



REVIEW ARTICLE

A decade of infliximab: The Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease

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Received 20 November 2009; accepted 1 December 2009

KEYWORDS

Infliximab;
Crohn's disease;
Ulcerative colitis;
IBD;
Safety;
Consensus

Abstract

Infliximab (IFX) has tremendously enriched the therapy of inflammatory bowel diseases (IBD) and other immune mediated diseases. Although the efficacy of IFX was undoubtedly proven during the last decade numerous publications have also caused various safety concerns. To summarize the immense information concerning adverse events and safety issues the Austrian Society of Gastroenterology and Hepatology launched this evidence based consensus on the safe use of IFX which covers the following topics: infusion reactions and immunogenicity, skin reactions, opportunistic infections (including tuberculosis), non-opportunistic infections (bacterial and viral), vaccination, neurological complications, hepatotoxicity, congestive heart failure, haematological side effects, intestinal strictures, stenosis and bowel obstruction (SSO), concomitant medication, malignancy and lymphoma, IFX in the elderly and the young, mortality, fertility, pregnancy and breast feeding. To make the vast amount of information practicable for routine application the consensus was finally condensed into a checklist for a safe use of IFX which consists of two parts: issues to be addressed prior to anti-TNF therapy and issues to be addressed during maintenance. Both parts are further divided into obligatory and facultative items. © 2009 European Crohn's and Colitis Organisation. Published by Elsevier B.V.

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1. Introduction

One decade ago the introduction of infliximab (IFX), a monoclonal antibody against TNF- α , has tremendously enriched the therapy of Crohn's disease (CD). It is highly effective in various other immune mediated diseases, mainly rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriasis arthritis and ulcerative colitis (UC). The high prevalence of these diseases and the frequent frustration by conventional therapies have pioneered the broad application of IFX. However, we had to learn early that the other side of the coin were relevant safety issues. Up to now numerous publications have brought elucidating knowledge of how, when and why adverse events can occur. The profound knowledge of these informations is the basis for the safe use of IFX and other biological anti-TNF agents which followed IFX subsequently. This is why the Working Group for Inflammatory Bowel Diseases (IBD) of the Austrian Society of Gastroenterology and Hepatology launched this evidence based consensus on the safe use of anti-TNF therapies. Since most experience exists for IFX the consensus primarily applies to this biological agent. However, some of the evidence concerning safety issues was also adopted from studies using other anti-TNF agents. A few issues were not specifically elaborated within this consensus process but discussed in depth by a recent consensus on opportunistic infections by the European Crohn's and Colitis Organisation (ECCO) and are therefore only mentioned shortly within this paper.¹

This consensus covers a broad spectrum of safety issues. To make the vast amount of information practicable for routine application the consensus statements were condensed into a checklist for a safe use of anti-TNF agents which can be found in Appendix A of this paper. The checklist consists of two parts: part one focuses on issues to be addressed prior to anti-TNF therapy, part two is aimed to monitor safety during maintenance with anti-TNF agents. Both parts consist of obligatory and facultative items.

2. Infusion reactions and immunogenicity

Consensus statement:

Acute infusion reactions occur in 3–27% of patients treated with IFX [EL 2, RG B].

The frequency of infusion reactions is lower during scheduled vs. episodic treatment [EL 1b, RG A].

Routine measurement of antibodies to infliximab (ATIs) is not recommended [EL 5, RG D].

2.1. Infusion reactions and antibodies to infliximab (ATI)

IFX is a monoclonal chimeric antibody comprised of 75% human sequences and 25% murine sequences. Like all exogenous

proteins IFX has the potential to induce immunogenicity partly reflected by the production of so called antibodies to infliximab (ATIs). The relevance of ATI formation concerning safety, namely occurrence of infusion reactions, and loss of efficacy is matter of debate and has most recently been discussed in a thorough review by Cassinotti and Travis.²

The frequency of ATI development during or after IFX administration has been reported with a wide variance. Several reasons are responsible for this variation.² On the one hand the frequency of ATI positivity was found to be higher with episodic treatment vs. scheduled treatment. In the study by Baert et al. 61% of patients had developed ATIs by the fifth episodic infusion, although more than 40% had detectable ATIs even after the first infusion.³ In contrast under scheduled treatment, as reported by the ACCENT 1 trial, ATIs were measurable with a prevalence of 28% in patients after induction with IFX followed by placebo and in 6–9% of patients who received scheduled IFX every 8 weeks.⁴ However, 46% of patients had an inconclusive ATI status. It needs to be mentioned that the presence of IFX interferes with the assessment of ATIs impeding the interpretation of ATI measurements during maintenance treatment.^{2,5} Another factor influencing immunogenicity of IFX is concomitant immunosuppression. In patients who received episodic treatment those under concomitant immunosuppression developed ATIs less often and with lower titers as compared to patients without immunosuppression.^{3,6,7} In analogy reduction of ATI formation during concomitant immunosuppression was also found under scheduled IFX treatment in the ACCENT 1 trial although not confirmed in another study by Maser et al.^{4,8}

The relevance of ATIs with regard to infusion reactions is debatable. Two types of infusion reactions have been described: acute infusion reactions generally occur during or shortly after the infusion of IFX and typically consist of fever, chills, nausea, dyspnoea and headaches and may culminate in anaphylactoid shock. Delayed reactions, characterised by myalgias, arthralgias, fever, rash, pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache may occur 3–12 days after infusion.

Symptoms of an acute infusion reaction resemble the symptoms of an anaphylactic reaction. Nevertheless, these reactions are not true type I hypersensitivity reactions and are better named anaphylactoid infusion reactions for several reasons.^{9–11} First, most of these reactions are usually not IgE-mediated.¹² Second, symptoms of an acute infusion reaction can be managed by reduced infusion rate. Third, serum tryptase levels, usually elevated in type I hypersensitivity, were normal in 20 patients after acute infusion reactions to IFX.⁹ And fourth, acute infusion reactions have been described during the first infusion of IFX without previous exposition to IFX.^{9,11,13}

Infusion reactions are related to the type of treatment (episodic vs. scheduled) and concomitant immunosuppression. During episodic treatment the cumulative prevalence was 27% in the study by Baert et al., with increasing likelihood at each subsequent infusion.³ Colombel reported 3.8% acute infusion

reactions after a median of 3 infusions.¹⁴ In the ACCENT I trial infusion reactions occurred during 6% and 4% under scheduled maintenance with 5 mg/kg and 10 mg/kg, respectively compared to 3% in the placebo group.⁴ It needs to be stressed that infusion reactions led to discontinuation of IFX in only 3% of IFX treated cases. There is only a weak association of ATIs with occurrence of infusion reactions. ATIs were evaluated in 442 patients of the ACCENT 1 trial and were positive in 64 patients (14%). Twenty four of 64 ATI positive patients (37%) had an infusion reaction but so did 42 of 173 ATI negative patients (24%). The positive predictive value of ATIs for infusion reactions was only 36%.

Delayed infusion reactions usually occur 3–12 days after IFX infusion and have a frequency of 1–3%.^{4,9} They resemble symptoms of serum-sickness, a type III hypersensitivity reaction which originally results of tissue deposition of circulating antigen-antibody complexes.^{15,16} However, typical laboratory findings of type III hypersensitivity as presence of immune complexes and complement activation have not been demonstrated in delayed reactions to IFX.⁹

2.2. Management of infusion reactions

Acute infusion reactions are usually easy to manage and rarely lead to discontinuation of therapy [EL 2, RG B]. In case of an acute infusion reaction the infusion has to be stopped and vital signs have to be assessed and monitored [EL 5, RG D]. The management of an acute infusion reaction depends on its severity and can include antihistamines, acetaminophen, steroids, adrenalin and beta-2-sympathomimetics [EL 5, RG D]. Infusion may be resumed with a low infusion rate after normalization of vital signs [EL 2b, RG B]. Premedication should be given prior to subsequent infusions [EL 2b, RG B]. In any case the expected benefit of a subsequent infusion of IFX has to outweigh the risk of a subsequent infusion reaction [EL 5, RG D].

Infusion reactions to IFX are most often easily managed and rarely lead to discontinuation of therapy. Several authors have developed algorithms for the management of infusion reactions which are very similar.^{9,11,17,18} In the case of an acute infusion reaction, the infusion should be stopped (or slowed down in mild cases) followed by antihistamines (diphenhydramine 25–50 mg) and/or acetaminophen (500–650 mg). After normalization of vital signs the infusion may be resumed with an infusion rate of 10 ml/h for 15 min with stepwise increments of infusion rates every 15 min. In severe cases steroids are recommended and in cases of hypotension and wheezing adrenalin should be given immediately.^{9,11} In addition oxygen and beta-2-sympathomimetics may be necessary.

Evidence about the efficacy of premedication before subsequent infusions in patients with a positive history of an infusion reaction is scarce. Jacobstein et al. reported subsequent infusion reactions in 20% of patients with premedication (antihistamines, antipyretics, steroids) and 50% in patients without.¹⁹ Nevertheless, the numbers in this study are very low which is also why there was no statistical significance and detailed information concerning premedica-

tion is also missing. Colombel reported re-treatment of 11 patients after previous infusion reactions of whom 8 developed subsequent reactions despite methylprednisolone, diphenhydramin and paracetamol.¹⁴ Cheifetz et al. reported that subsequent infusions were successfully administered in all patients with previous mild to moderate infusion reactions following a standardised protocol of premedication.⁹ Also after severe reaction retreatment was possible without problems in 2 of 4 patients. Most experts advocate a premedication at least with diphenhydramin and paracetamol and start infusion at a very low rate (10 ml/h) with subsequent increments every 15 min.^{9,11,17,18} Some authors additionally recommend a premedication with steroids (up to 1 mg/kg of prednisolone) at least if the previous infusion reaction was severe. Steroids have a delayed onset of action of at least 15 min which has to be borne in mind when using them in this setting. Duburque et al. reported on the successful induction of tolerance to IFX in patients with CD and prior severe infusion reactions: Each infusion of IFX (5 mg/kg) was divided into 11 escalating 15 min increments over a 3-h time period.¹⁰ In any case the expected benefit of a subsequent infusion of IFX has to outweigh the risk of a subsequent infusion reaction and should be considered in the light of the possibility of a switch to an alternative anti-TNF agent.

Delayed reactions often resolve without treatment although some authors suggest antihistamines and/or paracetamol.^{9,11,18} Steroids may be added if treatment is unsatisfactory.

2.3. Autoantibodies and drug induced lupus

Consensus statement:

Treatment with IFX may be associated with autoimmune phenomena and the development of antinuclear antibodies (ANA) and of antibodies to double-stranded DNA. [EL 3, RG C]

Monitoring of autoantibodies is not currently considered necessary as associations with treatment response, toxicity or autoimmune events are controversial [EL 3 RG C].

Cases of true systemic lupus erythematosus or IFX related eruption in the context of autoimmunity are rare. All cases reported were reversible upon discontinuation of treatment. (EL 4, RG D).

In 35 CD patients with IFX treatment induction of ANA and anti-dsDNA autoantibodies was observed in 53% and 35% of infliximab-treated patients with CD, respectively.²⁰ A single patient who developed ANA and anti-dsDNA autoantibodies showed clinical features consistent with drug-induced lupus. According to the Mayo clinic's experience in 500 CD patients 3 patients developed drug-induced lupus.¹⁴ A literature search for the isolated single-case reports of drug-induced lupus erythematosus (DILE) due to anti-TNF- α agents resulted in 33 cases, which were distributed among IFX ($n=21$), etanercept ($n=10$) and adalimumab ($n=2$). The authors delineate, that TNF- α DILE has significant clinical and laboratory manifestations which distinguish it from DILE due to drugs other than anti-TNF agents and may be difficult to diagnose in patients treated for autoimmune diseases.²¹ Another paper reviewed 105 cases of lupus-like syndrome

through 2008 under anti-TNF treatment.²² Forty five cases occurred under IFX and 90% of cases occurred in patients with rheumatoid arthritis suggesting a subclinical pre-existing overlap between rheumatoid arthritis and lupus.

3. Skin reactions

The spectrum of adverse reactions with dermatological manifestations caused by TNF alpha antagonists subsumed under the term “drug eruption” are strongly dependent on the source of information and the medical discipline (Gastroenterology, Rheumatology, Dermatology) the authors belong to. The different approach explains why it is not easy to compare the frequencies of cutaneous side effects caused by IFX reported in different publications. In addition the clinical diagnosis is only exceptionally verified by histopathology.

3.1. General frequency of skin reactions

Consensus: Skin symptoms are frequent adverse reactions induced by IFX. [EL 1b, RG B].

Recently Fidler et al. presented data of a large single-centre cohort on the long-term safety of infliximab for the therapy of IBD.²³ In 150 of 734 patients (20%) of the IFX group skin eruptions developed. Sixty four patients were referred to the dermatologist due to severity of symptoms. Of these 61% were diagnosed with psoriasiform lesions. Also eczema was frequently diagnosed. The most frequent symptoms were itching and pain. Fifteen percent of patients underwent biopsy revealing three types of lesions: eczema with spongiotic dermatitis; psoriasis with psoriasiform acanthosis; and parakeratosis, dilated capillaries and subcorneal pustule formation. Most cases responded to topical steroids. IFX had to be discontinued in only two patients.

3.2. Exacerbation or *de novo* development of psoriasis

Consensus: Infliximab may induce first manifestation of psoriasis or exacerbation of pre-existing psoriasis [EL 4; RG C].

In mild and moderate cases IFX may be continued or switched to an alternative anti-TNF agent in addition to topical and/or systemic anti-psoriatic therapy [EL 4; RG C]. If this strategy fails discontinuation of TNF alpha antagonist therapy is inevitable [EL 4, RG C].

