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TNF-α blockers in inflammatory bowel diseases: Practical consensus recommendations and a user's guide

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Introduction

More than seventy years after their initial characterisation, the aetiology of inflammatory bowel diseases remains elusive. A recent review evaluating the incidence trends of the last 25 years concluded that an increasing incidence has been observed almost worldwide [1]. A north-south gradient is still found in Europe. Genetic associations are variably reproduced worldwide and indicate a strong impact of environmental factors.

Tumour necrosis factor α (TNF-α) has been shown to play a critical role in the pathogenesis of inflammatory bowel disease (IBD). TNF-α blockers are biological agents that specifically target this key cytokine in the inflammatory process and have become a mainstay in the therapy of inflammatory bowel diseases. This paper reviews the necessary investigations before using such agents, the use of such agents in pregnancy and lactation, the role of co-immunosuppression, how to monitor efficacy and safety, dose-adaptation, and the decision as to when to switch to another TNF-α blocker. Finally it gives recommendations for special situations.

Currently there are three TNF-α blockers available for clinical use in IBD (table 1) in Switzerland: infliximab (Remicade®), adalimumab (Humira®) and certolizumab pegol (Cimzia®) [2]. Infliximab is a chimeric monoclonal antibody composed of a human IgG1 constant region and a murine variable region and is administered intravenously. Adalimumab is a humanised monoclonal antibody, with both human IgG1 constant and variable regions. Certolizumab pegol is a pegylated, humanised monoclonal anti-TNF fragment antigen binding fragment. Both adalimumab and certolizumab pegol are administered by subcutaneous injection.

The efficacy and safety of TNF-α blockers in Crohn's disease has been reviewed [3]. The authors conclude that the three above-mentioned agents are effective in luminal Crohn's disease. In fistulizing Crohn's disease, TNF-α blockers other than infliximab require additional investigation.

Key words: Crohn's disease; ulcerative colitis; infliximab; adalimumab; certolizumab pegol

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Abbreviations

TNF-α	Tumour necrosis factor a
IBD	inflammatory bowel disease
BW	body weight
PEG	polyethylene glycol
NYHA	New York Heart Association
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
MRI	Magnetic resonance imaging
CMV	cytomegalovirus
TB	tuberculosis
INH	isoniazide
HIV	human immunodeficiency virus
anti-HBc Ab	anti-hepatitis B core antibody
ISS	immunosuppressive
HAV	Hepatitis A virus
HPV	human papilloma virus
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRP	C-reactive protein
FDA	Food and Drug Administration

Table 1

Overview of the TNF-α antagonists registered for the treatment of Crohn's disease in Switzerland.

Active substance (trade name)	Mode of use Recommended dosage in IBD (for adults)	Properties and action mechanism	Registered indications
Infliximab (Remicade®)	Intravenous infusion 5 mg/kg BW in weeks 0, 2, and 6, then every 8 weeks (maintenance therapy) or 5 mg/kg on reappearance of the symptoms (repeat treatment)	Chimeric monoclonal antibody to TNF-α	Crohn's disease in adults and children (from 6 years) Ulcerative colitis Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Plaque psoriasis
Adalimumab (Humira®)	Subcutaneous injection 160 mg in week 0, 80 mg in week 2, and then 40 mg every 2 weeks	Human monoclonal antibody to TNF-α	Crohn's disease in adults Rheumatoid arthritis Psoriatic arthritis Plaque psoriasis Ankylosing spondylitis
Certolizumab pegol (Cimzia®)	Subcutaneous injection 400 mg in weeks 0, 2, and 4, then every 4 weeks	PEG*-conjugated Fab fragment of a recombinant, humanised antibody to TNF-α	Crohn's disease in adults

As at: December 2008

Investigations before the use of TNF-α blockers

Medical history (see table 2)

A thorough medical history must be taken before the introduction of a TNF-α blocker as any existing chronic non IBD disease could be exacerbated. NYHA III and IV cardiac failure is a contraindication for TNF-α blocker therapy [4, 5]. Any history of neurological problems must in particular be looked for as case reports of demyelinating neuropathies secondary to the use of a TNF-α blocker have been described in several reports [6]. TNF-α blockers may also be associated with lymphomas and other malignancies, and they should thus be used with caution in patients with a history of neoplasia.

TNF-α blockers are also only indicated when no stricture is suspected as a cause of symptoms.

