Towards therapeutic disease control in inflammatory bowel diseases

Vos, A.C.W.

Chapter two

Early intensive treatment for Crohn's disease

Anne Christine W. Vos and Daniel W. Hommes

Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands

IBD Springer Text Book
Under review

Abstract

During recent years, the treatment for patients with Crohn's disease has changed substantially. With the introduction of anti-TNFα antibodies, the treatment goals have been more ambitious. Today, upon diagnosing Crohn's disease, clinicians are able to use predictors of a complicated disease course and act accordingly when designing an individual medical strategy.

Crohn's disease typically progresses from an inflammatory disease phenotype in the early stage of the disease to a more severe complicated disease phenotype, characterized by fibrosis and stenoses. At this point, the disease is difficult to treat and fibrotic lesions are often irreversible. Therefore, intensive therapy in an early disease stage, within the so-called 'Window of Opportunity', is favorable in patients who are likely to develop a complicated disease phenotype. This disease-modifying strategy is aimed at avoiding late stage disease-related complications and at inducing steroid-free remission as soon as possible. Indeed, with this approach, higher response rates, higher rates of mucosal healing, and a higher percentage of patients achieving steroid-free remission is observed. However, not all patients will need this early intensive approach, and long-term safety is one of the concerns.

In this chapter, we discuss which patients can be selected for an early intervention approach, which safety measures should be undertaken, how patients should be monitored, and how therapy might be de-escalated once remission has been achieved.

Introduction

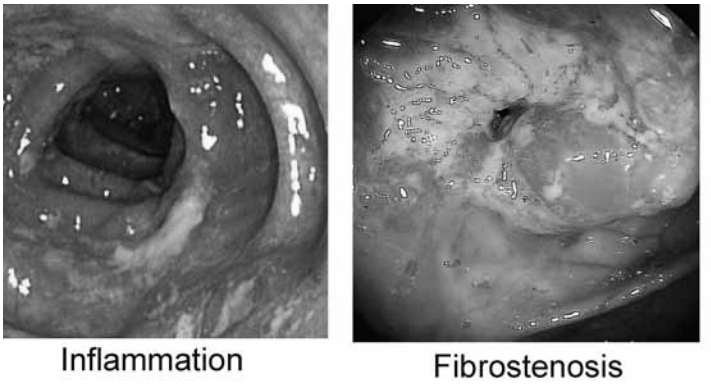
In recent years, the medical care for patients suffering from Crohn's disease (CD) has changed considerably. Nowadays, clinicians are equipped with a robust set of tools, supported by a substantial body of literature, on how to act upon diagnosing Crohn's disease for the first time. There seems general consensus on the diagnostic process, using a full endoscopic work-up in combination with radiologic and histopathologic assessments. [1] Once diagnosed, it is up to the team of IBD health professionals to fully inform and educate the patient and his/her relatives, and to install and monitor a vigorous medical regime.
The main treatment goals are 1) to achieve clinical remission of steroids as soon as possible 2) to achieve endoscopic remission 3) to avoid hospitalization and surgery 4) to improve the quality of life. Indeed, today we are able to monitor the success of each of the treatment goals very effectively: ad 1) monitoring the rate of clinical remission in daily practice can be performed on a week to week basis by, for example, a specialized IBD nurse, using well defined and validated parameters of general well being, abdominal pain, stool frequency, extra intestinal manifestations and general symptoms like fever and weight. More and more, IBD centers are establishing *remote care* delivery systems for monitoring disease activity indices on a regular basis and thus partly allowing self-management. [2] Next to clinical parameters, a defined set of laboratory values like CRP is recommended nowadays for monitoring. In addition, most steroid tapering schedules can be completed within 8 weeks. Intervention is required much sooner than 8 weeks should patients continue to have active disease. Ad 2) the paradigm of mucosal healing has been well accepted upon publication of a large number of studies showing the relevance of endoscopic assessments for the prediction of clinical remission. [3-5] Alternative biomarkers for mucosal healing, for instance fecal calprotectin and fecal lactoferrin, are under development since endoscopy remains an invasive procedure. [6-8] Again, these fecal tests could also be very well for home monitoring of mucosal healing. Ad 3) it has also been shown that induction of clinical and endoscopic remission decreases the number of hospitalizations and surgeries in CD patients. [9] Ad 4) Similar to clinical remission, the quality of life of CD patients dramatically improves upon reaching the previously discussed treatment goals. [4, 10, 11]
In summary, today's physicians are able to act immediately upon diagnosing CD with effective and safe drugs. This chapter clarifies i) why there is this '*Window of Opportunity*' the first years after the diagnosis of CD ii) why intensive treatment (also referred to as Top Down) is superior in selected cases iii) which safety measures should be taken to prevent (serious) adverse events during intense therapy iv) how to optimally monitor patients and lastly v) the possibilities for de-escalating therapy once deep remission is achieved.