In 2004 the first reports were published on an interesting because paradoxical side effect of IFX.^{24,25} Although anti-TNF alpha antagonists are used successfully for the treatment of “high-need” plaque psoriasis and psoriatic arthritis some patients who receive anti-TNF therapy for various indications including IBD may develop *de novo* psoriatic skin lesions 1–14 months after initiation.^{26–28} The prevalence ranges between 0.6% and 5.3%.²⁹ Psoriasis may be induced by

IFX, etanercept and adalimumab although half of the 120 cases reported received IFX.³⁰ Pustular psoriasis – frequently on palms and soles – is the most common type of anti-TNF induced psoriasis. Anti-TNF induced psoriasis does not necessarily require discontinuation of anti-TNF therapy. With (mostly topical) anti-psoriatic therapy complete remission was reported in 45% of patients stopping TNF antagonists and 47% in patients continuing TNF antagonists.³⁰ Collemar et al. also reviewed 104 cases of psoriasis induced by different anti-TNF agents from the literature.³¹ Thirty percent of patients had complete resolution and 31% had partial resolution under continued anti-TNF therapy. Further 5% had resolution after change to another anti-TNF compound. Unfortunately it was not specified which substance was the primary or the subsequent anti-TNF agent, respectively. Seventeen percent were discontinued all of which had complete (13%) or partial (4%) resolution. Thus, the majority of patients in these two analyses (with some redundancy) could be kept on anti-TNF therapy. In contrast Rahier et al. reported that switching the anti-TNF antagonist led to recurrence of psoriasis in 16/16 patients.³² The most recent review, compiled of 127 cases (55% under IFX), came to a different result, too:²⁹ in this paper resolution after switch to another anti-TNF agent led to resolution in only 15%, topical steroids led to improvement in 27% and stopping anti-TNF therapy plus systemic therapy led to resolution in 64%.

3.3. Malignancies of the skin

Consensus:

The risk of malignancies of the skin is increased under IFX treatment. [EL3 RG C].

Patients with additional risks for the development of skin malignancies should be referred for skin examinations at baseline and followed up regularly [EL 5RG D]. In patients with a history of malignant melanoma the decision for IFX therapy should be made in conjunction with the dermatologist and the patients should remain under close dermatologic observation [EL5, RG D].

IFX slightly increases the frequency of malignant skin tumours, both malignant melanoma (MM) and non-melanoma skin cancer (NMSC) although true incidences are possibly confounded by concomitant use of phototherapy and other immunosuppressants.^{33–35} In a large observational study among patients with rheumatoid arthritis use of anti-TNF agents was associated with an increased risk of MM (OR 2.3) and NMSC (OR 1.5).³⁶ In IBD Fidler et al. reported 8 NMSC besides 15 “malignancies” (not specified further) per 3775 patient-years in patients receiving IFX and 5 NMSC plus 37 “malignancies” per 6704 patient-years in patients not receiving IFX.²³ There was no significant difference in the total number of “malignancies” in the two groups whereas the number of NMSC seems to be higher among patients with IFX therapy.

Whether IFX has to be stopped after the diagnosis of cutaneous malignancy or if it is contraindicated in patients with a positive history of skin malignancies has not been evaluated so far. Therefore no clear recommendation can be given in this respect. In a recent review Kerblesky and

Gottlieb stated that anti-TNF treatment has not necessarily to be withdrawn.³⁵ The decision has to be made in conjunction with the treating dermatologist and the informed patient. Important factors include type and prognosis of the skin malignancy, complete excision, appropriate management and follow up, as well as a fortunate risk/benefit ratio. A history of excised basalioma is usually no exclusion criterion in clinical trials and thus far should not withhold a routine patient from an effective therapy.

To prevent the development of serious malignant complications of the skin patients with additional risk factors for the development of skin malignancies (high cumulative UV exposure, melanoma precursor lesions, history of photochemotherapy, and history of other immunosuppressive therapies) or with unclear dermatologic conditions should see a dermatologist before starting anti-TNF therapy.

3.4. Infliximab-induced vasculitis

Drug-induced hypersensitivity reactions may present with a wide spectrum of clinical pictures including cutaneous vasculitis.³⁷ The precise rate of these adverse skin reactions is not known at present because in most reports the eruptions are not specified. After marketing, the number of reports on cases of anti-TNF antagonist induced vasculitis is increasing.^{38–42} In a recent review 118 cases have been described, of which 51 occurred under infliximab. Over 90% of these cases occurred in patients with rheumatoid arthritis which is by itself associated with vasculitis.⁴³ Some cases present with typical leucocytoclastic vasculitis, but also urticaria vasculitis and lymphocytic vasculitis have been described. The typical clinical symptoms are painful hemorrhagic nodules which predominantly develop on the lower limbs and appear intermittently. A nationwide survey in France identified 29 cases of vasculitis in patients taking TNF- α antagonists. Antinuclear factor (ANF) was present in 22 patients, hypocomplementemia in 6, and antineutrophil cytoplasmic antibody in 5. However, the relative contributions of TNF-alpha antagonist therapy and of the underlying disease to the development of vasculitis are undetermined.⁴⁴ Systemic glucocorticosteroid therapy is the treatment of choice.³⁹ According to the classification by Pichler lymphocytic vasculitis induced by TNF alpha antagonists would be a type γ reaction (immune/cytokine imbalance syndrome) and not a true type III hypersensitivity reaction.⁴⁵ In patients with severe hypersensitivity reactions and hypersensitivity reactions which regularly relapse and worsen with every new administration anti-TNF therapy should be discontinued.

3.5. Steven Johnson syndrome and toxic epidermal necrolysis

Although rarely, IFX is also reported to induce bullous drug eruptions such as Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).^{13,46,47} SJS presents with an eruption of wide spread atypical target-like lesions whereas typical target lesions are rare. The reaction also involves the mucous membranes (conjunctivae, mucous membrane of mouth and genitals). TEN is a rare but potentially life-threatening complication of IFX therapy. One to two days after start of therapy extended light red macules appear which

may reach erythrodermic dimensions. Finally flabby blisters develop and there is hair loss and loss of nails. Involvement of inner organs (e.g. necrotizing tracheitis, bronchiolitis, esophagitis, glomerulonephritis) is possible. Paradoxically, the pathogenetic mechanism of both, SJS and TEN is characterized by extensive apoptosis of keratinocytes via massive release of TNF- α from cytotoxic T-lymphocytes.³⁷ This is the reason why the number of reports on the successful use of anti-TNF therapy for drug-induced SJS and TEN is increasing.⁴⁸ Thus, SJS and TEN may be both induced by IFX and treated with IFX (unless induced by IFX). If new cutaneous eruptions with mucosal involvement, suggestive for SJS or TEN, occur in the context of IFX therapy, IFX has to be stopped and the patient has to be immediately referred for inpatient management.

3.6. Other cutaneous lesions

Infliximab induced drug eruptions show a broad spectrum of clinical manifestations.⁴⁹

Among these lichenoid exanthems are the most frequently reported.⁵⁰ The interval between start of TNF alpha antagonist therapy and the onset of this adverse reaction is several months. Polygonal-shaped, red blue, confluent papules are the characteristic lesions of this type of delayed type hypersensitivity reactions. The exanthema is both clinically and histopathologically difficult to distinguish from genuine lichen planus.

4. Opportunistic infections

TNF- α antagonists suppress the activity of tumor necrosis factor (TNF)- α , a proinflammatory cytokine that plays an essential role in the human immune response to infection. Not unexpectedly, various infections with opportunistic pathogens including *Mycobacterium tuberculosis*, *Listeria* spp., *Histoplasma capsulatum*, *Coccidioides immitis*, Pneumocystis, and Cytomegalovirus have been observed in association with the use of these anti-TNF agents.

4.1. Tuberculosis

Consensus statement:

The risk of clinical tuberculosis is increased in patients receiving treatment with IFX. Application of official recommendations to prevent reactivation of latent tuberculosis infection reduces the incidence of active tuberculosis disease associated with IFX therapy. [EL 2b RG B] Any patient who is a candidate for IFX therapy must be screened for infection with *Mycobacterium tuberculosis* according to the local guidelines. [EL1b, RG A] Chemoprophylaxis for latent tuberculosis infection should be started before initiation of IFX therapy [EL4, RG D]. During IFX treatment regular monitoring for symptoms suggestive of clinical tuberculosis is recommended [EL4, RG D].

Of foremost concern is reactivation of latent tuberculosis to tuberculosis disease, because tuberculosis has implications on

the health of the patient as well as on public health. According to an estimate of the WHO about one third of the world population is infected with tuberculosis.⁵¹ The risk of active tuberculosis after latent infection is approximately 10% within a lifetime, but is increased in individuals whose immune systems are compromised by disease or drugs.^{52,53} The first case of tuberculosis during treatment with IFX was observed in 1999. Through May 2001, 70 patients who developed active tuberculosis in association with IFX use had been reported.⁵⁴

The frequency of tuberculosis in randomized clinical trials with TNF-blockers was low. In 16 randomized clinical studies on IFX, 3 cases of tuberculosis were reported in 3882 patients receiving IFX, and none were reported in 2430 receiving placebo or comparator control.⁵⁵ Westhovens et al. performed a placebo-controlled trial to assess the safety profile of IFX during one year in 1084 patients with rheumatoid arthritis.⁵⁶ Seven patients developed active tuberculous disease which occurred more frequently at a higher dose (>3 mg/kg). All seven patients had baseline negative tuberculin skin tests (TST) and the majority had extrapulmonary disease.

There are detailed case reports of more than 40 patients who developed tuberculosis during or after anti-TNF therapy e.g.^{57–68} Most of these patients had received IFX for therapy of rheumatoid arthritis but tuberculosis was also reported under etanercept^{69,70} and adalimumab.^{71–73} Based on pharmacovigilance data the incidence of tuberculosis under IFX was estimated between 144 and 173 cases per 100,000 patients – several times higher than the background rate in most European countries.^{74–76} In these pharmacovigilance studies the incidence of tuberculosis may be underestimated since reporting is voluntary. Databases established in the USA and in Europe allow long term follow-up and assess the safety of biologic response modifiers noting relevant adverse events during treatment. In the USA, Wolfe et al. evaluated 10,782 rheumatoid arthritis patients in 1998–1999 prior to the widespread use of IFX, and 6460 IFX-treated patients in 2000–2002.⁷⁷ Prior to the use of IFX the rate of tuberculosis was 6.2 cases per 100,000 patient years, similar to the general US population. In contrast, in IFX exposed patients the rate was 52.5 per 100,000 patients years. An even higher incidence was estimated for Canada.⁷⁸ A Spanish multicenter active-surveillance report estimated an incidence of tuberculosis associated with IFX of 1503 cases per 100,000 patients with rheumatoid arthritis as compared to 95 per 100,000 patients without IFX exposure and 21 cases per 100,000 inhabitants of the Spanish background population.^{79,80} A Swedish population-based registry calculated a 4-fold increased risk of tuberculosis for the use of IFX.⁸¹ Tuberculosis was diagnosed at a medium interval of 12 weeks after the beginning of anti-TNF- α therapy and occurred in the majority of patients within three cycles of treatment, more than half of the patients had extrapulmonary disease and 24% had disseminated disease.⁵⁴ Similar results were found in a British registry⁸² and in a Japanese postmarketing surveillance study which additionally identified the lack of chemoprophylaxis as risk factor tuberculosis.⁸³

Although not studied in detail, the risk for active TB might be increased in patients with IBD that have not been treated with anti-TNF drugs.⁸⁴ Similarly, in patients with rheumatoid arthritis without therapeutic TNF blockade, the incidence of TB was higher than in a control population in most (but not all) studies (see above). IFX increases the background risk of tuberculosis by approximately fivefold in both Crohn's disease

and rheumatoid arthritis.^{85,86} A comparison of AERS data among patients from the US found a significantly higher rate of reported cases with active tuberculosis after administration of IFX than after etanercept. The risk of granulomatous infection was 3,3-fold greater among patients who received IFX than in patients who received etanercept, and the clustering of reports shortly after initiation of IFX treatment likely represents re-activation of latent infection.⁷⁶ Overall, there exist no prospective data that compare rates of tuberculosis between the various anti-TNF drugs. Despite the fact that there may be differences, tuberculosis should be considered a risk with all of these agents.

4.1.1. Practical aspects

Before anti-TNF therapy is initiated, patients need to be screened for latent tuberculosis (LTBI).^{17,86,87} Of foremost importance is a detailed medical history that includes tuberculosis risk factors such as birth or extended residence in a region of high tuberculosis prevalence, previous tuberculosis or tuberculosis treatment, or a history of any of the following: residence in a congregate setting (e.g. prison, homeless shelter, or long-term care facility), substance abuse, health-care employment in centers that treat tuberculosis patients, a positive TST result, and chest radiographic findings consistent with previous tuberculosis.^{88,89} Patients should then be screened with a TST, which relies on a delayed type hypersensitivity response to intradermal inoculation of tuberculin purified protein derivative. Unfortunately, the reliability of the TST is limited. The positive predictive value of the TST in populations at low risk of *M. tuberculosis* infection is less than 50%,⁹⁰ as false positive results may occur in people infected with non-tuberculous mycobacteria, and in recipients of the Bacille Calmette–Guérin (BCG) vaccine, if the vaccine was given after the first year of life.^{75,91} In patients with weakened cellular immunity the TST is more likely to yield false-negative results – a limitation that has particular importance when treating patients with IBD who are frequently immunosuppressed due to medical therapy other than infliximab. In one study, the prevalence of anergy among IBD patients has been reported to amount 71%.⁹⁰ In such patients the TST may fail to detect LTBI, and accordingly, several cases of active tuberculosis occurred in patients who had negative TST results before initiation of anti-TNF therapy.⁵⁶ Thus, a negative test result should be considered suspect. The performance of a booster TST diagnoses 8–14% additional cases of LTBI in patients with IBD and rheuma, and may thus be considered 1–8 weeks after the first negative TST according to national guidelines.^{92–95}

Two new interferon γ release assays (IGRA) target unique proteins that are highly specific of *Mycobacterium tuberculosis* but absent from BCG vaccine. These tests are commercially available (QuantiFERON-TB and ELISPOT) and have been shown to be more sensitive and specific than standard TST in immunocompetent and immunocompromised patients. If available, IGRA can complement the TST and have a preferred role in BCG vaccinated patients.^{96–103}

If clinical suspicion for past exposure to tuberculosis is high, consideration should be given to prophylactic antimicrobial therapy despite negative TST. Chest radiography is widely used to screen patients for tuberculosis before anti-TNF therapy. Chest radiographs are useful in screening for active tubercular disease, but are not useful in screening for LTBI, as most latently infected individuals have normal chest

radiographs.^{88,89} Furthermore, granulomatous lesions seen on chest radiography are nonspecific for LTBI and can result from a variety of infectious and noninfectious diseases. If chest radiography is abnormal, or patients have symptoms raising a suspicion of tuberculosis, they should be thoroughly investigated to exclude active disease. Before exclusion of active tuberculosis, anti-TNF therapy must be withheld. There is evidence to suggest that after implementation of screening and treatment of latent tuberculosis, the incidence of active tuberculosis disease following anti-TNF therapy decreased. In a survey including 6460 IFX-treated RA patients in the US four cases of tuberculosis were found and none of them had received tuberculosis screening before initiation of anti-TNF therapy; among patients who received TST before IFX therapy (about 50% of the cohort), none was diagnosed with active tuberculosis disease.⁷⁷ In addition, Carmona et al. found that after the implementation of official recommendations regarding the management of active tuberculosis in RA patients receiving anti-TNF therapy, rates of active tuberculosis dropped by 83% and reached the rate of RA patients not treated with TNF-blockers.¹⁰⁴

4.1.2. Treatment of LTBI

Before treatment of LTBI is initiated, active tubercular disease must be excluded.