TNF-α blockers can induce elevation of liver enzymes and reactivate chronic viral hepatitis, with chronic hepatitis B being a major concern since severe flare-ups have been described [7]. In case of doubt, specialist advice should be sought before initiation of TNF-α blocker therapy.

A detailed history of any heart failure, chronic liver disease, neurological disorder and neoplasia is mandatory

Anti-TNF-α agents are contra-indicated in NYHA III or IV cardiac insufficiency and must be used with caution in patients with chronic liver disease, neurological pathology or history of malignancy, especially lymphoma.

Table 2

Indications and contra-indications of anti TNF-α therapy with respect to findings during screening before treatment.

Evaluation	If yes
1. Suspicion of abscess confirmed on MRI	Contra-indicated
2. Flare of colitis	
a. *Clostridium difficile* toxin positive in stools	Contra-indicated
b. CMV infection proven by biopsies	Contra-indicated
3. Cardiac failure NYHA III or IV	Contra-indicated
4. Neurological disease	Use with caution
5. Chronic liver disease	Use with caution
6. History of malignancy	Use with caution
7. Positive interferon-gamma assay for tuberculosis and/or chest X-ray prior to a 4 week-treatment with isoniazid	Contra-indicated
8. Positive HIV uncontrolled disease	Contra-indicated
9. Positive HBV serology	
a. elevated liver enzymes	Start treatment
b. normal liver enzymes	Discuss prophylaxis
c. isolated anti-HBc Ab	Monitoring and booster
10. Negative Varicella zoster virus history and serology	Discuss vaccine
11. Recurrent urinary tract infections	Urine analysis
12. Patient has travelled to or lived in a tropical area	Parasites in stools
13. Abnormal complete blood cell count or CRP	Further evaluations
14. Abnormal transaminases levels	Further evaluations
15. Women: gynaecological examination >1 year	Obtain exam

Screening for infections, blood tests, urine and stool analysis

Active infections may be exacerbated and quiescent infections activated during TNF-α blocker therapy [8] and patients should therefore be screened for infections before starting treatment. Screening tests can be applied either to all patients or be individualised according to their medical history.

If a patient has a suspected abscess, an MRI is indicated [9]. In presence of a relapse of colitis, a superinfection with *Clostridium difficile* or CMV must be ruled out. Patients with a history of recurrent urinary tract infections should have a urine culture [10].

Potential reactivation of granulomatous diseases, in which host defences are predominantly macrophage-dependent, is of particular concern. Active or latent tuberculosis should be excluded. A tuberculin skin test (Mantoux test) can give false results in patients with IBD as it is negatively affected by immunosuppressant therapy and falsely positive following BCG vaccination [11]. Apart from taking a clinical history, both an *in*

vitro test (T-cell Interferon-γ Releasing Assay-TIGRA-) and a chest X-ray should be performed, since latent TB infections can affect the abdominal and mesenteric area, with the result that a chest X-ray on its own is often not sufficient. TIGRAs are minimally (Quantiferon-TB®Gold) or unaffected (T-SPOT.TB®) by immunosuppressant therapy. A Swiss conference has recommended that both an interferon gamma assay for tuberculosis and a chest X-ray be undertaken [12]. Patients with a positive screening should first be treated for at least 4 weeks with isoniazid before starting TNF-α blocker therapy. After a month of INH treatment for latent TB, anti-TNF-α therapy can be initiated as recommended for all patients.

Moreover endemic mycoses can lead to fatal invasive fungal infections in patients treated with TNF-α antagonists [13].

Results from two studies indicate that anti-TNF-α therapy with infliximab [14] or etanercept [15] may be associated with increased mortality in patients with liver failure due to alcoholic steatohepatitis. Treatment should not be instigated in such patients.

Viral diseases may take a life-threatening course in a patient taking a TNF-α blocker. Case reports of reactivation of chronic hepatitis B have been described. No acute flare-up of hepatitis has been reported in the literature in concomitant chronic hepatitis C [7]. A blood test to rule out an HBV infection should thus be performed. Patients with a positive HBsAg and elevated liver enzymes must receive a specific treatment. In patients with positive HBsAg and normal liver enzymes, a prophylaxis must be discussed and regular monitoring of liver enzymes and HBV-DNA be performed. Patients with a negative serology should be vaccinated. Uncontrolled HIV infection is a contra-indication to TNF-α blocker therapy. Due to enhancement of abnormal Papanicolaou smears and cervical dysplasia, probably in relation with chronic human papilloma virus infection in women taking immunosuppressants for IBD, a gynaecological examination is mandatory before starting TNF-α blocker therapy [16, 17] (table 2).