Window of opportunity in Crohn's disease

When a patient is diagnosed with CD, it is an important and challenging issue how to optimally treat the patient and at which point a certain therapy should be initiated. In established CD, early disease should be distinguished from late disease, since CD is characterized by progression of inflammatory disease (early disease) to a more complicated stricturing, penetrating and fibrotic disease (late disease). [12] Fibrostenosis and perforations are

not *per se* associated with early CD, usually patients with recently diagnosed CD have pure inflammatory lesions (Figure 1). However, when the disease evolves, the number of complications increases and many patients will develop strictures or fistulae formation. In this stage, complications caused by tissue remodeling and fibrosis following long-standing disease are irreversible and difficult to treat with the anti-inflammatory agents. Often, surgery can't be avoided at this stage. The progression from early to late disease is accompanied by a change in mucosal cytokine profiles. Early CD is characterized by a pronounced Th1 response, whereas in late disease Th2 cytokines are predominating. [13] The concept that mucosal T cell regulation is different in early and late disease, suggests that patients with late disease respond different to therapies. Indeed, superior therapy efficacy is observed in patients with newly diagnosed CD compared to patients with a longer disease duration. [14-17] The progression from early to complicated late disease course has also been reported in rheumatoid arthritis (RA). [18, 19] In RA patients, therapy is aimed at preventing late disease when complications and bone destruction are irreversible. In this light, intervening in an early stage of the disease has proven to be very effective and superior to treatment in a late disease stage. [19-21]

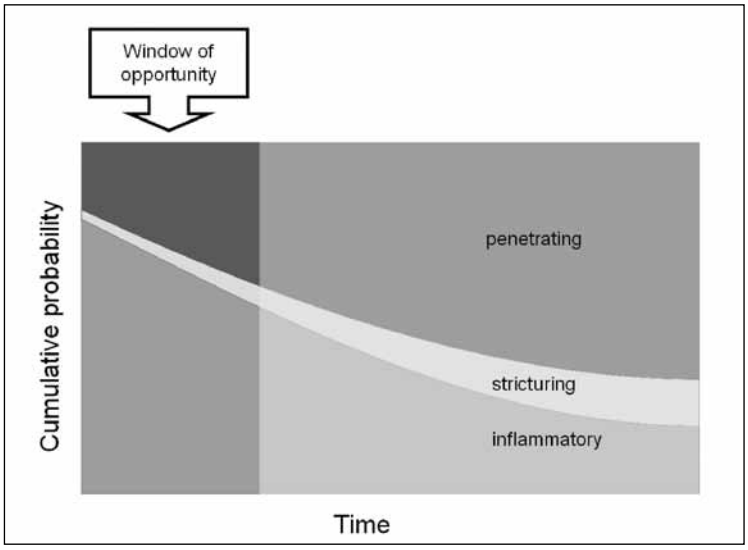
Figure 1 Inflammation (left panel) and fibrostenosis (right panel).



C

The fact that disease progresses to complicated disease suggests that there is a particular time window at which therapy is most effective and favorable. In order to prevent progression to a complicated phenotype, it is of great importance to intervene in an early stage of the disease, the so-called "Window of Opportunity" (Figure 2). At this point, it is most likely still possible to change the course of the disease towards a less aggressive phenotype, to control symptoms, induce mucosal healing and to induce and maintain clinical and endoscopic remission.

Figure 2 Window of opportunity.



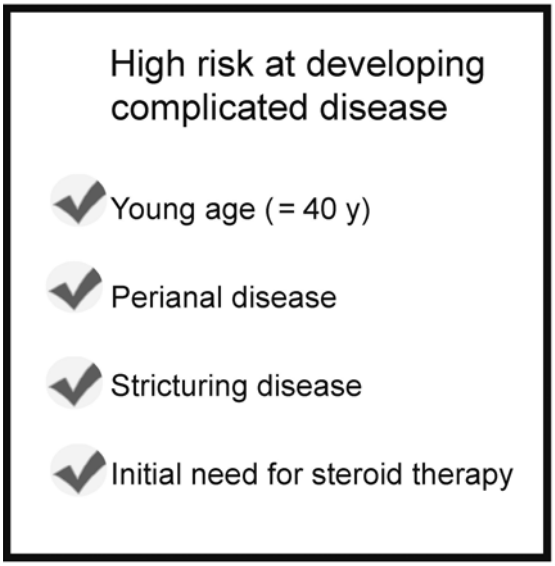
Adapted with permission from Cosnes *et al.* Inflamm Bowel Dis. 2002

Early intensive treatment ("Top-Down")

Selecting patients for early intensive treatment

The window of opportunity is especially important for patients who are likely to develop a disabling disease course. Risk factors that predict a disabling disease course have now been identified and confirmed in several studies (Figure 3). Although "disabling disease" has various definitions in different studies, clinical factors predicting the course of disease have been independently verified. In a retrospective study involving 1188 patients, disabling disease was defined as more than 2 steroid courses, hospitalization, immunomodulators or surgery within the first 5 years of diagnosis. [22] *Young age* at diagnosis, presence of *perianal disease* at diagnosis and initial *need for corticosteroids* were found to be predictive factors for disabling disease. In addition, when 2 of these factors were present at diagnosis, 84% of the patients developed disabling disease within 5 years; when 3 factors were present, 91% developed a disabling disease course. These factors were all independently confirmed in another study. In this study, disabling disease was defined as complex perianal disease, colonic resection, ≥ 2 small bowel resections or a definitive stoma, also within the first 5 years of diagnosis. [23] Using one definition or the other, several factors that are present at diagnosis have been identified and confirmed that predict a disabling disease outcome, including a young age (≤ 40 y), presence of perianal disease, stricturing disease and the initial need for steroid therapy. [22-24] Patients with these symptoms at diagnosis are at high risk for a complicated disease course. Therefore, early intensive treatment in selected patients could prevent the development of complicated disease, and thereby prevent hospitalization and surgery.