In patients whose clinical or epidemiological circumstances suggest a probability of LTBI, prophylactic antimicrobial therapy despite a negative TST should be considered. Patients diagnosed as having LTBI should receive preventive treatment before TNF-blocking agents are started. Most commonly, treatment with daily isoniazide for 6–9 months is recommended, although therapy may vary according to geographic area or the patient's epidemiological background. For patients who undergo anti-LTBI treatment, the optimal time for commencing TNF-antagonist therapy is undetermined. A conservative approach is to postpone therapy with TNF antagonists until treatment for LTBI is completed; in severe cases anti-TNF therapy may be instituted earlier (e.g. 3 weeks after starting chemoprophylaxis), provided the patient is compliant in taking the prescribed anti-tuberculosis medication. It is important to recognize that no chemoprophylaxis regimen is wholly effective; protective effects of 60% have been reported for therapy with isoniazide for 6 months,¹⁰⁵ and of 50% for rifampicin plus isoniazid for 3 months.⁸⁵ Gastroenterologists treating IBD patients with TNF-blockers are advised to closely collaborate with a specialist tuberculosis physician. Considering that LTBI may remain undetected, and that treatment for LTBI may fail, all patients on anti-TNF therapy must be monitored carefully for symptoms suggestive of clinical tuberculosis.

4.2. Listeriosis

Consensus statement:

Patients treated with IFX are at increased risk of infections with *Listeria monocytogenes* [EL 4, RG C]. Before initiation of IFX patients should be educated to avoid potentially infected foods such as unpasteurized milk products and undercooked meat [EL 5, RG D].

Listeria monocytogenes is a gram-positive intracellular bacterium that is supposed to enter the body by ingestion of certain foods including soft cheeses, unpasteurized milk, undercooked meats and hotdogs. Infection most commonly occurs among newborns, pregnant women, and hosts with compromised immunity and cellular deficits. Usually *L. monocytogenes* causes meningoencephalitis and/or septicemia. Case reports and postlicensure surveillance indicate that *L. monocytogenes* infection is linked to the treatment with IFX.^{106–111} Slifman reviewed the AERS passive monitoring system and identified 15 cases of *L. monocytogenes* infection.¹⁰⁶ Most of the patients were older than 60 years, and received concurrent immunosuppressant drugs during anti-TNF therapy; six of the 15 patients died. If patients treated with anti-TNF drugs present with meningitis or other neurological symptoms they should receive full attention and be investigated intensively (including lumbar puncture). Diagnosis relies on appropriate microbiological culture. In case of infection anti-TNF drugs should be stopped.

4.3. Histoplasmosis

Histoplasma capsulatum is transmitted by inhalation of mycelial fragments and microconidia of the organism after disturbance of contaminated soil. As of September 2002 there were 37 cases of histoplasmosis reported in the AERS data among patients receiving IFX and three with etanercept.⁷⁶ Ten of these cases were evaluated in detail; all patients lived in areas where histoplasmosis is endemic and received concomitant immunosuppressive medications in addition to the anti-TNF therapy.¹¹² Three additional case reports of histoplasmosis associated with IFX therapy were published.^{113–115} The rate of histoplasmosis in US patients following treatment with IFX or etanercept was estimated to be approximately 19:100,000 and 3:100,000, respectively.⁷⁶ Histoplasmosis also occurred after treatment with adalimumab.¹¹⁶

4.4. Other fungal infections

Consensus statement:

During IFX therapy reactivation of granulomatous fungal infections may occur [EL 4, RG C]. Although the incidence of opportunistic fungal infections is very low, physicians should be vigilant while using IFX, especially in areas of high disease prevalence [EL 5, RG D].

Spontaneous cases of other fungal infections in association with IFX therapy have been reported in the literature including *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, *Cryptococcus immitis*, *Sporothrix schenckii*, *Coccidioidomycosis*, and *Nocardia* spp.^{83,117–122}

4.5. *Pneumocystis jiroveci*

Several reports document a temporal relationship between anti-TNF-therapy and infection with *Pneumocystis jiroveci*

(formerly *carinii*), an atypical fungus that has been classified as a protozoan for many years.^{83,123–127} The risk of *Pneumocystis* pneumonia appears to be relatively high in Japan, where in a population of 5000 patients with RA the incidence was 0.4%.⁸³ The median length of time from the first infliximab infusion to the development of pneumonia was 8.5 weeks. Diagnosis is based on the identification of *P. jiroveci* from bronchopulmonary secretions and on polymerase chain reaction test for the organism. Most patients respond to appropriate treatment, but mortality rate may be more than 25%.

Although the level of evidence is low all 22 participants of the ECCO consensus on opportunistic infections agreed to commence chemoprophylaxis with cotrimoxazole in patients under triple immunosuppression including IFX or cyclosporine given the high mortality of *P. jiroveci* infection [EL 4, RG D].¹ It is important to stress that concomitant immunosuppression to IFX should be restricted to the shortest time possible.

5. Non-opportunistic infections

Consensus statement:

The risk for infections in general and the risk of serious infections (need for hospitalisation, parenteral antibiotic treatment) is increased under immunomodulatory therapy including IFX [EL1a, RG B].

Patients should be informed about the risk of infections and instructed to consult a physician or general practitioner when signs of infection occur [EL 5, RG D].

Data concerning the rate of non-opportunistic infections in association with an anti-TNF α agent derive from studies and applications of these substances in patients with rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), mainly Crohn's disease (CD), and patients with psoriasis. Most data are available from RA patients. However, the validity of an extrapolation of data from patients with RA to patients with other diseases like IBD may be limited for several reasons: 1) RA is by itself associated with an increased risk of infections such as pneumonia or joint infections.¹²⁸ 2) Patients with rheumatoid arthritis are on average older than patients with IBD. 3) The standard dose of IFX is almost twice as high in IBD than in RA. 4) Three different anti-TNF agents are licensed for the use in RA for several years now, whereas the main experience for the use in IBD comes from IFX. It cannot be excluded that there are some differences between IFX, adalimumab and etanercept concerning safety issues with regard to infections.

5.1. Bacterial infections

Data concerning the risk of bacterial non-opportunistic infections under anti-TNF therapy are conflicting: A meta-analysis of 9 randomised controlled trials of IFX or adalimumab in RA including 3493 patients allocated to anti-TNF agents and 1512 patients allocated to placebo showed an increased rate of infections under anti-TNF agents (OR 2.0, 95%CI 1.3–3.1).³⁴ In IBD another meta-analysis of 21

randomised controlled trials including 5356 patients with Crohn's disease did not reveal an increased risk for severe infections.¹²⁹ Given that patients included in RCT are usually informed about the risk of and signs for infections and are under thorough observation of specialised physicians with high awareness for infection such data do not reflect real life.

Other data sources draw another picture: Data from the RABBIT registry, which included 346 RA patients under IFX and 601 controls, showed that overall the rate of infections was significantly increased under IFX (21% vs. 6%, $P < 0.0001$).¹³⁰ These results were not supported by British data from the BSRBR which did not show an increased risk of serious infections in RA under anti-TNF agents compared to DMARDs.⁸² However, the rate of respiratory tract infections, as most frequent site of infection, was considerable high in the DMARD group of the BSRBR compared to other studies which carries the risk of a beta-error. Additionally, the comparability of the anti-TNF group and the DMARD group may be biased by the possibility that patients with a high risk for infections may have been more likely to be withheld from an anti-TNF therapy. Interestingly the rate of intracellular bacterial infections and skin and soft tissue infections was increased in the BSRBR registry. Concerning the risk of infection in patients with IBD under anti-TNF therapy several studies have been published. In the study by Ljung et al. 217 patients with IBD received a median of 2.6 infusions.¹³¹ In 41 patients severe adverse events were reported including 11 (5%) infections. Three patients died from an infectious complication. Another series of 500 IBD patients treated with IFX reported 41 infections (8.2%) at least possibly related to IFX.¹⁴ Fifteen patients had serious infections including fatal sepsis ($n=2$) and pneumonia ($n=8$), fatal in 2 cases. The largest registry concerning serious infections in IBD is the TREAT registry including 3179 CD patients who received IFX and 3111 patients receiving other therapies.¹³² Without adjustment for other factors the risk for serious infections was significantly higher in IFX treated patients (1.37 vs. 0.6 per 100 patient years; RR 2.15; 95%CI 1.44–3.21; $P < 0.001$) and these infections mainly occurred within 3 months of IFX exposure. However, when adjusting for confounders (race, moderate-severe CD, disease duration, prednisolone, use of narcotic analgesics) the effect of IFX on serious infections was not significant (OR 0.99; 95%CI 0.64–1.54; $P=0.97$). The study by Lees et al., including 202 patients with IBD with 620 patient years of follow up reported infectious events in 21% of patients and serious infections in 11%.¹³³ When compared to other immunomodulatory agents population based data of 10.622 IBD-patients from British Columbia showed that the risk of serious bacterial infections was not higher under infliximab.¹³⁴

5.1.1. Respiratory tract infections

There are conflicting data whether the risk for pneumonia and other lower respiratory tract infections is increased under anti-TNF therapy. Most of the differences are perhaps due to methodological issues which concern the comparability of IFX groups and control groups in registries as well as the case ascertainment.¹³⁵ As reported by the RABBIT registry the rate of serious and non-serious upper respiratory tract infections, pneumonia and other lower respiratory tract infections excluding tuberculosis was increased under

IFX as compared to conventional DMARDs.¹³⁰ In RA the incidence of pneumonia was 2.4–4.7 times higher under IFX as compared to patients under DMARDs. These data were not confirmed by others.^{82,136}

We have to consider an increased risk of lower respiratory tract infections under IFX. Since the majority of community acquired respiratory tract infections are caused by *pneumococci*, vaccination against *pneumococci* is recommended (see below). The French RATIO registry following 486 patients under anti-TNF treatment reported an increased risk of pneumonia due to *Legionella* species.¹³⁷ There are no data on diphtheria under anti-TNF therapy.

5.1.2. Urinary tract infections

In IBD a urinary tract infection has been reported in 1 of 500 IFX treated patients.¹⁴ Also in RA the risk for urinary tract infections was not significantly increased under anti-TNF treatment (IRR 1.7, 95%CI 0.3–9.0).⁸² The RABBIT registry reported no increased risk of urinary sepsis under anti-TNF therapy.¹³⁰

5.1.3. Skin and soft tissue infections

Lethal sepsis due to skin and soft tissue infections in association with IFX therapy has been reported.^{14,138} The RABBIT registry showed that RA patients under IFX experienced more episodes of erysipelas, furuncle, abscess and paronychia than patients under DMARDs (7.7 vs. 2.6 per 100 patient years, $P=0.0017$).¹³⁰ Also data from the BSRBR showed an incidence risk ratio of 4.3 (95%CI 1,1–17,2) concerning skin and soft tissue infections under anti-TNF α agents. In IBD 6 of 500 patients treated with IFX experienced a skin or soft tissue infection.¹⁴ There are no data on scarlatina under anti-TNF therapy.

5.1.4. Abscess

Consensus statement:

Abscess formation can occur under a therapy with IFX for perianal fistulising CD. The exclusion of abscesses by imaging procedures and sanitation of abscesses by drainage or seton placement must precede the therapy with IFX [EL 2b, RG B].

Fistulas occur in approximately one third of patients with CD and can lead to abscess formation somewhere along the fistulous tract. The efficacy of IFX concerning the healing of fistulas is proven for short term as well as for maintenance.^{139,140} Patients with clinical signs of abscesses at baseline were excluded from both mentioned studies. Development of abscesses was reported in 11% under IFX and 3% under placebo in the study by Present et al. In patients who all received an induction therapy with IFX for fistulising CD development of abscesses was reported in 12% under IFX maintenance and 17% under Placebo maintenance. These abscesses could occur in the induction phase as well as in the early or late maintenance phase and there was no difference between both groups.¹⁴¹ It is known that abscesses occur in a large number of patients with perianal fistulas and can be detected by imaging procedures or surgical exploration under anaesthesia. It has been shown that surgical sanitation of abscesses by incision or seton

placement prior to IFX improves the outcome of these patients and may avoid abscess formation during IFX treatment.^{142–144}

5.1.5. *Clostridium difficile*

The literature concerning *C. difficile* was reviewed in depth for the ECCO consensus on opportunistic infections.¹ The statements (OI 7O–OI 7S) mainly concluded that IBD is a risk factor for *C. difficile* infection, while patients with colonic involvement are particularly susceptible. Need for hospitalisation and mortality are increased by *C. difficile* infections in IBD [EL 2; RG B]. Thus, testing for both *C. difficile* toxins is recommended in every IBD patient with colonic involvement and flare. This item was adopted into our safety-checklist. The therapy consists of metronidazole or vancomycin. The immunomodulation should be stopped if positive. Risk and benefit of continued therapy should be questioned in such patients [EL 5; RG D].

5.1.6. Food hygiene

In the consensus on opportunistic infections the ECCO recommended (statements OI 7G and H) food hygiene (avoiding raw eggs, unpasteurized milk products and insufficiently cooked meat) for the prevention of *Salmonella sp.* infections in patients under immunomodulatory therapy [EL 5, RG D] [1]. Food hygiene is also relevant concerning travel diarrhoea (see ECCO statement OI 8 J) and *Listeria* infections (see above Section 4.2 as well as ECCO statement OI 7 J). The facultative recommendation to instruct a patient about food hygiene before start of anti-TNF therapy was therefore added to our safety-checklist.