Before treatment with TNF-α antagonists is initiated, all patients should be checked both for an active and for an inactive (latent) TB infection. This check should include the following steps:

– Detailed medical history
– In-vitro test: Quantiferon-TB® Gold or T-SPOT.TB®

Table 3

Recommendations for vaccinations.

Vaccination	Dose(s)	Schedule	
Maintenance of routine vaccinations			
Diphteria-tetanus vaccine ± pertussis ± inactivated poliomyelitis	1		Maintenance: every 10 years (1 dose) Combined vaccine available
Influenza vaccine	1		Revaccination annually (1 dose)
23-valent pneumococcal vaccine	1		Maintenance: every 5 years (1 dose)
Vaccinations to be discussed before initiating an anti-TNF-α therapy			
Hepatitis B vaccine	3	0, 1 and 6 months	Additional dose(s) if anti-HBs Ab <100
Varicella vaccine	2	0 and 1 months	In patients with negative serology and temporarily off ISS
Tick borne-encephalitis vaccine	3	0, 1 and 6 months	Maintenance every 10 years if continuing residence in endemic area (1 dose)
Human papilloma virus vaccine	3	0, 2 and 6 months	Recommended for women <25 year-old with normal Pap smear
Vaccinations for travellers (depending on risk of exposure)			
Hepatitis A vaccine	2	0 and 6 months	Combined HAV-HBV vaccine available
Typhoid (non oral) vaccine	1		
Poliomyelitis (non oral) vaccine	1		
Japanese encephalitis vaccine	1		
4-valent ACWY meningococcal vac.	1		
Rabies vaccine	3	0, 1 and 4 weeks	
Live vaccines contra-indicated in patients on ISS			
Combined measles-mumps-rubella			
Varicella			
Oral poliomyelitis			
Oral typhoid			
Yellow fever			

Sources: Bundesamt für Gesundheit (BAG) [Swiss Federal Office of Public Health] Richtlinien und Empfehlungen [Guidelines and Recommendations]: Impfungen für Auslandsreisende [Vaccinations for those travelling abroad], version: January 2007; BAG Richtlinien und Empfehlungen [Swiss Federal Office of Public Health Guidelines and Recommendations]: Schweizerischer Impfplan 2008 [Swiss Vaccination Plan 2008], version: January 2008; drug compendia of the relevant vaccines

– Chest X-ray

The following tests must also be carried out:

– HBsAg, anti-HBcAb
– HIV serology
– complete blood cell count
– transaminases

Vaccinations

The recommendations are summarised in table 3.

Vaccines are under used in adult patients with IBD [18] even though it is known that these patients are at higher risk of severe infections. Several studies have shown that patients with a chronic immunological illness treated with immunosuppressants have an adequate antibody response to vaccine administration and do not experience increased clinical activity of the underlying chronic disease as a result of the immune response to immunisation [19–21]. Vaccinations should, however, preferentially be given prior to immunosuppressive (ISS) therapy or in patients with an ISS monotherapy in order to minimise the risk of decreased response. Live vaccines (oral poliomyelitis, oral typhoid, yellow fever and combined measles-mumps-rubella vaccines, see table 3) are contra-indicated in patients taking immunosuppressants, but may be given at least 3 weeks before initiation and ≥3 months after cessation of immunosuppressive therapy or at any time in patients on steroids monotherapy at a daily dose <20 mg [8]. There is currently no data on use of live vaccines in patients on single TNF-α blocker therapy and they are thus contra-indicated on safety grounds.

Regular immunisations in adults include booster doses against diphtheria and tetanus (dT) and, in persons aged 65 or over, vaccination against influenza and pneumococci. Any additional immunisations with inactivated vaccines recommended in specific indications or for at-risk groups should be carried out after consideration of the patient's individual risk and at the doctor's discretion.

Vaccinations against influenza and pneumococci are recommended for at-risk patients of any age and for persons aged 65 years or over. The influenza vaccine must be given annually and the 23-valent pneumococcal vaccine every 5 years in case of continuous immunosuppressive therapy. In women, human papilloma virus (HPV) vaccination should be considered owing to the risk of cervical cancer caused by HPV. Any young woman who is not yet sexually active should be vaccinated before anti-TNF-α therapy is started. In the case of women who have not been vaccinated against HPV as an adolescent, a cervical smear with cytodiagnosis (PAP test) should be carried out each year on account of the risk of HPV infection.