Figure 3 Predictive factors at diagnosis for selection of high-risk patient.



Biomarkers predicting disease outcome in CD are currently lacking. Serological- genetic- and immunological factors are being studied and would be helpful to further adequately select patients for a certain therapy strategy. Elevated levels of CRP correlate with more severe clinical, endoscopic and histologic disease. [25] However, CRP did not very well predict milder disease, and some patients with severe disease have normal CRP levels. Consequently, additional markers are needed. Positive anti-Saccharomyces cerevisiae antibody (ASCA) status has been associated with early surgery, [26] ileal disease [27] and poor outcome [28] and might therefore be a useful marker in the selection of patients. In another study, a well defined correlation was found between triple positive status for ASCA, anti-OmpC as well as anti-I2 and small bowel surgery. [29] Furthermore, mutations in NOD2 [30] and CARD15 [31] increase the risk for surgery in patients with pediatric-onset CD.
Large trials should further confirm the value of these markers in predicting disease course. When combining these factors, a profile can be established including phenotypic, genetic and serologic markers to facilitate the selection of patients.

Early intensive strategy in Crohn's disease

The benefit of the disease-modifying strategy has been shown in several studies. The first clues pointing towards the benefit of so-called early intervention strategies in CD, result from retrospective analyses from large randomized, placebo-controlled trials. In a study evaluating the maintenance of response and remission of adalimumab, a clear difference was observed in patients with different disease durations. [32] The rate of patients with remission maintenance at week 26 was 56% in patients with a disease duration less than 2 years, 35% in patients with a disease duration of 2 – 5 years and 37% in patients with a disease duration more than 5 years.

In a prospective, randomized controlled trial, including 130 patients with newly diagnosed CD naïve to corticosteroids, immunomodulators or anti-TNF agents, efficacy of step-up versus top-down therapy was evaluated. [33] The top-down approach involved a *treatment algorithm* starting with infliximab 5 mg/kg at weeks 0, 2 and 6 and azathioprine 2.5 mg/kg/d. Patients randomized to the step-up treatment algorithm were initially treated with corticosteroids (current standard around 1999), followed by azathioprine in case the corticosteroids were not able to control disease activity. Should this combination fail to avoid relapse, infliximab treatment was initiated. The co-primary endpoint in this study was clinical remission off steroids and without surgery at weeks 26 and 52. At both time points, a significant greater proportion of patients in the early combined intervention group met this endpoint compared to the conventional therapy group. At week 26, 39 (60.0%) of 65 patients in the top-down group were in remission without corticosteroids and without surgical resection, compared with 23 (35.9%) of 64 step-up patients, with an absolute difference of 24.1% (95% CI 7.3 - 40.8, $p = 0.0062$). Corresponding rates at week 52 were 40/65 (61.5%) and 27/64 (42.2%) (absolute difference 19.3%, 95% CI 2.4 - 36.3, $p = 0.0278$). Furthermore, after two years, mucosal healing was observed in 73% of the patients in the early intervention group, whereas mucosal healing was seen in only 30% of the patients in the conventional treatment group. Importantly, 19% of the patients in the step-up group were still on steroids at this time point, whereas 0% of the patients in the early intervention group were receiving steroids. Also, it has been shown that complete mucosal healing in patients with early-stage Crohn's disease is associated with significantly higher steroid-free remission rates 4 years after therapy began. [3] Complete mucosal healing, defined as a Simple Endoscopic Score of 0 after 2 years of therapy, was the only factor that predicted sustained, steroid-free remission 3 and 4 years after therapy was initiated; it was observed in 17 of 24 patients (70.8%) vs 6 of 22 patients with lesions detected by endoscopy (27.3%, Simple Endoscopic Score >0) ($p = 0.036$; odds ratio = 4.352; 95% confidence interval, 1.10-17.220). Fifteen of 17 patients with mucosal healing at year 2 maintained in remission without further infliximab infusions during years 3 and 4 ($p = 0.032$; odds ratio = 4.883; 95% confidence interval, 1.144 - 20.844). Finally, in this step-up versus top-down study, the number of side effects did not differ significantly between the two groups. Obviously, remission rates in the two groups did not differ significantly after 1 year since the two treatment algorithms were both designed to control disease, and allowed intensification when disease activity persisted.

Effective early intervention has also been reported in children. Twenty-nine patients receiving infliximab in either step-up (11 patients) or top-down (18 patients) regimen where evaluated 8 weeks after initiation of treatment. [34] Remission was achieved in 3/11 patients in the step-up group and in 15/18 in the top-down group. In the top-down group, significant improvement was observed in PCDAI score and perianal fistula status. Furthermore, in a retrospective study of 36 pediatric CD patients, [35] relapse rate after 24 months was significantly lower in the early intervention group than in the conventional therapy group.