5.2. Viral infections

5.2.1. Hepatitis B

Consensus Statement:

IFX therapy can lead to an exacerbation of hepatitis B with fatal hepatic failure [EL4, RG C]. Therefore, all patients must be screened for hepatitis B before initiation of IFX [EL 2b, RG B]. In patients who are HBs-Ag positive viral load should be determined and antiviral treatment should be initiated prior to IFX [EL 4, RG C]. Serum aminotransferases and HBV viral load should be monitored in these patients [EL 4, RG C].

Chronic hepatitis B as indicated by HBs-Ag positivity is found in 2% of patients with Crohn's disease.¹⁴⁵ Immunosuppressive therapy of any type may lead to reactivation of chronic hepatitis B.^{146,147} Acute hepatic failure requiring liver transplantation due to HBV reactivation associated with IFX therapy has been reported.¹⁴⁸ Acute hepatitis due to HBV reactivation occurred between 10 days and 6 months after IFX therapy. Prophylactic administration of lamivudine can prevent reactivation of chronic Hepatitis B due to immunosuppression of other types and indications.^{149–151} In a Spanish study 80 patients with Crohn's disease requiring IFX were assessed for chronic hepatitis B which was found in 3 cases.¹⁵² Two patients with positive HBs-Ag and negative

HBV-DNA at baseline developed acute hepatitis and one of them died due to hepatic failure. The third patient was HBV-DNA positive and received lamivudine 100 mg/d before initiation of IFX therapy. No signs of acute hepatitis occurred and HBV-DNA was cleared. In other cases no relevant increases in AST/ALT and HBV-DNA were noted under concomitant lamivudine therapy of 100 mg/d during anti-TNF treatment.^{153,154} It was also shown that acute hepatitis due to HBV reactivation after IFX could be controlled with lamivudine in one RA patient and one CD patient.^{155,156} The possibility of developing resistance to lamivudine has to be kept in mind.¹⁵⁷

5.2.2. Hepatitis C

Consensus statement:

Treatment with IFX appears to be safe in patients with chronic hepatitis C [EL 3b RG C].

Evidence of chronic hepatitis C infection should be sought in all patients before initiation of IFX. Patients with concomitant HCV infection should be monitored by determination of aminotransferases and HCV viral load [EL 4, RG D].

Up to 6% of patients with IBD have concomitant hepatitis C.¹⁵⁸ The course of chronic hepatitis C under anti-TNF treatment on a regular basis has been evaluated in 24 patients with rheumatoid arthritis (16 retrospectively and 8 prospectively, 21 under etanercept and 3 under IFX).¹⁵⁹ HCV viral load and liver function test were recorded at baseline and followed up at varying times (on average every three months) after initiation of anti-TNF treatment. Neither liver function tests nor viral load changed significantly during follow up. Another study followed 31 RA patients with concomitant HCV under anti-TNF therapy over a median of 22 months and found a significant increase of viral load under anti-TNF therapy in 4 patients; a close monitoring of viral load was therefore recommended.¹⁶⁰ Also several other authors reported cases of patients with either IBD or RA who had concomitant chronic hepatitis C and received anti-TNF treatment (mainly IFX) once or several times.^{153,154,161–164} Based on these reports anti-TNF therapy appears to be relatively safe in patients with chronic hepatitis C. However, since data are limited and the long-term outcome has yet to be evaluated evidence of HCV infection should be sought in patients before anti-TNF therapy and its monitoring of aminotransferases and HCV viral load has to be recommended.^{165,166}

5.2.3. EBV, EBV and lymphoma

Epstein-Barr virus is associated with the occurrence of lymphomas under immunosuppression due to solid organ transplantation.¹⁶⁷ Also in IBD a few cases of lymphomas in association with EBV reactivation under conventional immunosuppression^{168–170} as well as under IFX have been reported.^{171,172} The viral load of EBV increased more than 100-fold in 8 of 21 pediatric patients with CD under infliximab.¹⁷³ Two larger studies did not confirm these data in adult patients with CD.^{174,175} No significant difference in EBV viral load between patients with CD and controls and no significant influence of immunosuppression and IFX on the

viral load was found. Mononucleosis has occasionally been reported but not as a serious adverse event.

5.2.4. Varicella-zoster, measles, rubella

Exacerbation of varicella zoster has been described in some IBD patients after IFX infusion but whether the risk is increased due to IFX cannot be concluded.^{14,176} Three cases of severe primary varicella infections under combined immunosuppression including IFX have been reported and were complicated by visceral affections necessitating intensive care treatment and death due to fulminant hepatic failure.^{177–179} Up to now, there are no data on infections with measles or rubella under anti-TNF therapy.

5.2.5. Herpes simplex

Herpes simplex (HSV) infection during a combined immunosuppression including IFX has been reported.^{180,181} Also one case of HSV infection after solely IFX therapy has been reported by Colombel et al. but not as serious adverse event.¹⁴ Whether the risk of herpes simplex reactivation is higher under IFX as compared to other agents in IBD is unknown. Also no data exist on how to proceed with an anti-TNF therapy during herpes reactivation. It seems rational to postpone the application of IFX until after cutaneous herpetic lesions have healed and to consider antiviral therapy in recurrent HSV reactivation under IFX. This is in agreement with the ECCO consensus on opportunistic infections.

5.2.6. Cytomegalovirus (CMV)

Although regarded as opportunistic infection CMV is mentioned in the section of other viral infections for clearness. In the statement OI 4A of the ECCO consensus on opportunistic infections screening for latent CMV infection was not recommended (EL 2; RG B).¹ Latent or subclinical CMV was not considered a contraindication for immunomodulation [EL 2, RG B]. However, CMV colitis should be excluded (tissue PCR, immunohistochemistry) in cases refractory to immunomodulatory therapy before escalating the therapy [EL 3, RG C]. This has also to be applied to anti-TNF therapy and was therefore adopted into the safety-checklist. In case of severe colitis immunomodulatory therapy should be discontinued and antiviral therapy should be initiated. In systemic CMV infection immunomodulatory therapy must be discontinued [EL2, RG B].

5.2.7. Human immunodeficiency virus (HIV)

ECCO recommended (statement OI 3G) to consider testing for HIV before initiation of immunomodulating therapy due to anecdotal reports of increased risk and severity of HIV related infections [EL 4, RG D].¹ However, immunomodulators were not considered as necessarily being contraindicated in HIV positive patients [EL 4, RG D]. There are some data that anti-TNF therapies have not that detrimental effect in HIV positive patients one would assume.¹⁸² Nevertheless, the physician treating a patient with an anti-TNF agent has to calculate the risk of therapy and has to know if the patient is HIV positive. Therefore, this item was adopted into the safety-checklist.

6. Vaccination

6.1. Live vaccines

Consensus statement:

There are no data on safety and efficacy of live vaccines in patients who receive IFX. In otherwise immunosuppressed individuals live vaccines including oral polio vaccine, vaccinia, bacillus Calmette–Guerin, varicella and live oral typhoid are contraindicated. Therefore these vaccines should also be avoided under IFX therapy and, if considered necessary, be given before initiation of immunomodulatory therapy including IFX. [EL 5, RG D]

Some live vaccines are absolutely contraindicated in solid-organ transplant recipients (oral polio vaccine, vaccinia, bacillus Calmette-Guerin, live oral typhoid).¹⁸³ Oral polio vaccine is also contraindicated in family members of transplant recipients. If these recommendations are also reasonable for patients under anti-TNF treatment has yet to be evaluated. However, since an inactivated polio vaccine is available and has proven safety and efficacy in renal transplant recipients it should be favoured if indicated.¹⁸⁴ Also a killed parenteral Vi polysaccharide vaccine for typhoid fever is available instead of the live attenuated oral Ty21a, but there are no data on its safety and efficacy under anti-TNF therapy.¹⁸⁵ Concerning measles vaccine two small studies were conducted in 31 children who underwent liver transplantation.^{186,187} In patients who received only one vaccine post-transplant 41% had seroconversion and 29% retained protective titers after 6 months, whereas these numbers were 85% and 64%, respectively, in children who received one dose prior to transplantation and one dose after transplantation. Measles vaccination was considered safe in both studies which was also concluded from data of 51 bone marrow transplant recipients of whom half received current immunosuppression.¹⁸⁸ There are no data concerning measles vaccination under anti-TNF therapy.

Severe varicella infection has been reported in relation to IFX therapy but there are no data concerning safety and efficacy of varicella vaccine. In 17 children who underwent kidney transplantation and who received live attenuated varicella vaccine (Oka strain) post transplant protective titers were achieved in 94% after one year.¹⁸⁹ One case of mild post vaccination varicella occurred. Some concerns about varicella vaccination in immunosuppressed individuals have been raised and include the possibility of reactivation of the Oka strain, transmission of vaccine virus to the general population and development of zoster.¹⁸³ The ECCO recommends VZV vaccination in every IBD patient with a negative history for chickenpox, shingles or prior VZV vaccination before initiation of any immunomodulatory therapy (statement OI 4C).¹ Passive immunisation after exposure to varicella or herpes zoster is appropriate in non-immunised, seronegative patients under immunosuppression including IFX.

Rubella vaccination is rarely required in adults except for prevention of rubella in young females. Rubella usually does

not cause severe infection in transplant recipients, however, to prevent congenital rubella syndrome, vaccination might be necessary in some instances. The vaccine has shown safety and efficacy in a combination with mumps and measles vaccine in 31 pediatric liver transplant recipients.¹⁹⁰ There are no data on these vaccines in patients receiving anti-TNF therapy.

6.2. Killed vaccines

Consensus statement:

Killed (inactivated) vaccines against pneumococci and influenza are safe under IFX [EL 2b, RG B]. Both vaccinations are recommended for patients with chronic diseases as well as immunocompromised individuals. Since the risk of infection increases with age all IBD patients over 65 years should undergo vaccination for influenza and pneumococci prior to IFX. Response to some killed vaccines may be reduced under IFX therapy and should therefore precede IFX if possible [EL 2b RG C]. Vaccination against influenza should be repeated yearly under ongoing therapy with IFX.

Safety and efficacy of the 23-valent pneumococcal polysaccharide vaccine was evaluated in 149 patients with RA compared to 47 healthy controls.¹⁹¹ Patients with RA were either treated with anti-TNF agents without methotrexate (IFX $n=27$, etanercept $n=35$), anti-TNF agents with methotrexate (IFX $n=37$, etanercept $n=13$) or methotrexate alone ($n=37$). Vaccination was safe and response to vaccination was higher in patients treated with anti-TNF agents without concomitant methotrexate or methotrexate alone. In another controlled study using a 7-valent pneumococcal vaccine the vaccine was well tolerated but response was altered under anti-TNF therapy; the authors concluded that vaccination should precede anti-TNF therapy.¹⁹²

Trivalent vaccination against influenza was studied in 62 RA patients who received IFX or etanercept alone, in 50 RA patients who received IFX or etanercept in combination with methotrexate, in 37 RA patients receiving methotrexate alone and in 18 healthy controls.¹⁹³ All groups responded well although response was better in patients receiving methotrexate alone as compared to both anti-TNF groups. In a controlled study on influenza vaccination Fomin et al. reported that although the overall response was good in RA the percentage of responders to the Hong Kong antigen was significantly lower as compared to healthy controls¹⁹⁴; there was no difference between anti-TNF agents and other DMARDs regarding response to vaccination. In another two trials evaluating the response to influenza vaccine under adalimumab and infliximab, respectively response was only modestly impaired under anti-TNF therapy.^{195,196} Nevertheless Elkayam et al. demonstrated that the response to influenza vaccination was higher if the vaccine was applied before IFX therapy as compared to patient receiving the vaccine three weeks after IFX administration.¹⁹⁷ Vaccination was well tolerated in all mentioned trials.

7. Neurological complications

Consensus statement:

Treatment with IFX has to be avoided in patients with pre-existing demyelinating diseases such as multiple sclerosis and optic neuritis since it may worsen the disease [EL 4, RG C].

In case of new-onset of neurological and/or visual symptoms IFX therapy has to be stopped and a neurologist and/or ophthalmologist has to be consulted [EL 4, RG C].

The risk of demyelinating diseases in patients with IBD has been investigated in several studies.^{198–202} Most of these studies revealed an increased risk for MS in IBD reported to be up to four-fold. In a retrospective study concurrent cases of IBD and multiple sclerosis (MS) were characterized by mild severity of both diseases.²⁰³ Demyelinating diseases such as MS, optic neuritis (ON), Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and other demyelinating neuropathies have been reported in association with TNF- α antagonist treatment.²⁰⁴ MS is generally believed to be an inflammatory immune-mediated disorder, the pathologic hallmark of which is the demyelinated white-matter plaque in the central nervous system.²⁰⁵ Tumor necrosis factor alpha (TNF- α) is thought to be a potential mediator in this disorder.²⁰⁶ However, anti-TNF- α agents for MS treatment unexpectedly worsened the disease. Negative results were described in two patients with rapidly progressive MS who have been treated with two IFX 10 mg/kg infusions at intervals of two weeks in an open-label phase I trial.²⁰⁷ Although clinical worsening of MS was not reported, the number of gadolinium enhanced brain lesions on MRI increased.

The mechanism by which TNF- α antagonists improve inflammatory diseases such as IBD and RA, but not MS is unknown. It might be explained by the fact that IFX does not seem to be able to cross the blood-brain barrier and neutralize local TNF- α mediated tissue injury, since it was not detected in the cerebrospinal fluid after treatment. Furthermore, IFX could enhance the activation of myelin-specific autoreactive T cells, thereby exacerbating autoimmune demyelinating disease.²⁰⁸ In large trials in patients with IBD treated with IFX^{4,139,140,209–211} 4 cases of neurological complications have been described.^{140,211}

Three safety analyses of large series of IBD patients under IFX revealed one patient with demyelination suggestive of MS, who was reported in detail elsewhere,²¹² out of 500 patients with CD treated with IFX at the Mayo Clinic, one patient with verified MS out of 651 IBD patients of the Danish Crohn Colitis Database treated with IFX (followed for a total of 2009 person-years post-treatment), and 3 cases of confirmed demyelination in IBD patients treated with IFX in Edinburgh covering 620 patient-years of follow-up.^{14,133,201}

Very recently the relative reporting of IFX adverse events to the U.S. Food and Drug Administration (FDA) was assessed with the public release version of the adverse event reporting system (AERS) database by using a disproportional analysis to calculate the empiric Bayes geometric mean and the corresponding 90% confidence intervals (EB05, EB95).²¹³ The data revealed a relationship between IFX treatment and

neuropathy (EB05=3.8). Mohan et al. described 20 cases of demyelinating disease reported to the AERS in association with anti-TNF therapy in patients with inflammatory arthritides.²¹⁴ Two of them had received IFX and 18 had received etanercept. The most common neurological symptoms were paresthesias, visual disturbances, confusion and gait disturbances that developed after a mean of 5 months of therapy (range 1 week–15 months). Partial or complete resolution of symptoms was seen in all patients after drug discontinuation, and one patient demonstrated a positive re-challenge with exacerbation on re-exposure to etanercept.