Children must receive the usual scheduled vaccinations and adults the maintenance routine vaccinations against tetanus and diphtheria every 10 years. Some countries propose administering a combined vaccine for diphtheria, tetanus, pertussis and inactivated poliomyelitis due to the increased prevalence of pertussis and frequent influx of tourists.

In naïve patients, a three-dose vaccination against hepatitis B is recommended with evaluation of response (anti-HBs-Ab titer) 1 month after the final injection. Additional vaccine dose(s) may be necessary to obtain an adequate response. A combined HAV-HBV vaccine may be considered [7, 8]. As a severe form of varicella has been described in IBD patients on TNF-α blockers, two doses of varicella zoster vaccine can be considered for patients with a negative history and serology for varicella zoster virus [22]. This is a live attenuated virus vaccine and can thus only be given to patients not under ISS therapy. A tick born-encephalitis vaccine should be proposed every 10 years for patients living in endemic areas [8].

– Vaccinations with live vaccines (see table 3) are contraindicated during treatment with biological agents as with other immunosuppressant therapies. Vaccination with inactivated (killed) vaccines can be carried out during anti-TNF-α therapy.
– Usual scheduled and routine maintenance vaccinations must be given both in paediatric and adult IBD patients.
– Live vaccines are contra-indicated in patients on ISS therapy, except if they are on steroid monotherapy of <20 mg/day.
– Influenza vaccine should be given annually and 23-valent pneumococcal vaccine every 5 years.
– Hepatitis B vaccination should be administered in naive patients. Other vaccinations (Hepatitis A, varicella, human papilloma virus and tick borne-encephalitis) should be proposed to specific patients.

Pregnancy, lactation and contraception

Pregnancy

Infliximab is classified by the Food and Drug Administration (FDA) as a pregnancy class B agent meaning that there has as yet been no documented human toxicity. However, data are limited and come mostly from uncontrolled studies. Mahadevan et al. were the first to report the intentional use of infliximab during pregnancy [23]. Ten women were identified of whom eight received infliximab throughout their pregnancy. All

ten pregnancies ended in a live birth. None of the infants had any congenital malformation or intrauterine growth retardation. None were small considering their gestational age parameters. Three infants were premature and one had low-birth weight. More recently, Schnitzler et al. reported about 20 pregnancies in which infliximab was needed to maintain remission and intentionally continued in the first 2 trimesters [24]. Infliximab was stopped thereafter, given the demonstrated risk of increased maternofoetal transfer of infliximab during the last trimester. No congenital abnormalities were observed in the children. Infliximab was restarted in 14 women immediately after delivery.

Data are also available from a safety registry. Centocor maintains a safety database for all reports of pregnancy. Katz et al. analysed 146 cases with infliximab exposure before pregnancy or after pregnancy was confirmed [25]. Inflximab exposure during pregnancy resulted in outcomes that did not differ from those in the general US population of pregnant women and pregnant women with Crohn's disease not exposed to infliximab. Finally, Vasiliaukas et al measured infliximab levels in the newborn of a mother treated with infliximab [26]. Six weeks after delivery, the breast-fed infant's serum infliximab level was 39.5 ug/mL which is a clinically significant level. Infliximab was not detected in the breast milk. Serial measurements revealed a continued slow decline in the infant's infliximab levels during the following 6 months, despite resumption of breast-feeding.

Adalimumab is also classified by the Food and Drug Administration (FDA) as a pregnancy class B agent. However only case reports have been published on its use in Crohn's disease during pregnancy.

There are no published data regarding certolizumab pegol use in pregnancy.

It should also be kept in mind that there can be an exacerbation of Crohn's disease during pregnancy.

- Women of child-bearing age should be instructed to avoid becoming pregnant during anti-TNF-α therapy by using appropriate methods of contraception. The doctor should weigh the risks and benefits of such therapies during pregnancy and consult expert centres for advice in such cases.
- If, however, administration is necessary to control IBD, the benefits of infliximab seem to outweigh the risks when given during the first two trimesters of pregnancy. Adalimubab is also probably safe during pregnancy.
- Until further evidence is available, infliximab should be stopped during the last trimester of pregnancy.

Anti-TNF-α can be safely restarted after delivery.

How should anti-TNF-α therapy be started? Co-immunosuppression with TNF-α blockers?