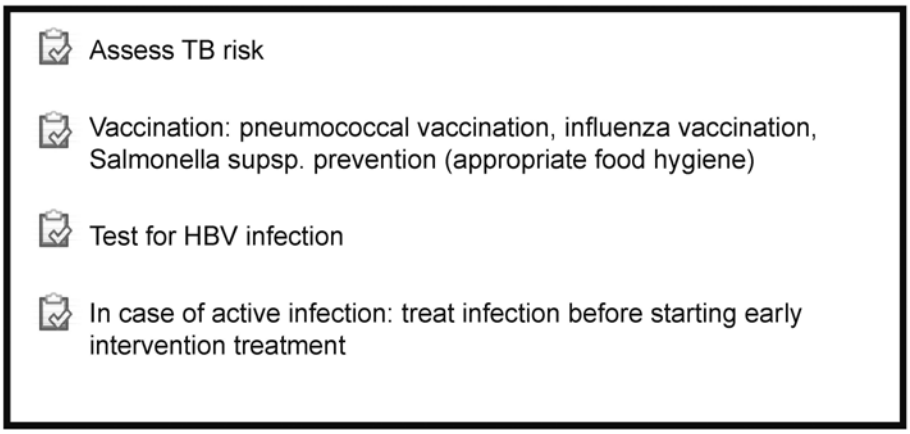
Finally, the SONIC trial evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy, and the two drugs combined in 508 adults with moderate-to-severe Crohn's disease who had not undergone previous immunosuppressive or biologic therapy. [15] Patients were randomly assigned to receive an intravenous infusion of 5 mg of infliximab per kilogram of body weight at weeks 0, 2, and 6 and then every 8 weeks plus daily oral placebo capsules; 2.5 mg of oral azathioprine per kilogram daily plus a placebo infusion on the standard

schedule; or combination therapy with the two drugs. Of the 169 patients receiving combination therapy, 96 (56.8%) were in corticosteroid-free clinical remission at week 26 (the primary end point), as compared with 75 of 169 patients (44.4%) receiving infliximab alone ($p = 0.02$) and 51 of 170 patients (30.0%) receiving azathioprine alone ($p < 0.001$ for the comparison with combination therapy and $p = 0.006$ for the comparison with infliximab). Similar numerical trends were found at week 50. At week 26, mucosal healing had occurred in 47 of 107 patients (43.9%) receiving combination therapy, as compared with 28 of 93 patients (30.1%) receiving infliximab ($p = 0.06$) and 18 of 109 patients (16.5%) receiving azathioprine ($p < 0.001$ for the comparison with combination therapy and $p = 0.02$ for the comparison with infliximab). Thus, infliximab plus azathioprine was shown to be the superior combination for inducing remission.
In conclusion, early intensive treatment, consisting of the combination of a thiopurine with an anti-TNF, should be considered in *all* patients who have a high risk for a complicated disease course, i.e. young age at diagnosis, presentation with peri-anal or stricturing disease, or initial needs of steroids.

Safety measures for early intensive treatment

An important issue related to early intensive treatment is the safety of long-term use of biologics and immunomodulators. Patients are exposed to potentially toxic agents, and therefore appropriate safety measures should be undertaken before immunomodulators and biologicals are initiated (Figure 4). Safety measures are aimed at prevention of infections and awareness of several rare complications.
It appears that patients treated with immunomodulators have an increased risk for influenza infections, pneumococcal infections, and *Salmonella* supp. infections. [36] Therefore, influenza vaccination, pneumococcal vaccination and appropriate food hygiene (avoiding raw eggs, unpasteurized milk, raw meet) is recommended. Also, reactivation of latent HBV is considered a serious risk, and therefore all IBD patients should be tested to exclude HBV. [36] Patients with active chronic infection should be treated according to standard antiviral therapy. Nucleoside/nucleotide analogues are preferred since IFN therapy might exacerbate the colitis. Seronegative patients should receive HBV vaccination, patients might need a higher dose of immunizing antigen since vaccination efficacy is affected by the number of immunomodulators.
Screening for cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Herpes simplex virus (HSV) before starting immunomodulator therapy is not recommended. In case of severe EBV infection, immunomodulator therapy should be discontinued. Latent subclinical CMV infection is also no contra-indication for starting immunomodulators. However, CMV colitis should be excluded in refractory IBD cases and in case of systemic CMV, immunomodulator therapy should be discontinued. [36]

Figure 4 Safety measures.



Anti-TNF use is associated with an approximately 21-fold increased risk of tuberculosis (TB) without appropriate safety measures. [37] The TB incidence has been reported to decrease with 78% when suitable safety measures where undertaken. Most cases are presented during the first three months of treatment and have an atypical presentation, which makes the diagnosis more complicating. [38] For that reason, international guidelines advise to assess the risk of TB before starting treatment with an anti-TNF agent, including an X-ray, tuberculin skin testing (depending on national guidelines) and careful evaluation of the TB history. [36] Latent TB may be suspected in case of a positive initial tuberculin skin test and when the patient has recently been exposed to the disease.