Optical neuritis (ON) can be caused by a variety of different aetiologies. Acute demyelinating ON is one of the most frequently encountered optic neuropathies and is best known for its association with MS.^{215,216} In the review of Mohan et al. ON was reported to be the second most common presentation of demyelinating disease (8 of 20) including two patients in whom ON was the sole presenting symptom.²¹⁴ In a very recently published review 15 additional cases of isolated ON associated with TNF- α antagonist treatment have been described.²¹⁶ Eight of these patients had received IFX (2 patients with CD and 6 patients with RA), 5 had received etanercept, and 2 patients had received adalimumab.^{217,218} All patients but one received steroids as treatment for ON. Eleven patients experienced complete or partial resolution. Several additional cases of MS or ON in patients with IBD while on IFX therapy have been described in the literature.^{212,219–222}

The evidence that the described neurological complications are associated with IFX treatment is based on the temporal relationship between treatment and onset of neurological symptoms, on the improvement after IFX was stopped and, additionally, the positive re-challenge in some cases.^{214,223,224} Thus, patients under IFX treatment should be monitored for neurological symptoms. Data on other neurological adverse events are sparse. Seizures seem to be very rare under IFX treatment without evidence of causal relationship.²⁰⁴ Furthermore, in a large cohort of patients with juvenile idiopathic arthritis 17 neuropsychiatric adverse events occurred under 81 IFX treatments, including psychoses (2), depression (2), anxiety (2), and nervousness (4).²²⁵

8. Hepatotoxicity

Consensus statement:

In patients with clinically significant liver disease IFX therapy may be considered in selected cases [EL 5, RG D]. Treatment with IFX should be avoided or discontinued in patients with transaminases more than three times the upper limit of normal [EL 5, RG D]. Liver function tests should be determined prior to IFX treatment, after induction treatment, and at least every 4 months while on IFX maintenance treatment. [EL 5, RG D]

Abnormal hepatic biochemistries (defined by any elevation of serum aspartate aminotransferase, alanine aminotransferase and/or alkaline phosphatase above the upper limit of normal) can be found in nearly one-third of IBD patients regardless of disease activity.²²⁶ Hepatic adverse events in patients while on IFX treatment include elevated

transaminases, jaundice, cholestasis, autoimmune hepatitis and acute liver failure. However, severe hepatic adverse events in patients with IBD are very rare. In clinical trials hypertransaminasaemia was observed in a greater proportion of patients receiving IFX than those receiving placebo.^{4,140,211,227–232} Usually the patients with elevated transaminases were asymptomatic and the increased liver function tests decreased or normalised regardless of whether IFX was continued or not. Elevations of alanine aminotransferase (ALT) were observed in 44% of CD patients (placebo 38%) and in 19% of UC patients (placebo 12%) under infliximab therapy. Most of the elevations were mild and in only up to 2% $\geq 5 \times$ the upper limit of normal. Two CD patients receiving IFX in clinical trials developed markedly elevated transaminases and were diagnosed with acute hepatitis possibly related to IFX.²²⁷ Data available from the TREAT-Registry suggested a potential of IFX for liver toxicity since hepatic enzyme abnormalities were reported in 1.05 per 100 patient-years in IFX-exposed patients and 0.69 events per 100 patient-years in patients not exposed to IFX.¹³² However, this could not be confirmed in a recently performed assessment of the relative reporting of IFX adverse events to the U.S. Food and Drug Administration (FDA) (public release version of the adverse event reporting system (AERS) database) using a disproportionality analysis²¹³: A relationship between IFX treatment and hepatitis was not observed.

A review of voluntary post-marketing data (576,000 patients with over 1.3 million patient-years of exposure) identified 31 cases of severe hepatic reactions until 2004, including 5 patients with acute liver failure.²²⁷ Two of them died and 3 requiring liver transplantation. Seven of these 31 cases occurred in CD patients, including one death and one liver transplantation. Most of these cases are confounded by hepatotoxic concomitant medications and serious comorbid diseases making it difficult to establish a causal relationship between IFX and these hepatic adverse events. Furthermore, several hepatic adverse events under IFX treatment have been published as case reports.^{233–240} These reports included 3 cases of autoimmune hepatitis in patients with chronic arthritis/spondylitis with resolution of transaminases under steroid treatment.^{233,237,239} Two case reports described cholestatic liver injury in women with CD and UC, respectively, after a single infusion of IFX.^{234,235} Other case reports run from courses of acute hepatitis (including one patient with Crohn's disease) with complete normalization of liver tests^{238,240} to cases of severe liver dysfunction.^{236,237} These included a 39-year-old female patient with RA who developed severe cholestatic liver disease with hepatic failure necessitating liver transplantation. She was on IFX treatment for 8 months and had no history of hepatic disease and exposure to hepatotoxic drugs.²³⁷

The reason for liver toxicity associated with IFX is unknown. However, it did not re-occur in 3 patients who were subsequently treated with etanercept.^{236,240,241} It is noteworthy that preexisting liver disease and/or concomitant medication with potentially hepatotoxic drugs may increase the risk of hepatic adverse events of IFX. Until now, available data could not clearly ascertain this hypothesis, especially if liver cirrhosis is a significant predictor for hepatic adverse events under IFX treatment. In patients with primary sclerosing cholangitis IFX seems to be safe, but not effective. While a report of 2 patients described an improvement of liver function tests after IFX treatment,²⁴²

a small double-blind, placebo-controlled, randomized study failed to demonstrate efficacy of IFX.²⁴³ The risk of IFX treatment in patients with chronic hepatitis B and C is discussed elsewhere in this consensus.

9. Congestive heart failure

Consensus statement:

In patients with mild congestive heart failure (NYHA classes I and II) but a normal ejection fraction IFX therapy may be considered after a fully informed discussion with the patient [EL 5, RG D].

In patients with a reduced ejection fraction, especially in case of NYHA class III and IV, IFX therapy has to be avoided [EL 1b, RG A].

In patients who develop new onset or worsening of congestive heart failure IFX therapy has to be stopped and a cardiologist has to be consulted [EL 4, RG C].

The estimate for the co-morbidity of CHF and inflammatory bowel disease is likely to be low. A recently published meta-analysis revealed no evidence of an increased cardiovascular-disease-specific standardized mortality ratio for CD as well as for UC.²⁴⁴ New onset and worsening of congestive heart failure (CHF) has been described in association with anti-TNF- α treatment.²⁰⁴ This cognition was astonishing since TNF- α inhibition has previously been thought to be a promising treatment in patients with CHF. First preclinical and open pilot studies with etanercept in CHF showed an improvement of the left ventricular ejection fraction and in the 6-min walking distance.^{245,246} However, a large, randomized, placebo-controlled trial evaluating etanercept in patients with CHF could not confirm this described therapeutic effect and ruled out a clinically relevant benefit of etanercept on the rate of death or hospitalization due to CHF.²⁴⁷ In the American arm of the trial (RENAISSANCE trial) a trend towards higher mortality in etanercept treated patients was even noted. Very similar results were produced by a phase II, randomized, double-blind, placebo-controlled pilot study named ATTACH (Anti-TNF alpha Therapy Against Chronic Heart Failure).²⁴⁸ This trial evaluated the efficacy and safety of IFX in patients with NYHA class III and IV and a left ventricular ejection fraction $\leq 35\%$ representing patients with severe disease. One hundred fifty patients were randomly assigned to receive placebo, IFX 5 mg/kg or IFX 10 mg/kg at 0, 2, and 6 weeks. The combined risk of death from any cause or hospitalisation for heart failure through 28 weeks was increased in the patients randomized to 10 mg/kg IFX (hazard ratio 2.84; $P=0.043$). All-cause mortality at 1 year showed that 4 patients (8.2%) in the placebo group died compared with 4 patients (8%) in the IFX 5 mg/kg group and 8 patients (15.7%) in the IFX 10 mg/kg group. Thus, the conclusion was that short-term treatment with IFX did not improve and high doses (10 mg/kg) adversely affected the clinical condition of patients with moderate-to-severe CHF. IFX has not been studied in patients with mild heart failure (NYHA class I and II). In several large studies investigating the efficacy and safety of IFX in IBD only a single patient with heart failure was reported who died from multisystem organ

failure including heart failure, renal failure, pneumonia, and amyloidosis.²¹¹

In the post-marketing period of IFX rare cases of new-onset or worsening of CHF have been described. In an analysis of data from the U.S. Food and Drug Administration's (FDA) Med Watch program 47 patients who developed new onset ($n=38$) or worsening ($n=9$) of CHF during treatment with etanercept ($n=29$) or IFX ($n=18$) were reported.²⁴⁹ Half of the patients with new-onset of CHF had no identifiable risk factors. The median time interval from the first dose of TNF- α antagonist to new-onset or exacerbation of CHF was about 4 months (range 24 h to 24 months). Ten of the 38 patients who developed new-onset CHF were under the age of 50 years, six of them had received IFX and 4 had received etanercept. After TNF- α inhibitor therapy was discontinued and heart failure therapy was started in these 10 patients, 9 had complete or partial resolution of CHF and one patient died. Six of the patients with new-onset CHF had CD, and in 3 of them no risk factor could be identified. In a review of the safety data of anti-TNF- α agents obtained from the FDA Freedom of Information Database 132 cases of heart failure were reported in the postmarketing period from 1998 to March 31, 2002.²⁵⁰ This corresponded to 0.6/1000 patients. Very recently the relative reporting of IFX adverse events to the FDA was assessed with the public release version of the adverse event reporting system (AERS) database by using a disproportionality analysis.²¹³ A relationship between IFX and CHF could not be established. Thus, CHF is a rare adverse event under anti TNF- α treatment. Several trials revealed similar rates of CHF under and without anti TNF- α treatment in patients with CD and RA.^{251–255} Two safety analyses of large series of IBD patients under IFX revealed only one patient with worsening of heart failure out of 500 patients with CD treated with IFX at the Mayo Clinic and no case of CHF in IBD patients treated with IFX in Edinburgh covering 620 patient-years of follow-up.^{14,133} Reports suggested that IFX may be associated with life-threatening tachyarrhythmias and bradyarrhythmias. A single-blind, placebo-controlled cross over study of 75 patients with chronic arthritis revealed a non-significant trend of more new-onset cardiac arrhythmias, particularly ventricular tachyarrhythmias, developed during IFX infusion.²⁵⁵

10. Haematological side effects

Consensus statement:

In case of relevant haematological dyscrasias such as pancytopenia, leukopenia, neutropenia, thrombocytopenia, and aplastic anaemia during IFX treatment, IFX should be discontinued if no other reason has been identified [EL 5, RG D].

Blood count should be examined prior to start of IFX treatment, after induction treatment, and at least every 4 months while on IFX maintenance treatment [EL 5, RG D].

Different haematological dyscrasias such as pancytopenia, leukopenia, neutropenia, lymphopenia, thrombocytopenia, and aplastic anaemia have rarely been reported in association with IFX administration, some with fatal outcome. Considering

clinical trials, performed primarily in adult patients with IBD, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis data of safety of IFX in 5706 IFX-treated patients and 1600 placebo-treated patients are available.^{256,257} The overall incidence of hematologic abnormalities was low: anaemia 2.6% (IFX-treated) vs. 2.8% (placebo-treated); leukopenia 1.5% vs. 0.9%; neutropenia 1.1% vs. 0.4%; pancytopenia 0.0% vs. 0.1%; thrombocytopenia 0.5% vs. 0.2%. Some of these hematologic adverse events have been reported more commonly in paediatric CD patients, such as leukopenia (9%) and neutropenia (7%).^{258,259} Further haematologic adverse events are reported primarily from post-marketing surveillance data from the FDA²⁵⁰ or have been published as case reports. Several cases of pancytopenia,^{260–263} leukopenia, and neutropenia^{250,264–266} under IFX treatment administered due to different indications have been published. Some of them have been associated with requirement of blood transfusions and G-CSF or severe infections including fatal outcome. It is noteworthy, that in many of these cases a concomitant treatment with azathioprine, methotrexate or leflunomide was administered.

Also thrombocytopenia has rarely been observed in patients while on IFX therapy and reported to the FDA.²⁵⁰ Several additional cases have been published^{267–271} including a 15-year-old male patient with Crohn's colitis who developed thrombocytopenia 6 days after the first IFX infusion and was diagnosed to have idiopathic thrombocytopenic purpura.²⁶⁷ The described haematological side effects of IFX are not specific and have also been reported in association with other anti-TNF- α inhibitors such as etanercept and adalimumab.^{250,272–277}

Concomitant medications make it difficult in some cases to ascertain causality between haematological abnormalities and IFX. However, three cases of rechallenge of anti-TNF- α inhibitors have been published which are strong arguments of causality between haematological abnormalities and anti-TNF- α antagonist.^{266,271,273}

11. Intestinal strictures, stenosis, or bowel obstruction (SSO)

Consensus statement:

IFX does not seem to increase the risk for the development of intestinal strictures, stenosis, or bowel obstruction (SSO) [EL 2b, RG B].

Patients with pre-existing SSO are less likely to respond to IFX treatment [EL 4, RG C].