The best time to introduce anti-TNF-α therapy remains controversial and only limited data are available [27]. In Switzerland, TNF-α blockers are reimbursed only when conventional therapy such as steroids and/or immunosuppressants has failed. Thus, early aggressive therapy with TNF-α blockers is not recommended in our country. We still feel that, due to the limited long-term safety data, TNF-α blockers should be reserved for patients failing conventional immunosuppression.

When initiating anti-TNF-α therapy, one needs to decide whether existing treatment with steroids or immunomodulators such as 6-mercaptopurine (6-MP), azathioprine (AZA), or methotrexate (MTX) should be continued and combined with the TNF-α blocker or whether it should be stopped. The use of TNF-α blockers is associated with the formation of antibodies against these substances, thus decreasing their efficacy. Baert et al. showed that antibodies against infliximab were detected in 61% of the patients treated episodically with infliximab [28]. The development of these antibodies was associated with an increased risk of infusion reactions and a reduced response to treatment. Concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine or methotrexate reduced the immunogenic response. This observation led to the concept of co-immunosuppression during TNF-α blocker therapy. However, a scheduled maintenance therapy after an induction therapy instead of an episodic treatment is associated with much less immunogenicity, which led to the high levels of anti-infliximab antibodies reported by Baert et al. [28–30].

Recently, rare but fatal, cases of hepatosplenic T cell lymphoma have occurred in young patients co-treated with TNF-α blockers and azathioprine, which suggests that co-immunosuppression may be hazardous, especially in young males [31]. In addition, one trial looked specifically at the withdrawal of immunosuppression in patients with Crohn's disease treated with scheduled maintenance therapy [32]. The conclusion was that continuation of immmunosuppressors for more than 6 months offers no clear benefit over scheduled infliximab monotherapy. The only caveat is that CRP levels were significantly higher and infliximab trough levels significantly lower in the discontinuation group. The impact of these observations on the long-term outcome is still unclear

but needs further evaluation, since in Crohn's disease patients treated with scheduled maintenance infusions of infliximab, the trough serum concentration of infliximab predicts clinical outcome [33]. The significance of the serum trough level has also been shown for adalimumab [34]. In this study, trough levels significantly correlated with clinical response (6.93 for complete versus 5.52 for partial, versus 3.51 for non-responders, p = 0.009). Another study could not find any link between adalimumab trough levels and clinical response [35]. No data currently exist concerning the trough levels for certolizumab pegol.

The SONIC study, presented at UEGW 2008 in Vienna, specifically investigated the role of a concomitant immunomodulator with infliximab in azathioprine naïve patients suffering from Crohn's disease. Patients were randomised to receive azathioprine 2.5 mg/kg + placebo, infliximab 5 mg/kg + placebo or both infliximab and azathioprine. The primary end-point of the study was the steroid-free remission at week 26. 57% of the patients on both drugs were in clinical remission without corticosteroids at week 26 versus 44% in the infliximab alone group and 31% in the azathioprine alone group. This indicates that about 10% of all patients benefit from the combination of both drugs. We feel that the benefit-risk ratio should be carefully evaluated when considering the combination of both drugs. Furthermore the confirmation of this benefit after one year of therapy has not yet been proven. Finally as already mentioned the continuation of immunosuppressants beyond 6 months seems to offer no clear benefit over scheduled infliximab monotherapy.

In contrast another study by Feagan and colleagues demonstrated no additional effect of a combination of infliximab with methotrexate in patients with active CD (also treated with steroids) [36].

Azathioprine and 6 MP

- For patients naïve to azathioprine or 6-mercaptopurine, a monotherapy with TNF-α blockers is recommended; some patients may however, also benefit from combination therapy.
- For patients already treated with a TNF-α blocker and azathioprine or 6-mercaptopurine and in remission (and with normal CRP levels), we generally recommend ceasing azathioprine or 6-mercaptopurine therapy and pursuing monotherapy with the TNF-α blocker.
- Patients not completely in remission with a combined therapy of a TNF-α blocker and azathioprine or 6-mercaptopurine should be discussed with a reference centre.
- An episodic therapy with TNF-α blockers should be avoided

Glucocorticoids

The aim of anti-TNF-α therapy is to reduce steroid ingestion and, if possible, these should be gradually withdrawn entirely. Regular observation is necessary as long as the patient has not achieved remission.

Methotrexate

The combination of methotrexate and infliximab is not more effective than infliximab alone in active CD patients. Therefore, the combination of TNF-α blockers and methotrexate should be avoided.