Physicians should be aware of the possibility of false-negative skin tests, especially when patients are immunocompromised. When the patient is diagnosed with latent TB, treatment with the full therapeutic antituberculous regimen should be initiated and it is advised to delay anti-TNF treatment with at least 3 months. The full anti-TB regimen consists of isoniazid (INH) for 6 to 9 months. An association between isoniazid related hepatoxicity and methotrexate and sulphasalazine has been reported in the rheumatology setting, but this is not clear for IBD. When active TB is diagnosed, anti-TNF treatment is ideally delayed until anti-TB treatment is completed. However, solid data on the ideal timing during anti-TB treatment are lacking and in case of medical urgency, physicians may consider to start anti-TNF therapy despite positive TB diagnosis. Advice from a TB expert is in that case recommended. When TB is diagnosed during anti-TNF treatment, the anti-TNF agent should be discontinued and TB therapy should be started. Anti-TNF therapy can be resumed if needed after 2 months. In any event, supervision of a thoracic physician or infectious disease specialist is advised. 5-ASA, azathioprine, methotrexate and steroids can be continued during anti-TB therapy. All patients should be monitored carefully for signs of cough, fever and weight loss and treating physicians should be aware of uncommon extrapulmonary TB as well as the more common lung disease.

How to optimally monitor patients

1 Disease activity

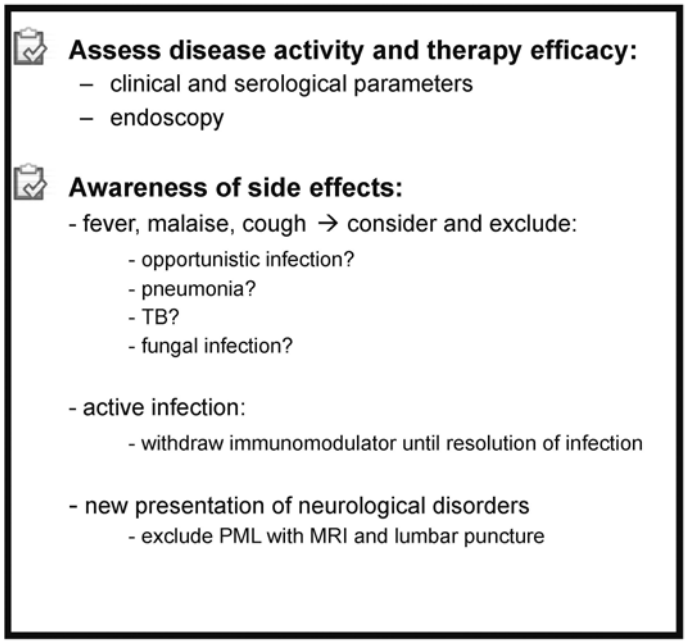
Prior to installing a medical strategy, it is essential to discuss the monitoring scenario with each patient. Monitoring of both disease activity and drug safety is mandatory, irrespective of early- or late stage disease. Although guidelines discuss monitoring practices, the evidence in the literature is currently lacking. Optimally, the clinical monitoring of Crohn's disease activity should be done in a standardized manner using for instance the Crohn's Disease Activity Index (CDAI), the Harvey Bradshaw Index (HBI) or other validated indices. However, for routine clinical practice this is usually not accepted. Using simple Physician Global Assessments is very simple and easy to do, and a reasonable alternative. These clinical assessments are required on a weekly basis once remission induction is initiated, and less often once remission is achieved. In addition to monitoring clinical disease activity, clinicians should also monitor CRP each time a clinical assessment is made. Finally, the correct monitoring strategy of early intensive treatment also involves assessment of mucosal healing. It has been shown that, following surgical remission, Crohn's ulceration can be detected within 3 to 6 months following surgery preceding clinical symptoms. [39] Mucosal healing predicts long-term outcome and is associated with less surgery and hospitalization.[4, 40] In a retrospective study, it has been shown that patients with severe ulcerations at colonoscopy are more likely to have a complicated disease course, [41] and in an ongoing study, a strong association was found between mucosal healing and decreased risk of relapse. [42] Therefore, assessing mucosal healing is a useful tool to predict the course of disease, to monitor disease activity and to further optimize treatment.

Non-invasive fecal markers such as fecal lactoferrin and calprotectin are currently being evaluated for their usefulness to measure disease activity. Increased levels of calprotectin and lactoferrin have been shown to correlate with CDEIS scores [7, 43] and therefore these markers might be useful tools to assess disease activity. In addition, it has been shown that lactoferrin and calprotectin are valuable markers to predict relapse. [44] In patients with high (>150 microgr/gr) calprotectin levels or positive lactoferrin, a higher risk for relapse was observed. The value of lactoferrin and calprotectin as markers for disease activity has also been demonstrated in paediatric disease. [45] However, it has been suggested that these markers may be less valuable in patients with ileal CD, [46] since the disease location might interfere with accurate fecal detection. Future studies are needed to further confirm the value of these markers in daily practice, define clear cut-off values and to finally identify a combination of markers with higher sensitivity and specificity.