Intestinal strictures, stenosis, or bowel obstruction (SSO) are common complications of CD. During the early stages of CD, inflammation may result in intermittent obstructive manifestations due to bowel wall edema and accumulation of inflammatory cells in the mucosa. Persistent inflammation induces thickening of the bowel wall with enhanced collagen production and subsequent fibrostenotic narrowing and stricture formation.^{278,279} Thus, bowel obstruction may primarily result from florid inflammation or from irreversible fibrostenosis or from a combination of both. While the inflammatory component is likely to respond to anti-inflammatory drugs, this is not the case in fibrotic changes.^{280,281} The

available literature about the development of intestinal SSO due to IFX is somewhat conflicting. In randomized controlled trials as well as in two retrospective studies some patients with newly developed bowel obstructions under IFX treatment have been described, especially at the site of earlier severe ulcerations.^{139,282–284} Furthermore, in an open-label trial including patients with active CD the ulcerative lesions markedly improved after giving IFX, but the intestinal diameter evaluated by colonoscopy tended to narrow.²⁸⁵ In an analysis of the post-marketing experience of adverse events of IFX a signal for bowel obstruction was found specific for CD, which might be due to confounding by indication.²¹³ On the other side data from the ACCENT I trial revealed that the incidence of new presentation of intestinal SSO during the study period was lower in patients on IFX maintenance treatment than in the placebo maintenance group suggesting that the use of IFX does not lead to an increase in the development of intestinal SSO.^{4,286} Data from the TREAT registry, a prospective, observational, multicenter registry in North American patients with CD, confirmed these results.²⁸⁷ Multivariate analysis revealed that severity and duration of disease, ileal location, and new corticosteroid use were predictors of intestinal SSO but neither previous nor new use of IFX. Thus, considering all available data IFX does not seem to increase the risk for the development of SSO. Data of open-label and retrospective studies revealed that patients with SSO have an increased risk of not responding to IFX treatment.^{288–291} This poorer response was especially found in patients with bowel dilation proximal to the strictures.²⁸⁸ An open-label trial evaluating the safety and efficacy of IFX in patients with symptomatic SSO refractory to steroids and/or immunosuppressive agents was discontinued prematurely due to safety thresholds of more than two surgeries within the first 5 patients.²⁸⁹ However, the indications for surgery were primarily due to additional perforating disease. Very recently data from Japanese nationwide surveys confirmed that stricturing behavior was a risk factor for ineffectiveness of IFX.²⁹² In contrast to these data successful IFX treatment of inflammatory stenosis in CD has been reported in case reports as well as in retrospective analyses and prospective investigations suggesting that a subgroup of patients may respond to anti-TNF- α therapy, especially those with florid inflammation and no or minor fibrosis.^{293–297} Thus, under consideration of available data and the difficulty to distinguish between inflammatory and fibrotic obstruction IFX should only be used cautiously in patients with documented SSO and cannot be recommended in this situations in general.

12. Concomitant medication

Consensus statement:

During therapy with IFX concomitant medication with steroids, AZA/6-MP, and MTX should be restricted to the minimum required for clinical effectiveness [EL5, RG D]. Combination of IFX with other types of immunosuppressant and immunomodulators, including cyclosporine, tacrolimus, mycophenolate mofetil, as well as anakinra, etanercept, and other anti-TNF agents, is not recommended [EL5, RG D].

Concomitant medication allowed in the large studies of infliximab included 5-ASA, steroids, AZA/6-MP and MTX.^{4,298,299} Toxicity data did not reveal additional risk due to any specific combination of infliximab with any of these drugs in RCTs, which is in accordance with post-marketing data. Several reports suggested that addition of an immunomodulator (AZA/6-MP or MTX) might decrease the likelihood of occurrence of anti-infliximab antibodies, which might be related to a decreased incidence of infusion reactions.³ Additionally, some reports suggested that addition of an immunomodulator might prolong the duration of remission/response during infliximab treatment by virtue of decreased antibodies to IFX.³ However, several more recent reports including data from the large ACT1/2 studies did not support this view.²¹¹ Therefore, addition of an immunomodulator is not a prerequisite in IFX treated patients. IFX administration on a fixed schedule rather than on-demand treatment might be equally effective in this regard.^{3,4,300,301}

However, concerning safety issues other than infusion reactions, mainly infections, ECCO concluded in its consensus on opportunistic infections that the combination of immunomodulator therapies poses a risk for opportunistic infections [EL 3b, RG C].¹ It is obvious that multi-modal immunosuppressive treatment increases the likelihood of infectious complications, in some analogy to the situation in organ transplantation. This notion was recently supported by data from a large cohort study including 22,310 patients with CD and 111,550 controls which revealed that the combination of anti-TNF therapy with immunosuppression was associated with 1,7-fold increased risk of sepsis.³⁰² This risk was even increased by 2,4-fold with the addition of steroids. Therefore, this combination should be avoided on the long-term whenever possible. This view might be further supported by the occurrence of several cases of hepatosplenic T cell lymphomas in adolescent patients treated with both, IFX and AZA/6-MP,³⁰³ which is discussed elsewhere in this paper in more detail. Triple immunosuppressive treatment with steroids, AZA/6-MP and IFX should be restricted to the minimum time required, and should be administered under vigilant surveillance for infectious complications. Steroids should be tapered as quickly as possible in this situation. This is particularly relevant as TREAT registry data indicate significantly increased risk for serious infections and mortality in steroid-treated patients.¹³² Immunosuppressive drugs used in transplant medicine, like cyclosporine, tacrolimus and mycophenolate mofetil, have not been formally tested along with IFX in IBD patients. Their use can therefore not be recommended along with IFX.

13. Malignancy and lymphoma

13.1. Malignancy and lymphoma in IBD

Consensus statement:

There is an increased risk for malignancy of colon and liver in IBD [EL 2b; RG B]. There may be only a borderline risk for lymphoma in IBD [EL 2a, RG C] and this risk is probably higher in severe IBD [EL 5, RG D].

An increased risk for colonic cancer has been known for UC patients for a long time and is summarized in a corresponding meta-analysis.³⁰⁴ A similar risk was discovered in CD.^{305,306} A large Canadian population matched study found an increased risk for cancer in IBD patients³⁰⁷; there was an increased risk for colon carcinoma for patients with UC (incidence risk ratio 2.8; 95%CI: 1.9–4.0) as well as for CD (IRR 2.6; 95%CI 1.7–4.1). There was an increased IRR of rectal carcinoma only in patients with UC (1.90; 95% CI, 1.05–3.43) and an increased IRR of carcinoma of the small intestine only in CD patients (17.4; 95% CI, 4.16–72.9). An increased IRR of extraintestinal tumors was observed for the liver and biliary tract in both CD patients (5.22; 95% CI, 0.96–28.5) and UC patients (3.96; 95% CI, 1.05–14.9).

Mostly lymphoma arise in areas involved in IBD and symptoms of lymphoma may mimic symptoms of underlying IBD. Earlier studies especially from tertiary centers tended to have more positive results than recent studies which are population based.³⁰⁸ There are two systematic reviews^{308,309} on lymphoma in IBD with conflicting results (cohort studies): The RR differed between 0 and 10 in different studies. Most population- and also hospital-based studies failed to identify an increased risk for lymphoma in IBD. Only two studies from tertiary centers (Mt. Sinai and Chicago University) showed an increased risk possibly due to referral bias and ascertainment bias. Summarizing some of the bigger studies an absolute risk of 0.03%/person year was calculated. In contrast to IBD there is a clearly increased risk (SIR 1.8; 95% CI, 1.5–3.2) of lymphoma in patients with rheumatoid arthritis,^{310,311} especially in patients with high inflammatory activity.³¹²

13.2. Immunosuppression and malignancy/lymphoma

Consensus statement:

There is no increased risk for non-hematopoietic malignancy in IBD patients treated with immunosuppressives [EL 2a, RGB].

A slightly increased risk for lymphoma cannot be excluded for patients with IBD on immunosuppressives [EL2a, RG C].

During the last 15 years immunosuppressives have become the gold standard especially in severe cases with IBD and as long-term maintenance treatment for more than one year. There were concerns about the possible risk of malignancy under these conditions. One extensive review found no increased risk of non-hematopoietic malignoma in immunosuppressively treated patients with IBD in larger population based studies.³¹³ There are multiple cohort studies on patients with IBD and immunosuppressives with contradictory results with respect to the risk of lymphoma. Most of the studies were carried out in IBD-patients on thiopurines (azathioprine, 6-mercaptopurine). Their risk seems to be lower than in patients with RA³¹¹ or post-transplant patients.³¹⁴ A recent interim analysis of the CESAME cohort suggest an overall increased risk of non-Hodgkin lymphoma in IBD (SIR=1.89; 95% CI 1.08–2.97, $P=0.03$) compared with the general population. The excess risk appears to be related to thiopurines since $\frac{3}{4}$ of the incident cases of non-Hodgkin lymphoma occurred in

patients receiving azathioprine.³¹⁵ A meta-analysis found the risk of IBD patients on immunosuppression to be 4 times higher (CI 2–7.5) compared with the general population.³¹⁶ Another meta-analysis of population based studies could not find any increased risk for lymphoma comparing patients with IBD, CD or UC, on immunosuppressives with the corresponding group without immunosuppressives.³¹³ A higher risk possibly due to severity of disease cannot be differentiated from an adverse effect of immunosuppressives.

13.3. IFX and malignancy/lymphoma

Consensus statement:

In general, there is no evidence for an increased risk for malignancy in IBD associated with IFX [EL 2b, RG B] and no significantly increased risk for lymphoma up to now [EL 2b; RB B].

Elderly smokers with COPD and IBD might have an increased risk for lung cancer under IFX treatment [EL4, RG D].

An increased risk for malignancy in IBD patients treated with IFX could not be identified neither in cohort studies²³ nor in a matched pair study.³¹⁷ In the follow-up also no increased risk was observed (2.9% vs. 3% malignoma in each group for the whole 8 years).³¹⁸ Also the analysis of the TREAT data with more than 15,000 patient-years did not reveal any significant increase of malignancy.¹³² In a recent single-center retrospective cohort study with a control group without IFX ($n=743$) patients under IFX with malignancy were younger, with a median age of 42 years vs. 55 years in non-IFX treated controls with cancer ($P=0.01$).²³

There is one study of infliximab in patients with COPD in which a nonsignificant increase of malignoma was found in IFX-treated patients vs. the placebo group.³¹⁹ Although lacking a control group another study suggests an increased risk for lung cancer in IBD-smokers under IFX – three out of 13 smokers older than 65 years developed lung cancer under anti-TNF treatment (2 under IFX).¹³³ Therefore IFX should be recommended in elderly IBD smokers only very cautiously.

Prior to FDA approval of IFX an association of lymphoma and IFX treatment was concluded to be unlikely, but not finally excluded (0.06 vs. 0.05/100 patient-years in IFX vs. non-IFX treated Crohn's patients (RR=1.3; 95%CI: 0.36–5.3).¹³² Since approval more patients with IFX treatment were reported with lymphoma, but no significantly enhanced risk could be found. The majority of these patients had a more severe disease than controls as shown in the TREAT registry. As a consequence of disease severity many patients with lymphoma under IFX also had another concomitant immunosuppressive therapy which by itself could increase the lymphoma risk. Nevertheless, the mortality rate because of neoplasms was similar for IBD patients taking IFX and those without preceding IFX therapy.^{287,317} Although suspected^{165,320} IFX has no direct effect on apoptosis of EBV infected B-cells.³²¹ Even taking a small, but insignificant rate of lymphoma into account a simulation of two 100,000 patients' cohorts suggested a benefit for treatment with IFX.³²²

13.4. IFX and history of malignancy

Consensus statement:

Therapy with IFX is absolutely contraindicated in patients with active malignancy outside clinical trials [EL 5; RG D].

Patients with a history of malignancy may only be considered for IFX therapy if the risk of tumour recurrence is low, with a reasonable time of complete remission from the tumor and depending on the tumour type, response to therapy and negative metastatic work-up [EL 5; RG D].

Since patients with a history of cancer of any origin were usually excluded from randomised controlled trials on IFX in immune mediated diseases there is barely evidence on the safety of IFX in this situation. In patients with advanced pancreatic cancer IFX plus gemcitabine was studied with respect to amelioration of tumor cachexia in one randomised controlled trial.³²³ No statistical difference was noted with respect to cachexia nor with respect to survival. However, since survival is usually very short in these patients and due to the small study size a possible negative impact of IFX might have been subject to beta error. Another randomised controlled trial studied the combination of IFX with docetaxel also with respect to weight gain in non small cell lung cancer.³²⁴ This trial was closed prematurely due to worse outcome in the IFX group with respect to fatigue. In patients with renal cell carcinoma refractory to previous immunotherapy two small trials suggested a possible oncological benefit of IFX but this cannot be taken as robust evidence due to the lack of control groups.³²⁵ Physicians are usually reluctant to administer anti-TNF therapy in patients with a cancer history which might be the reason of rare reports in this field. Nevertheless, tumor recurrence after complete response to tumor therapy has been described after IFX.³²⁶ In patients requiring solid organ transplantation active neoplasm other than skin tumors are considered absolute contraindications.³²⁷ Patients with a history of malignancy may only be considered for transplantation if the risk of tumour recurrence is low, with a reasonable time of complete remission, depending on the tumour type, response to therapy and negative metastatic work-up.^{328,329} This approach should also be adopted to immunomodulation with anti-TNF agents.

13.5. Hepatosplenic T-cell lymphoma

Consensus statement:

In view of cases of hepatosplenic T cell lymphoma occurring in young male CD patients under combination therapy with IFX and azathioprine, the concomitant use of IFX and thiopurines in young males should be avoided, although no causal relationship has been established [EL 4, RG D].

Eight young patients with IBD and treated with IFX developed a very rare, but fatal hepatosplenic lymphoma.^{330,331}

As a consequence European pediatricians decided to stop concomitant therapy of thiopurines and IFX (personal communication) in children with IBD. Very recently 8 further patients with IBD under IFX and hepatosplenic T-cell lymphoma (all together up to now 16) were described. Most of the patients with these HSTCL were male (15/16), under thiopurines (15/16), had Crohn's disease (14/16) and were under 32 years of age (14/16).³³² No cases of this rare aggressive form of Non-Hodgkin-lymphoma have been reported in other established indications for IFX like rheumatoid arthritis. However, few reports exist on HSTCL in organ transplant recipients under immunosuppressive therapy and also CD patients under AZA/6-MP as single immunosuppressant. The causal relationship of HSTCL to IFX treatment remains unclear. However, strict adherence to indications and contraindications of IFX therapy outside of trials in young patients is advisable. A boxed warning for HSTCL was added to the revised product labelling in 2006. A recent update of the initial report by Mackey 2007 described additional cases of HSTCL in association with α -TNF therapy, including 3 cases on adalimumab, 2 of which had been switched from IFX.³³³ As in the original case series, the majority of patients were male, had CD and were receiving combined thiopurine/anti TNF- α treatment, almost all of them died rapidly despite chemotherapy. Early discontinuation of AZA/6-MP in young patients with IFX therapy for CD has been advocated. Lacking data in the pediatric age group this recommendation is supported in adults by the observation, that continuation of immunosuppressives beyond 6 months offers no clear clinical benefit over scheduled IFX monotherapy in previous thiopurine failures.³³⁴

14. Infliximab in the elderly and the young

14.1. Infliximab in pediatric/adolescent patients

Consensus statement:

IFX therapy in paediatric/adolescent patients with CD is safe considering indications, contraindications and precautions. Rates of infusion reactions and infections seem similar or even less than in adults. Little data are available in UC [EL 1b, RG A].