Efficacy and safety monitoring

Monitoring

The long-term outcome of treatment with infliximab in 614 patients with Crohn's disease has recently been published [37]. Sustained benefit was observed in 63% of patients receiving long-term treatment. The need for hospitalisation, surgery and steroids was decreased especially in the scheduled treatment group.

Patients should be followed up at each injection during the induction phase and then every eight weeks during the maintenance therapy with a TNF-α blocker, not only to allow the physician to evaluate the efficacy and tolerability of the therapy, but also to support patient adherence. In addition to the general monitoring during inflammatory bowel disease, regular checks on the major laboratory parameters are recommended at each patient visit.

The activity of TNF-α against tumours in laboratory models of carcinogensis and potentially in humans raises the possibility that TNF-α blockers might increase the risk of malignancy. Up to now, data on the risks of solid malignancy and lymphomas are conflicting. Long term follow up studies are still needed, however no increased risk for malignancies was observed in the TREAT registry with nearly 15,000 patient-years of follow-up [38]. Another study evaluated the long-term safety of infliximab in patients with IBD treated over a 14-year period and concluded that infliximab has a good overall safety profile [39].

In the largest studies evaluating the efficacy and the safety of adalimumab, certolizumab pegol and infliximab, response was determined as a decrease in CDAI of ≥70 or ≥100 points 6 to 10 weeks after the first induction dose. Clinical and biological evaluation was performed every other week during the first two months in most studies

then every 4 to 8 weeks during the maintenance therapy [5].

Time point for exclusion of non-responders

The Crohn's Disease Activity Index (CDAI) has been used to judge efficacy in clinical trials. A study reviewed the optimal response criteria for the CDAI for induction studies in patients with mildly to moderately active Crohn's disease [40]. They conclude that the efficiency criteria can be improved by using either a decrease in CDAI ≥70 points for the last two consecutive visits, or a decrease in baseline CDAI ≥100 points.

Non-response is defined as a decrease in CDAI of less than 100 points from baseline after a full induction, on an average 6 to 10 weeks after the first injection.

Frequency of efficacy and safety evaluation

On the basis of study designs and in view of the importance of monitoring during the initial phase of treatment with TNF-α blockers, it is recommended that patients be seen every other week during the induction phase (week 0, 2, and 4). Patients should be monitored every two months thereafter for as long as the anti-TNF-α therapy continues, to check efficacy, safety, and adherence.

Method for evaluation of efficacy

Efficacy of a TNF-α blocker therapy is based on clinical signs and symptoms as well as biological parameters (table 4). The aim of treatment is to achieve steroid-free remission. Clinical symptoms evaluated should include frequency of bowel movements per 24 hours, level of pain, general status, possible extra-intestinal symptoms, fever and steroid use. Blood examinations must at least include a full blood count and a marker of inflammation (CRP, ferritin). Until now, only a change in the faecal calprotectin value has been shown to be significant but there is not enough evidence to suggest that it can replace CRP and/or ferritin as a measure of inflammation. Endoscopy is proposed to evaluate mucosal healing, CT scan or MRI to confirm fistula closure (table 4).

The aim of TNF-α blocker therapy is to achieve a steroid-free remission. Complete blood count, CRP, and liver function parameters should be checked at every appointment, i.e. every two months, in all patients being treated with TNF-α antagonists.

Method for evaluation of safety

A recent case control study showed that the odds ratio for opportunistic infections was increased at 4.4 with infliximab use and at 12.9 when ≥2 immunosuppressors were used [41]. The risk of sepsis, malignancies and myelosuppression is much greater if biologicals are administered in combination with another immunosuppressive agent [5]. Patients must be instructed concerning possible adverse effects in order to be able to recognise early symptoms and should have rapid 24/24-hour phone access to a clinical team. In febrile patients, especially those with neutropenia or lymphopenia, a thorough clinical examination is mandatory and additional tests may be required [8].

Regular monitoring is necessary. Abnormal full blood count, renal or liver dysfunction should be ruled out through blood tests. Vaccinations must be kept up to date. In women, a regular gynaecological examination is mandatory to exclude lesions due to a chronic human papilloma virus infection [8, 16, 17].

- Regular biological examinations are necessary.
- Patients should be informed about possible adverse effects.
- Vaccinations should be updated.
- Women should have a regular gynaecological examination.

