson A, Halfvarson J, Reinisch W, Tysk C. Infliximab or cyclosporine as rescue therapy in hospitalized patients with steroid-refractory ulcerative colitis: a retrospective observational study. *Inflamm Bowel Dis* 2012; **18**: 212-218 [PMID: 21438096 DOI: 10.1002/ibd.21680]
- 120 **Mocciaro F**, Renna S, Orlando A, Rizzuto G, Sinagra E, Orlando E, Cottone M. Cyclosporine or infliximab as rescue therapy in severe refractory ulcerative colitis: early and long-term data from a retrospective observational study. *J Crohns Colitis* 2012; **6**: 681-686 [PMID: 22398101 DOI: 10.1016/j.crohns.2011.11.021]
- 121 **Laharie D**, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, Zerbib F, Savoye G, Nachury M, Moreau J, Delchier JC, Cosnes J, Ricart E, Dewit O, Lopez-Sanroman A, Dupas JL, Carbonnel F, Bommelaer G, Coffin B, Roblin X, Van Assche G, Esteve M, Färkkilä M, Gisbert JP, Marteau P, Nahon S, de Vos M, Franchimont D, Mary JY, Colombel JF, Lémann M. Cyclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet* 2012; **380**: 1909-1915 [PMID: 23063316 DOI: 10.1016/S0140-6736(12)61084-8]
- 122 **Fasanmade AA**, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther* 2010; **48**: 297-308 [PMID: 20420786]
- 123 **Seow CH**, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut* 2010; **59**: 49-54 [PMID: 19651627 DOI: 10.1136/gut.2009.183095]
- 124 **Reinisch W**, Feagan BG, Rutgeerts PJ, Adedokun O J, Cornillie F J, Diamond R, Marano CW, Sandborn WJ. Infliximab

- concentration and clinical outcome in patients with ulcerative colitis. *Gastroenterology* 2012; **142**: 5, S-114 [DOI: 10.1016/S0016-5085(12)60431-4]
- 125 **Panaccione R**, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, van Hoogstraten HJ, Chen AC, Zheng H, Danese S, Rutgeerts P. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014; **146**: 392-400.e3 [PMID: 24512909]
- 126 **Shale M**, Kanfer E, Panaccione R, Ghosh S. Hepatosplenic T cell lymphoma in inflammatory bowel disease. *Gut* 2008; **57**: 1639-1641 [PMID: 18667489 DOI: 10.1136/gut.2008.163279]
- 127 **Ochenrider MG**, Patterson DJ, Aboulafia DM. Hepatosplenic T-cell lymphoma in a young man with Crohn's disease: case report and literature review. *Clin Lymphoma Myeloma Leuk* 2010; **10**: 144-148 [PMID: 20371449 DOI: 10.3816/CLML.2010.n.021]
- 128 **Beaugerie L**. Immunosuppression-related lymphomas and cancers in IBD: how can they be prevented? *Dig Dis* 2012; **30**: 415-419 [PMID: 22796808 DOI: 10.1159/000338144]

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