2 Side effects

In order to evaluate the risk benefit of the early intensive treatment, a careful monitoring of potential, and sometimes avoidable adverse events is mandatory (Figure 5). Patients on immunosuppressive therapy and with malnutrition are at risk for opportunistic infections. [47] For that reason, patients with fever, cough and systemic illness should be carefully examined. In case of an active infection, it is advised to withdraw immunomodulators until the resolution of infection. In case of persistent fever and when the patient is treated with an anti-TNF agent, *mycobacterium tuberculosis* (TB) should be excluded. Patients diagnosed with pneumonia should be treated with an antibiotic covering *S. pneunomiae*. [36]

Figure 5 Monitoring strategies for patients with early intensive therapy.



Furthermore, about 60 – 80% of the European population has latent JC virus, which can cause progressive multifocal leukoencephalopathy (PML) upon reactivation. Since reactivation of the JC virus is associated with systemic immunosuppression, treating physicians ought to be aware of this rare situation, especially in patients presenting with new onset neurological symptoms, in which case the patient should receive an MRI scan and lumbar puncture.

Studies show divergent data on the occurrence of malignant lymphoma in IBD patients receiving immunomodulators. Whereas some studies do not show an increased risk, other studies do find a moderately elevated risk, especially in patients on thiopurine therapy. [48-50] Still, the absolute risk appears to be low and should be weighed against the beneficial effects of immunomodulator therapy. On the other hand, awareness is advised. Lethal hepatosplenic T cell lymphoma has been reported in young patients on azathioprine/infliximab combination therapy, [51-54] and therefore long-term combination therapy in younger patients is not recommended.

After all, when taking appropriate safety measures, anti-TNF and immunomodulator therapy appears to be relatively safe. Safety data from referral centers and randomized controlled trials do not show an increased risk of malignancies or infections in anti-TNF treated patients. In a large meta-analysis of 21 placebo-controlled trials including 5356 patients, no increased risk of death, serious infection or malignancy compared to controls was reported. [55] In line with this observation, no increased risk was found in infections, mortality or malignancy in 734 anti-TNF treated patients compared to controls, with a median follow-up of 58 months. [11] In addition, no increased risk of malignancy was observed in patients treated

with anti-TNF in a large cohort of CD patients. [56] However, long-term safety data are not available yet and therefore awareness of (serious) side effects is warranted.

Possibilities for de-escalating therapy once remission is achieved

Once remission is achieved, it is important to know if, when and how to de-escalate therapy. Although severe adverse events are rare, especially when appropriate safety measures are undertaken and patients are correctly monitored, they can occur and therefore establishing an individualized risk-benefit ratio is encouraged. The disadvantages of discontinuation of therapy should be taken into account, including relapse, possibly lower response to re-induction therapy, infusion reactions and surgery. Particularly important when considering de-escalation is the earlier pattern of the disease and response to therapies. In addition, several factors may predict relapse, including smoking, previous steroid use and elevated fecal calprotectin and CRP.

Anti-TNF and anti-TNF/azathioprine combination therapy

The question how and when to de-escalate infliximab therapy is of great interest. Trials investigating this matter are currently ongoing, and therefore there is not much data and consensus on this topic yet.

The proportion of patients with infliximab-induced remission that relapsed after discontinuing infliximab was assessed in a prospective single-center study. [57] In this study, infliximab was stopped in patients who were treated with infliximab for at least one year, and who were in steroid-free remission for 6 months. After the median follow up time of 12 months, about 50% of the patients relapsed. On the other hand, 35% of the patients were still doing well up to the end of the follow-up time (nearly 7 years). Therefore, it seems that the patients that are still doing well after 7 years represent a specific group of patients. Age, gender, number of infliximab infusions and disease location were all excluded as predictors for relapse in this study. These results were supported by data from an observational study evaluating the long-term effects of infliximab. [11] In this study, 20% of the patients who experienced a sustained clinical response to infliximab, maintained remission after infliximab discontinuation.

Interim results of the STORI (infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors) showed similar results. [58] In this prospective study, relapse was assessed in patients on combination therapy for more than 1 year and in stable remission for ≥ 6 months after stopping infliximab therapy. About 50% of the patients relapsed within 1 year of discontinuation; patients retreated with infliximab after relapse responded well. In addition, risk factors that predict relapse were detected. A univariate analysis revealed current smoking, previous steroid treatment, lower haemoglobin, higher CDAI, ultrasensitive C reactive protein and faecal calprotectin as predictive markers. In a multivariate analysis, CDEIS ≥ 2, usCRP > 5 mg/dl, haemoglobin ≤ 14.5 g/dl and infliximab trough levels ≥ 2 μg/ml were found to predict relapse. Furthermore, the risk of relapse increased as the number of risk factors increased. [42]

In a study investigating the ability to stop immunosuppressives in patients treated with combination therapy, an enduring response was observed after withdrawal of immunosup-

pressives. [59] Importantly, they reported low infliximab trough levels before immunosuppressive withdrawal as a predictor for surgery. Risk factors for relapse after azathioprine withdrawal in patients treated with infliximab/azathioprine combination therapy were identified in another study. [60] Infliximab/azathioprine exposure duration ≤ 811 days, CRP ≥ 5 mg/L and platelet count ≥ 298 x 10^9 were found to predict infliximab failure, which was defined as disease flare, hypersensitivity reactions leading to infliximab discontinuation or surgery. After 12 and 24 months, resp. 85% and 41% of the patients were infliximab-failure free.
In summary, it appears from these preliminary data that there is a distinct group of patients that does well after de-escalation therapy. It is of great interest to identify the factors that discriminate patients with sustained remission from the patients that relapse, in order to further tailor therapy and to prevent unnecessary side effects. Studies are currently ongoing, and the preliminary data need to be confirmed in large cohorts.