Preventive attitude in case of travel or holidays

As for every traveller, vaccinations are indicated when staying in high risk areas. Live vaccines (yellow fever, oral typhoid, oral poliomyelitis, combined measles-mumps-rubella vaccines) are contra-indicated in patients taking TNF-α blockers [16]. Patients going to endemic areas should receive either a prophylactic or an early therapeutic treatment against malaria [42]. Patients should carry with them a phone number enabling them to contact a clinical team in case of emergency at any time [8, 18]. Antibiotics such as ciprofloxacine and/or metronidazole may be provided for use in case of suspected superinfected colitis during the holiday period.

- Except for live vaccines, vaccinations and chemoprophylaxis against malaria are identical to those usually recommended.
- Patients should have a rapid 24/24-hour phone number contact in case of emergency.
- Antibiotics may be given to be taken if symptoms develop.

Table 4

Recommendations for general IBD monitoring.

Mandatory	**Clinical examination:**
	Number of bowel movements per day Level of abdominal pain Extra-intestinal symptoms Fever Other medications
	Laboratory: CRP Complete blood count Transaminases
Recommended	**Imaging to be discussed according to clinical symptoms:**
	Endoscopy CT scan or MRI
	Check on vaccination status
	PAP test

Additional safety aspects in case of home therapy

Whilst infliximab is administered by intravenous infusion, adalimumab or certolizumab pegol can be administered by subcutaneous injection. All 3 medications can be provided at home or at a medical practice. Adequate instruction is essential for patients who wish to self administer the TNF-α blocker. The duration of the induction phase corresponds roughly to the time taken by the patient to learn the injection technique and the possible complications. Whatever the case, patients should be monitored regularly.

- Patients with home therapy should have the same frequency of monitoring as patients with an hospital-based therapy.
- Patient education about possible adverse effects and risk of misuse of a TNF-α blocker is crucial.
- A minimal documentation should be communicated to the prescribing physician on a regular basis (e.g. administration) (table 5).
- Self-injection or administration at home can be considered if the patient is in stable remission, although no sooner than the end of the induction phase.

Table 5
Evaluation of efficacy and safety of home care TNF-α blockers.

Infections during the previous week
Number of bowel movements per day
Blood in stools (macroscopic)
Arthralgia
Skin disorders
Vital signs
Reason for possible skipped administration

Dose increase and switch to another TNF-α blocker

Dose-increase

The ACCENT I study has shown that 30% of patients on the 5 mg/kg scheduled treatment had to increase the dose to 10 mg/kg, approximately 90% of whom re-established response, and 26% of patients on the 10 mg/kg scheduled treatment had to increase the dose to 15 mg/kg [43], approximately 80% of whom achieved a response. It has been shown that dose intensification can be achieved with an increase in dose, a decrease in interval or both. Using this definition, Regueiro et al. demonstrated that, 30 months after beginning infliximab, 54% of the patients had a change in their initial dose and/or interval of infliximab administration [44]. Seventy six percent of these patients regain response with dose intensification. The Leuven group also reported their experience of analysing long term treatment with infliximab in 614 consecutive Crohn's disease patients [45]. They defined an intervention as every shortening of the interval between infusions, an increase of the dose of infliximab or a change from episodic to scheduled treatment every 8 weeks. Fifty percent of the patients needed such an intervention. A shortening of the interval became necessary in 108 patients (20%), an increase of the dose in 144 patients (26%) and an increase of the dose plus a reduction of the interval in 21 patients (4%). These interventions were successful since only about one fifth of patients had to stop infliximab treatment due to loss of response.

The benefits of dosage adjustment have also been shown for adalimumab in Crohn's disease [46]. In the CHARM trial, of the 260 patients randomised to receive adalimumab 40 mg every other week, 71 (27%) switched to open-label 40 mg every week for flare or non response. After the dosage adjustment, 45% achieved clinical remission (CDAI ≤150) and 76% obtained clinical response (diminution of at least 70 points in the CDAI score).

Two studies looked specifically at the effect of a re-induction therapy in case of loss of response. Karmiris et al. assessed the benefit of a 3-week course of 80 mg of adalimumab weekly as a rescue therapy for patients who lost response to 40 mg weekly [35]. Among 25 patients, 15 (60%) exhibited clinical response (12 partial and 3 complete). Eleven patients were able to sustain clinical response thereafter (10 stepping down to 40 mg every week and one continuing on 80 mg every week).