IFX is effective for induction and maintenance of remission in refractory paediatric CD, either luminal or fistulizing.^{335,336} IFX is registered for these indications in US and EU and a representative placebo-controlled RCTs for induction and maintenance IFX therapy in paediatric CD have been published.³³⁶ In addition, relevant experience with IFX therapy in children and adolescents is available, prospectively³³⁷ and retrospectively.^{338–340} In addition, reduced need for corticosteroids, a positive effect on growth, and possible use as first-line therapy in severe paediatric CD have been reported and discussed.^{341,342} Following the new concepts of IFX therapy in rheumatoid arthritis – early aggressive therapy to halt bone destruction and alter the course of the disease – similar ideas are discussed³⁴³ and studies under way in CD. Much less data are available on IFX therapy in paediatric UC.^{339,344–346}

The REACH study was an open-label multicenter randomized trial in 112 refractory CD patients aged 6–17 years comparing 8 and 12 weeks regimens of IFX maintenance therapy up to 54 weeks.³³⁶ Maintenance dosing with IFX every 8 weeks was superior to every 12 weeks dosing in maintaining response and remission. The most common serious adverse events were related to CD, 9 out of 103 randomized patients had infectious complications, leading to discontinuation of IFX in 6 (5%) of them. ATIs developed in 2.9% of patients during the observation period of 10 weeks. Infusion reactions were observed in 17% of patients. Anaphylaxis occurred in one randomized patient, no other serious infusion reactions or delayed hypersensitivity-like reactions were seen. No deaths, malignancies, tuberculosis, neurological or autoimmune disorders were noted. In conclusion adverse events and serious adverse events including serious infections were comparable among patients treated with IFX every 8 weeks vs. patients treated every 12 weeks. Safety findings in children were also comparable to those observed in adults. The REACH study was criticized for being underpowered and not really demonstrating long-term efficacy and safety.³⁴⁷

Recently, a long-term outcome study of IFX maintenance therapy was performed as a multicenter cohort study in children younger than 16 years and short disease duration, enrolled in a registry.³⁴⁸ Two hundred two out of 729 children received IFX. 158 patients received IFX as maintenance therapies, 29 episodic, 8 of those were switched to maintenance. Among 128 children administered maintenance IFX and followed >1 year, concomitant medication at IFX initiation included corticosteroids (52%) and immunomodulators (90%). By 1, 2, and 3 years, <10% of patients continuing on IFX maintenance were receiving corticosteroids ($P < 0.001$). Following therapy initiation, 26, 44, and 33% of patients continuing on maintenance IFX over 0–1, 1–2, and 2–3 years, respectively, had clinically inactive disease not requiring corticosteroids or surgery. The likelihood of continuing maintenance IFX at 1, 2, and 3 years was 93, 78, and 67%, respectively. Among the entire IFX-treated population of 202 children, 1 patient had conversion of PPD skin test with a normal chest X-ray. Nine months of antituberculous therapy was administered, 1 patient received antiviral therapy for varicella infection with progressive rash, both patients recovered without sequelae. One Stage II Hodgkin's disease was found intraoperatively with ileocecal resection in a 14 year old girl. One death due to cardiac arrhythmia associated with long QT interval occurred in a 11 year old boy. He had previously survived sudden death from arrhythmia before being diagnosed with CD.

To evaluate the efficacy and safety of IFX as maintenance therapy of severe pediatric CD, comparing scheduled vs. episodic treatment, was the aim of a randomized multicenter, open-label study by Ruemmele et al.³⁴⁹ Forty children with CD and a severe flare-up despite immunomodulator therapy combined with corticosteroids were included. 34/40 patients came into remission and were randomized. At week 60, 83% of children on scheduled IFX therapy (group A) were in remission compared to 61% with episodic treatment (group B). Relapse occurred in 23% of children in group A and 92% in group B. No serious adverse event, no death, malignancy/lymphoma was observed during the study period.

In general the rate of infusion reactions in children receiving IFX^{338,339,341,350} seems similar to that in adults (4–13%). The REACH study reported infusion reactions in the two patient groups of 17% and 18%, respectively.³³⁶ In a report on 361 IFX infusions in 75 children the number of infusion reactions (8.5%) was in the expected range, however the number of reactions per individual child (38.6%) was higher than reported in adults (17–24%).³⁵⁰ The majority of infusion reactions are mild and discontinuation of IFX therapy is not necessary in most cases. Female gender and the use of immunosuppressants for less than 4 months seem risk factors for a reaction up to the third infusion, but not for ongoing IFX therapy later on. In addition prolonged intervals between infusions seem to predispose to infusion reactions. Pre-treatment with corticosteroids and diphenhydramin with substantially decreased infusion reactions (8% of patients, 1.5% of patients) has been reported.³³⁹ Delayed hypersensitivity reactions are rare. Concerning infections, data in the paediatric literature are scarce, severe infections seem to be similar or even less than in adults.

The spectrum of infections – bacterial, most frequently upper respiratory tract (around 34% in the REACH study), fungal infections, and also listeriosis and tuberculosis – is not different to adults. The numbers for serious infections reported in larger series in children are 3.6%,³³⁹ 5%,³³⁸ 5.7% and 8%³³⁶ and within the 4–8% rate for adults reported in prospective and retrospective clinical trials.^{4,14} Data similar to the TREAT registry do not exist for children and adolescents up to now. For paediatric patients, few reports on severe infections exist and discontinuation of IFX therapy is rarely mandated. However, death of a child with severe fistulizing and stenosing CD under IFX therapy has been reported,³⁵¹ possibly due to bacterial sepsis caused by a hidden abscess. Similar cases have already been reported in adult CD patients.¹⁴

14.2. Hepatosplenic T-cell lymphoma in the young

See Section 13.5 in the above section about malignancies and lymphoma.

14.3. Infliximab in the elderly patient

Consensus statement:

IFX therapy in elderly patients with IBD follows the same indications, contraindications and precautions as in younger patients. The rate of infectious complications under IFX therapy increases with higher age. However, especially severe and fatal infections in elderly patients seem to be due in part to the underlying illness and steroid co-medication, rather than IFX [EL4, RG D]. Close monitoring for infectious complications is mandatory in IBD patients with higher age. Lung cancer has been observed in elderly IBD patients on IFX-treatment and a significant smoking history [EL4, RG D].

Observations on safety of IFX in elderly patients with CD or UC are rare, with not a single study focussing on this

question. The landmark RCTs of IFX in CD and UC did not include elderly patients. Colombel reported the Mayo Clinic experience in 500 patients aged 5–85 years, median age 37 years. In contrast the median age of deceased patients, of all causes, was 67 years (range 31–85 years). No clear relation between age and treatment complications was drawn.¹⁴ A population based cohort study of 217 patients in Sweden also gave the impression of a higher median age in the patients with fatal outcome, the numbers being too small for statistical evaluation.¹³¹ Interestingly, sub-analysis of the ACCENT trials looking for abscess development in fistulising CD under IFX maintenance therapy showed an inverse relation with age: the odds of abscess development were 0.24 times lower for patients older than 38 years than for patients 38 years or younger. Looking at the TREAT registry¹³² including 3179 IFX treated and 3111 otherwise treated patients with CD, without adjusting for other risk factors, patients who died were older (OR 1,07 for each 1-year increase in age; $P < 0.001$) and had a longer duration of disease (OR 1,06 for each 1-year increase in CD duration; $P < 0.001$). In an adjusted model, age (OR 1,07; $P < 0.001$), duration of CD (OR 1,03; $P < 0.006$) and use of prednisone (OR 2,10; $P = 0,016$) remained independent predictors of death. The use of IFX was not a significant predictor of mortality.

Some information can be drawn from rheumatoid arthritis. However, most of these patients are under concomitant immunosuppression with methotrexate, making comparisons with IBD questionable. In the ATTRACT (Anti-TNF in Rheumatoid Arthritis with Concomitant Therapy) trial 72 patients older than 65 years were treated with IFX, and there was no difference in the observed effectiveness or safety of this drug between older and younger patients.²²⁸ Similar results were obtained in France for elderly patients with rheumatoid arthritis.³⁵² The absolute number of patients stopping IFX for adverse effects was higher and a trend for severe infections in the older patient group (> 70 years) seemed obvious (18.2% vs. 2.8%, $P = 0,08$). Several other confounding factors concerning effectiveness and safety of IFX therapy in the elderly have been discussed in the literature, e.g. even more pronounced immunosuppressive effect of corticosteroids in elderly patients leading to more frequent and more severe infections, due to the underlying illness. Strictly observing the contraindications and close monitoring especially for infectious complications is mandatory in the older age group of IBD patients.

Recently concern has been raised for the development of lung cancer in elderly IBD patients treated with IFX. Data from all patients (202/207) treated with IFX in Edinburgh from 1999 to 2007 were analyzed¹³³ comprising 620 patient-years of follow-up. Seven deaths (3.3%) were observed and a total of 6 malignancies (3 haematological, 3 bronchogenic). All three cases of lung cancer were observed in patients > 65 years of age; inversely 3 of 13 patients > 65 years (23.1%) treated with IFX and with a significant smoking history developed lung cancer. One of them had been switched from IFX to adalimumab. Two cases of lung cancer had been observed also in Colombel's series of 500 patients treated at the Mayo Clinic, both elderly smokers.¹⁴ Interestingly, in a murine model of metastatic cancer TNF-dependent mechanisms appear critical in maintaining tumor dormancy.³⁵³

15. Mortality

Consensus statement:

Lethal adverse events are reported in controlled trials of IFX and in numerous other reports without a statistical difference to control groups [EL 3, RG C]. Thus, relationship between death and IFX treatment is unclear. Risk factors for lethal adverse events in IFX treated IBD patients are additional immunosuppression, especially steroids, duration of disease and higher age [EL 2 RG B]. Infections followed by malignancies are the main causes of all deaths associated with IFX [EL 2, RG B].

Mortality is the hardest endpoint for a disease or complication, and the worst imaginable complication or outcome. There are at the least 13 studies dealing with mortality in CD and 9 on UC before the introduction of IFX.^{306,354–370} The observation period in these studies were at least 3.7 years in CD (mean 10.9, 3.7–17 years) and 4 years (mean 12.9, 4–19 years) in UC. There is a trend to a slightly elevated mortality in CD (overall SMR 1.29) but not in UC (overall SMR 1.05). The overall death rate in IBD patients before introduction of IFX was 8.7% with a follow-up of 10.2 years (range 3.7–13.3).

Shortly after the introduction of IFX treatment in IBD reports of severe infections, cancer and lymphomas occurred and concerns about safety arose. Besides severe infections also deaths were reported. All available data on mortality rates in IBD patients treated with IFX are summarized in Table 1. The overall mortality rate according to published randomized controlled studies (CD and UC) was 0.3% (2/735) in the IFX groups vs. 0% (0/427) in the control groups. The mean follow-up in these studies was 22 weeks (range 6–52 weeks). Combining controlled trials and reports from routine clinical experience (excluding case reports) the mortality rate can be estimated with 1.1% (99/8896) at a mean follow-up of 16 months (see Table 1).

A recently published decision analysis based on 6 studies with 1711 patients calculated 779 deaths in comparison to an expected death rate of 508 in 100,000 patients.³²² The Centocor periodic safety report update of August 2006 reported 0.97 cases per 1000 patient years. This means that approximately 1 patient will die if 33 patients are treated for 33 years. In comparison, Lichtenstein calculated a death rate of 0.53 per 100 patient years (0.43 in control group), or approximately 1 death per 33 patients during a six-year treatment period.¹³² A similar death rate of 0.3 per 100 patient years was reported by Fidler recently.²³ These are striking differences. In contrast, the calculated annual mortality rate in IFX treated patients was 1.3% and 1.2% in the study of Colombel and Ljung^{14,131} and did not differ from older IBD population studies with 1.0–1.4%.^{306,355,364} There was also no difference in the mortality rate (1.6% vs. 2.4%) in a recently published study comparing 743 infliximab patient vs. 666 non-infliximab treated patients.²³ Also a meta-analysis of different TNF antagonist in the treatment of Crohn's disease did not show a statistical difference in the

Table 1 Documented and reported deaths in randomised controlled trials and observational studies of IFX treated patients with IBD.