Thiopurines

Furthermore, there are conflicting data with regard to discontinuation of thiopurine therapy once a patient is in remission. In a large randomized, placebo-controlled double blind trial, azathioprine discontinuation was associated with a 50% relapse rate after 54,5 months, regardless of the duration of remission. [61]
In a study evaluating disease recurrence after azathioprine withdrawal, a lower rate of relapse was seen in patients who received azathioprine ≥ 4 years than in patients treated with azathioprine ≤ 4 years. [62]

Concluding remarks

Early intervention therapy in CD is beneficial in selected patients who are likely to develop a severe disease course. Young age at diagnosis, the presence of perianal disease, stricturing disease and the initial need for corticosteroids are factors predicting a complicated disease course. When taking appropriate safety measures, this approach appears to be relatively safe. However, treating physicians should be aware of opportunistic infections and other rare complications, and patients should be monitored carefully on a regular basis. The value of serological, immunologic and genetic markers in monitoring and predicting disease are currently under investigation, and could be helpful to further optimize therapy.

Competing interests: none

Reference List

1. Dignass A, Assche GV, Lindsay JO et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. 4 ed. 2010:28-62.
2. Elkjaer M, Shuhaibar M, Burisch J et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. Gut 2010;59:1652-1661.
3. Baert F, Moortgat L, Van Assche G et al. Mucosal Healing Predicts Sustained Clinical Remission in Patients with Early-Stage Crohn's Disease. Gastroenterology 2010;138(2):463-8.
4. Schnitzler F, Fidder H, Ferrante M et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15(9):1295-301.
5. Geboes K, Rutgeerts P, Opdenakker G et al. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease. Curr Med Res Opin 2005;21:1741-1754.
6. Vieira A, Fang CB, Rolim EG et al. Inflammatory bowel disease activity assessed by fecal calprotectin and lactoferrin: correlation with laboratory parameters, clinical, endoscopic and histological indexes. BMC Res Notes 2009;2:221.
7. Sipponen T, Karkkainen P, Savilahti E et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther 2008;28:1221-1229.
8. Langhorst J, Elsenbruch S, Koelzer J et al. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. Am J Gastroenterol 2008;103:162-169.
9. Feagan BG, Panaccione R, Sandborn WJ et al. Effects of Adalimumab Therapy on Incidence of Hospitalization and Surgery in Crohn's Disease: Results From the CHARM Study. Gastroenterology 2008;135:1493-1499.
10. Bastida G, Nos P, Aguas M et al. The effects of thiopurine therapy on health-related quality of life in Inflammatory Bowel Disease patients. BMC Gastroenterol 2010;10:26.
11. Schnitzler F, Fidder H, Ferrante M et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58:492-500.
12. Cosnes J, Cattan S, Blain A et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis 2002;8:244-250.
13. Kugathasan S, Saubermann LJ, Smith L et al. Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease. Gut 2007;56:1696-1705.
14. Breedveld FC. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthirits Rheum 2006;54(1):26-37.
15. Colombel JF. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr 15;362(15):1383-95
16. Kugathasan S, Werlin SL, Martinez A et al. Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. Am J Gastroenterol 2000;95:3189-3194.
17. Lionetti P, Bronzini F, Salvestrini C et al. Response to infliximab is related to disease duration in paediatric Crohn's disease. Aliment Pharmacol Ther 2003;18:425-431.
18. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol 2003;21:S154-S157.