Schreiber et al. also evaluated the response to a re-induction with certolizumab 400 mg at weeks 0, 2 and 4 followed by maintenance therapy (400 mg every 4 weeks) in both relapsers of the active arm and patients coming from the placebo arm of the PRECISE 2 study [47]. In the relapsers, the remission rate was 35% at 6 and 12 months after re-induction and in patients coming from the placebo arm 44% after 6 months and 36% after 12 months.

Switch to another TNF-α blocker

A re-induction of response can also be obtained by switching to another TNF-a blocker. In the CHARM trial, 50% of the patients had previously received a TNF-α blocker [48]. The remission rate was 32% and 31% at week 26 and 52 respectively in the TNF-α blocker experienced versus 47% and 42% respectively in the TNF-α blocker naïve patients. In the PRECISE 2 study, 28% of the patients had previously received and discontinued infliximab [49]. More patients responded in the infliximab naïve group than in the infliximab experienced group of patients (69% versus 44%, $p < 0.001$). Two studies looked specifically at patients who were intolerant of infliximab

or had previously responded and then lost response. Sandborn et al looked at the efficacy of adalimumab in this situation [50]. To be included, patients must have been intolerant of infliximab or must have had previously responded to infliximab and then lost response. Patients with moderately to severely active Crohn's disease were randomised to receive either induction doses of adalimubab, 160 mg and 80 mg, at weeks 0 and 2, respectively or placebo at the same time points. Three hundred and one patients completed the trial. At week 4, 34 of 159 patients receiving adalimubab (21%) achieved clinical remission versus 7% in the placebo group. A similar study was done with certolizumab [51] with 539 patients enrolled. At week 6, 62% of the patients achieved response and 39% remission. Results have also been presented on the efficacy of a third anti-TNF-a monoclonal antibody in Crohn's disease after failure of two other anti-TNF-α [52]. A clinical response at week 6 was observed in 29 of 50 patients (58%). One centre reported their retrospective 3-year experience with adalimumab for Crohn's disease with intolerance or lost response to infliximab [53]. They conclude that half of patients maintained clinical response at 130 weeks.

Most clinical studies used a washout period when switching to another TNF-α blocker. The potential toxicity of a combination of TNF-α blockers favours this attitude. However patients who lost response often had low or undetectable serum levels of TNF-α blockers and high disease activity.

- An optimal use of each TNF-α blocker is mandatory.
- In case of loss of response, a dose intensification should be attempted either by an increase in dose, a decrease in interval or both.
- In case of no response to a dose intensification, the practitioner should seek advice from a specialist referral centre, to discuss a switch to another TNF-α blocker.

Recommendations for special cases

Treatment of externally draining fistulas

Once there are no abscesses present and as soon as all external fistulas have been drained, a combination of antibiotics with a TNF-α inhibitor in a standard induction dosage can be considered, depending on the patient's condition.

The anti-TNF-α therapy must be initiated in accordance with the indication, i.e. using a saturation dose for induction and then a dosage specified for the relevant substance in the compendium.

There are no data available on treatment with antibiotics even though these are often used in practice.

If externally draining fistulas are present, it is recommended that an imaging technique (pelvic or abdominal MRI) be used to identify or exclude abscesses. All abscesses should be eliminated before anti-TNF-α therapy is started.

Procedure in cases of liver disease

- If transaminases levels (ASAT, ALAT) are elevated up to 3 to 4 times the normal level prior or during therapy with TNF-α blockers, further investigation is necessary to establish the reason for the abnormal liver function parameters. Anti-TNF-α therapy can, however, be installed or continued. Transaminases levels should thereafter be checked more frequently, at monthly intervals, as long as no improvement is observed.
- If the values for ASAT and/or ALAT are more than 4 times the upper normal value, the anti-TNF-α therapy should be postponed or discontinued. A liver biopsy should be considered.

Closing remarks

Biotechnologically manufactured TNF-α blockers are now firmly established in the treatment regimen of severe active forms of inflammatory bowel disease and are an effective treatment option for patients with IBD who do not respond adequately to conventional therapy with steroids or immunomodulators, and, in many patients, enable the dose of steroids to be reduced.

With biological agents, as with other drug therapies, it is imperative to establish the indication carefully and to take adequate precautionary measures both before and during treatment. The purpose of this text, based on the experience of experts, is to provide gastroenterologists in private practice with relevant information and practical recommendations regarding the use of biological agents. Corresponding consensus recommendations were also prepared by the European Crohn's and Colitis Organisation (ECCO) in 2008, and their publication is expected soon.

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