19. Roberts LJ, Cleland LG, Thomas R et al. Early combination disease modifying antirheumatic drug treatment for rheumatoid arthritis. Med J Aust 2006;184:122-125.
20. Breedveld FC, Emery P, Keystone E et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 2004;63:149-155.
21. Durez P, Malghem J, Nzeusseu TA et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. Arthritis Rheum 2007;56:3919-3927.
22. Beaugerie L, Seksik P, Nion-Larmurier I et al. Predictors of Crohn's disease. Gastroenterology 2006;130:650-656.
23. Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. Scand J Gastroenterol 2008;43:948-954.
24. Lichtenstein GR, Olson A, Travers S et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol 2006;101:1030-1038.
25. Solem CA, Loftus EV, Jr., Tremaine WJ et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:707-712.
26. Forcione DG, Rosen MJ, Kisiel JB et al. Anti-Saccharomyces cerevisiae antibody (ASCA) positivity is associated with increased risk for early surgery in Crohn's disease. Gut 2004;53:1117-1122.
27. Linskens RK, Mallant-Hent RC, Murillo LS et al. Genetic and serological markers to identify phenotypic subgroups in a Dutch Crohn' s disease population. Dig Liver Dis 2004;36:29-34.
28. Kim BC, Park S, Han J et al. Clinical significance of anti-Saccharomyces cerevisiae antibody (ASCA) in Korean patients with Crohn's disease and its relationship to the disease clinical course. Dig Liver Dis 2007;39:610-616.
29. Mow WS, Vasiliauskas EA, Lin YC et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. Gastroenterology 2004;126:414-424.
30. Lacher M, Helmbrecht J, Schroepf S et al. NOD2 mutations predict the risk for surgery in pediatric-onset Crohn's disease. J Pediatr Surg 2010;45:1591-1597.
31. Kugathasan S, Collins N, Maresso K et al. CARD15 gene mutations and risk for early surgery in pediatric-onset Crohn's disease. Clin Gastroenterol Hepatol 2004;2:1003-1009.
32. Colombel JF, Sandborn WJ, Rutgeerts P et al. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. Gastroenterology 2007;132:52-65.
33. D'Haens G, Baert F, van AG et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008;371:660-667.
34. Kim MJ, Lee JS, Lee JH et al. Infliximab therapy in children with Crohn's disease: A one-year evaluation of efficacy comparing 'top-down' and 'step-up' strategies. Acta Paediatr 2010.
35. Lee JS, Lee JH, Lee JH et al. Efficacy of early treatment with infliximab in pediatric Crohn's disease. World J Gastroenterol 2010;16:1776-1781.
36. Rahier JF, Ben-Horin S, Chowers Y. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J. Crohn's and colitis (2009), doi:10.1016/j.chrons.2009.02.010

37. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde Vet al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum 2005;52:1766-1772.
38. Gardam MA, Keystone EC, Menzies R et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003;3:148-155.
39. Rutgeerts P, Geboes K, Vantrappen G et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956-963.
40. Froslie KF, Jahnsen J, Moum BA et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology 2007;133:412-422.
41. Allez M, Lemann M, Bonnet J et al. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol 2002;97:947-953.
42. Louis E, Vernier-Massouille G, Grimaud J. Infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors: a prosepctive ongoing cohort study. Gastroenterology 2009;136:A-146
43. Sipponen T, Savilahti E, Kolho KL et al. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. Inflamm Bowel Dis 2008;14:40-46.
44. Gisbert JP, Bermejo F, Perez-Calle JL et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis 2009;15:1190-1198.
45. Joishy M, Davies I, Ahmed M et al. Fecal calprotectin and lactoferrin as noninvasive markers of pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2009;48:48-54.
46. D'Inca R, Dal PE, Di L et al. Can calprotectin predict relapse risk in inflammatory bowel disease? Am J Gastroenterol 2008;103:2007-2014.
47. Toruner M, Loftus EV, Jr., Harmsen WS et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008;134:929-936.
48. Kandiel A, Fraser AG, Korelitz BI et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005;54:1121-1125.
49. Beaugerie L, Brousse N, Bouvier AM et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. The Lancet 2009;374:1617-1625.
50. Farrell RJ, Ang Y, Kileen P et al. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. Gut 2000;47:514-519.
51. Burger DC, Florin TH. Hepatosplenic T-cell lymphoma following infliximab therapy for Crohn's disease. Med J Aust 2009;190:341-342.
52. Mackey ACR, Green LP, Leptak CM et al. Hepatosplenic T Cell Lymphoma Associated with Infliximab Use in Young Patients Treated for Inflammatory Bowel Disease: Update. [Letter]. Journal of Pediatric Gastroenterology & Nutrition 2009;48:386-388.
53. 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.
54. Shale M, Kanfer E, Panaccione R et al. Hepatosplenic T cell lymphoma in inflammatory bowel disease. Gut 2008;57:1639-1641.

55. Lichtenstein GR, Feagan BG, Cohen RD et al. Serious Infections and Mortality in Association With Therapies for Crohn's Disease: TREAT Registry. Clinical Gastroenterology and Hepatology 2006;4:621-630.
56. Biancone L, Orlando A, Kohn A et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. Gut 2006;55:228-233.
57. Waugh AW, Garg S, Matic K, Gramlich L et al. Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort. Aliment Pharmacol Ther 2010;32:1129-1134.
58. Louis E, Vernier-Massouille G et a;. Infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors: interim analysis of a prospective cohort study. Gut 2008;57:A66
59. Bossuyt PJJ, Juergens M, Ballet V. Discontinuation of immunosuppressives in patients with Crohn's disease treated with scheduled maintenance infliximab: prospective long-term follow-up and influence on infliximab trough levels.Gut 2010;59 (Supll III) A79
60. Oussalah A, Chevaux JB, Fay R. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy. Am J Gastroenterol 2010;105(5):1142-9.
61. Treton X, Bouhnik Y, Mary JY et al. Azathioprine withdrawal in patients with Crohn's disease maintained on prolonged remission: a high risk of relapse. Clin Gastroenterol Hepatol 2009;7:80-85.
62. Pica R, Avallone EV, Cassieri C. Optimal duration of maintenance treatment with azathioprine in patients with inflammatory bowel disease. Gut 2010;59(Suppl III): A38.