Author	Deaths/patients under observation		Mean age survival/death	Observation time (months)	Comment
	IFX	Controls			
Targan et al. 1997 ²⁰⁹	0/83	0/25	37/ –	3	Single dose, CD
Rutgeerts et al. 1999 ²¹⁰	1/37 (2.7%)	0/36	34/61	12	Maintenance, CD
Present et al. 1999 ¹³⁹	0/33	0/31	38/ –	4.5	Fistula, CD
Cohen et al. 2000 ⁴¹¹	0/129		37/ –	3	Single center, clin. exp., CD
Farrell et al. 2000 ⁴¹²	0/100		41/ –	6	Single center, clin. exp., CD
Arnott et al. 2001 ⁴¹³	0/50		34/ –	3	Multicenter, clin. Exp., CD
Ricart et al. 2001 ¹⁷⁶	0/100		38/ –	10.75	Multicenter, clin. Exp., CD
Kaser 2001 ⁴¹⁴	0/6		46/ –	6 (mean)	Single center, clin. exp., UC
Sands 2001 ⁴¹⁵	0/7	0/3	37/ –	12	Multicenter, UC
Chey 2001 ⁴¹⁶	0/8		60/ –	8	Single center, clin. exp., UC
Hommes et al. 2002 ⁴¹⁷	0/71		35/ –	13.5	Maintenance, CD
Vermeire et al. 2002 ⁴¹⁸	0/240		36/ –	2.5	Multicenter, clin. exp., CD
Hanauer et al. 2002 ⁴	3/57 (0.5%)		35/?	13.5	Maintenance, CD
Doubremelle et al. 2002 ⁴¹⁹	0/69		31/ –	8	Multicenter, clin. exp., CD
Ardizzone et al. 2002 ⁴²⁰	0/63		33/ –	2.5	Single center, clin. exp., CD
Su 2002 ⁴²¹	1/27 (3.7%)		40/?	24 (mean)	Multicenter, clin. exp., UC
Actis 2002 ⁴²²	0/8		20–60/ –	Up to 30	Single center, clin. exp., UC
Kinney et al. 2003 ³⁰⁰	1/122 (0.8%)		43/?	13.25 (mean)	Single center, clin. exp., CD
Probert 2003 ⁴²³	0/41	0/40	41/ –	6	Multicenter, UC
Gornet 2003 ⁴²⁴	0/30		43/ –	40 (mean)	Multicenter, clin. exp., UC
Colombel et al. 2004 ¹⁴	10/500 (2%)		37/62	17	Single center, safety update, CD
Wenzl et al. 2004 ⁴²⁵	4/153 (2.6%)		37/47	29 (mean)	Multicenter, CD
Sands et al. 2004 ¹⁴⁰	0/306		36/ –	13.5	Fistula, CD
Ljung 2004 ¹³¹	6/217 (2.7%)		38/63	–	MC + UC
Ochsenkuhn 2004 ⁴²⁶	0/6	0/7	31/ –	13	Single center, UC
Armuzzi 2004 ⁴²⁷	0/20	0/20	36/ –	10 (mean)	Multicenter, UC
Kohn 2004 ⁴²⁸	0/13		12–62/ –	25.6 (mean)	Single center, clin. exp., UC
Bermejo 2004 ⁴²⁹	0/7		46/ –	8	Single center, clin. exp., UC
Rutgeerts 2005 ACT I u. II ²¹¹	1/484 (0.2%)	0/244	41/?	54	Multicenter, UC
Jarnerot 2005 ⁴³⁰	0/24	0/21	37/ –	12	Multicenter, UC
Lemann et al. 2006 ⁴³¹	0/108		26/ –	13	Controlled trial, CD
Poupardin et al. 2006 ⁴³²	0/137		36/ –	15 (mean)	Multicenter, clin. exp, CD
Lichtenstein et al. 2006 ¹³²	29/3179 (0.9%)	26/3111 (0.8%)	42/59	21 (mean)	Treat – Registry, CD
Caviglia et al. 2007 ⁴³³	1/50 (2%)	–	68/ –	12	Single center, safety update CD+UC
Lees et al. 2007 ⁴³⁴	1/39 (2.6%)	–	32/71	6.5 (median)	Multicenter, clin. exp. CU
Kohn et al. 2007 ⁴³⁵	1/83 (1.2%)	–	36/71	2	Multicenter clin. exp., CU
Jakobovits et al. 2007 ⁴³⁶	0/30	–	37/ –	13 (median)	Single center, clin. exp., CU
Fidder et al. 2009 ²³	12/743 (1.6%)	16/666 (2.4%)	–	58 (IFX, median) 144 (control, median)	Single center long term safety
Caspersen et al. 2008 ⁴³⁷	13/651 (2%)		32/54	29 (median)	Multicenter, CD+UC
Vries et al. 2008 ⁴³⁸	8/147 (5.4%)	–	38/53 (n=6)	59 (median)	Single center safety update CD+UC
Lees et al. 2009 ¹³³	7/202 (3.4%)	–	32/74	28.5 (median)	Multicenter, safety update, CD+UC

frequency of death between anti-TNF (0.21%) and control groups (0.05%).¹²⁹

Overall, the number of deaths is very low but fatalities related to infliximab are described. In one study that focused particularly on safety issues, 50% of deaths (1% of all patients) were regarded as IFX related.¹³¹ In addition in most case reports a close relationship to infliximab can be found.^{118,133,332,371–377} Looking at the specific causes of death, infections were the leading cause, followed by cancer and lymphoma. Risk factors for mortality in infliximab treated patients are corticosteroids (OR 2.1; 1.1–3.8) and age.¹³² In all studies where relevant data are available, the average age of those who died was significantly higher than that of survivors (60 vs. 36 years). Overall deaths due to IFX treatment are very rare but happen, and the death rate may increase over time. Suitable precautions should be taken to avoid fatalities.

16. Fertility, pregnancy and breast feeding

The onset of inflammatory bowel disease (IBD) mainly occurs in young adults within their reproductive age.³⁷⁸ Maintenance of remission of IBD as well as prompt and adequate treatment of active disease during pregnancy represents a major goal for both maternal health and foetal development.

16.1. Fertility

Consensus Statement:

IFX may lead to reduced semen quality by decreasing sperm motility and affecting sperm morphology [EL 3b, RG B].

Whether these findings result in reduced male fertility has not been examined. IFX treatment of men prior to planned conception does not seem to cause embryo toxicity [EL4, RG C].

Fertility in IBD is closely dependent upon disease activity. Active disease is associated with reduced fertility^{379–381} and female patients who underwent colectomy with construction of an ileal pouch-anal anastomosis have an increased risk for infertility.^{382–384} In remission, both, female fertility and male reproductive capacity do not seem to be diminished when compared to the general population.^{385,386} Therefore, one might speculate whether IFX treatment may restore or preserve fertility in female patients by inducing remission and down regulating inflammatory mediators.

A study in mice exposed to an analogous anti TNF- α monoclonal antibody revealed no negative effects on male reproduction.³⁸⁷ In men IFX treatment within 3 months prior to conception did not result in increased birth defects or foetal loss.³⁸⁸ IFX treatment in 10 men with IBD showed an increase in semen volume and a trend towards decreased sperm motility and morphology.³⁸⁹ Sperm concentration remained unaffected, although experimental *in vitro* studies demonstrated a pro-survival effect of TNF- α on germ cells in the seminiferous tubules during spermatogenesis, which can be blocked by IFX.^{390,391} Whether these semen analysis

findings may indicate impaired fertility has not been examined. There is one recent report on 4 patients with ankylosing spondylitis who fathered 6 healthy children during IFX treatment which may provide some reassurance for male patients treated with IFX.³⁹²

16.2. Pregnancy

Consensus Statement:

Data on the safety of IFX during pregnancy are still scarce and so far no general recommendation can be given to continue or initiate IFX treatment during pregnancy. However, referring that to date no increased risk for foetal abnormalities including immune defects nor for perinatal complications has been documented in association with IFX therapy, IFX seems to be low risk in pregnancy [EL 3b, RG B].

The decision to initiate or maintain IFX treatment during pregnancy has to be taken on the patient's individual clinical situation. In no case abortion might be considered due to IFX therapy.

The FDA classified IFX as pregnancy category B, which means that there are no data in humans and there is no evidence of teratogenicity or embryotoxicity in mice toxicity studies using an analogous antibody. In particular, animal reproduction studies have not been performed, because IFX only cross-reacts with TNF- α in humans and chimpanzees. One study on pregnant macaques that were exposed to an anti-TNF- α monoclonal antibody (golimumab) found no effect on T and B cell populations in blood and lymphoid tissues and did not indicate an impaired immune response to antigen challenge in the offspring.³⁹³ Human experience in using IFX during pregnancy is still limited since no controlled studies can be conducted in this sensitive issue. Several case reports and abstracts referring to the safety of anti-TNF medications in pregnancy found no evidence of an increased risk for abortion, congenital malformations or perinatal complications in patients with rheumatoid arthritis or CD.^{394–398} Only one case report can be cited that indicates an adverse foetal outcome due to intracerebral and intrapulmonary hemorrhage associated with IFX infusions in a woman who had concomitantly received mesalamine, metronidazole, azathioprine, steroids and methadone.³⁹⁹ However, the death of this neonate was more likely attributed to active refractory CD, but not to medical therapy.⁴⁰⁰ Small series of women who gave birth to a child after having been exposed to IFX during pregnancy indicated well tolerability and no increased risk for foetal harm. Live births were reported in more than 65%, whereas miscarriage occurred in less than 15% of women.³⁸⁸ These outcomes were similar when compared to non exposed CD patients or to the general pregnant population in the USA. Intentional IFX treatment of active CD during pregnancy in 10 women resulted in 10 live births.⁴⁰¹ In this study a total of 8 women received repeated IFX infusions for maintenance of remission during pregnancy. Except for two cases with neonatal illnesses, one with neonatal jaundice and the other with respiratory distress and a gastric ulcer, who did well at a 6-month follow-up,

there were no congenital anomalies, intrauterine growth retardation, or infants small for gestational age. So far, the increased rates of preterm delivery and lower birth weight in patients with IBD seem to be associated with the underlying disease (IBD or rheumatoid arthritis) but not with anti-TNF treatment. A review of the FDA database on the safety of tumour necrosis factor antagonists during pregnancy revealed a total of 61 congenital anomalies in 41 children exposed to etanercept ($n=22$) or IFX ($n=19$) due to rheumatoid diseases of the mothers. Twenty-four (59%) children had one or more congenital anomalies that were part of vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal and limb abnormalities (VACTERL) association. Because these malformations occurred at a rate higher than expected, a causative effect of anti-TNF- α treatment could not be excluded.⁴⁰² However, large registries with longer follow-up periods are urgently warranted before firm conclusions about the safety of anti TNF- α therapy during conception and pregnancy can be drawn.

Theoretically, the chimeric structure of the IFX molecule containing a human immunoglobulin G1 constant region represents a large antibody, which allows little transfer of the molecule during the first trimester. However, during the second and third trimester IgG subclasses readily pass across the placenta into the foetus.⁴⁰³ A case report by Vasiliauskas et al. clearly indicated that IFX crosses the placenta and revealed high IFX levels in an infant whose mother received five 10 mg/kg IFX infusions at 6- to 8 intervals until 2 weeks before delivery.⁴⁰⁴ Although at 6 months post partum low IFX levels could still be detected in the infant's serum, regular T and B cell development, normal immunoglobulin concentrations as well as an appropriate response to vaccination could be shown. Further development and health within the first year of life remained unremarkable. Nevertheless, since there are no case reports or studies that provide data on long term follow-up of children exposed to IFX, a possible anti-IFX antibody formation and/or negative effect on the developing immune system cannot be safely excluded.

A practical approach in this difficult situation might be to continue with IFX infusions every 8 weeks during the first 25 weeks of pregnancy and then to discontinue treatment in order to avoid IFX transfusion to the foetus.⁴⁰⁴⁻⁴⁰⁶ During the third trimester steroids may be used to control disease activity until delivery. Thereafter, the decision to restart IFX should be taken on an individual basis considering disease activity and the presence of perianal fistulas.

16.3. Breast feeding

Consensus statement:

Due to the lack of adequate data nursing cannot be generally recommended during IFX therapy, although the few case reports published to date indicate no toxicity [EL4, RG C].

It is not firmly known whether IFX is excreted in human milk or absorbed systemically after ingestion. Preliminary data have failed to detect IFX in breast milk of exposed women with IBD as assessed by enzyme-linked immunosor-

bent assay.^{404,407,408} The most recent study by Kane et al. on three children breastfed by women receiving IFX during and after pregnancy neither found IFX in the sera of the newborns nor in the breast milk of the nursing mothers.⁴⁰⁹ In contrast, there is one single report in abstract form that found positive levels of IFX in the breast milk from a woman with rheumatoid arthritis who received anti TNF- α treatment because of a flare of the disease 4 months after delivery.⁴¹⁰ However, all case reports of women with IBD who continued IFX treatment while nursing their children did not indicate toxicity.^{398,401,404,406-408}

Acknowledgements

The authors thank Centocor/Schering Plough/AESCA for the support in providing the literature as requested by the authors.

The authors thank Mrs. Eugenia Lamont for the editorial assistance with preparation of the manuscript.

Appendix A

Checklist for the safe use of Infliximab and other anti-TNF agents

A. Checklist before start of therapy

Obligatory	Yes	No
1. Patient instructed to seek medical care when clinical signs of infection occur (fever, dyspnoea, neurological symptoms...)	<input type="checkbox"/>	<input type="checkbox"/>
2. No clinical signs of active infection (including Varicella, Herpes, Influenza, parasites, fungal infections)	<input type="checkbox"/>	<input type="checkbox"/>
3. Screening for latent TB accomplished and negative (obligatory: Chest X-ray, TST, History for TB and epidemiologic risk factors; optional: interferon γ release assay)	<input type="checkbox"/>	<input type="checkbox"/>
3.b in case of latent TB chemoprophylaxis initiated before IFX?	<input type="checkbox"/>	<input type="checkbox"/>
4. Blood count	<input type="checkbox"/>	<input type="checkbox"/>
5. Transaminases $\leq 3 \times$ upper limit of normal	<input type="checkbox"/>	<input type="checkbox"/>
6. HBs-Antigen negative	<input type="checkbox"/>	<input type="checkbox"/>
		→ 6 b,c
6.b HBs-Antigen positive, viral load determined?	<input type="checkbox"/>	<input type="checkbox"/>
6.c HBs-Antigen positiv, antiviral therapy started?	<input type="checkbox"/>	<input type="checkbox"/>
7. HIV negative	<input type="checkbox"/>	<input type="checkbox"/>
8. CMV-colitis excluded (if refractory despite immunomodulation)	<input type="checkbox"/>	<input type="checkbox"/>
9. Stool negative for <i>C. difficile</i>	<input type="checkbox"/>	<input type="checkbox"/>
10. Informed about the risk of live vaccines	<input type="checkbox"/>	<input type="checkbox"/>
11. In perianal disease: perianal abscess excluded by imaging procedure or, if present, drained	<input type="checkbox"/>	<input type="checkbox"/>

(continued on next page)

A. Checklist before start of therapy (continued)

Obligatory	Yes	No
12. No signs indicative for high-grade bowel stenosis	<input type="checkbox"/>	<input type="checkbox"/>
13. History negative for demyelinating disease (multiple sclerosis, optic neuritis)	<input type="checkbox"/>	<input type="checkbox"/>
14. No signs of congestive heart failure (NYHA III–IV)	<input type="checkbox"/>	<input type="checkbox"/>
Facultative	Yes	No
15. Hepatitis B vaccination in a seronegative patient accomplished	<input type="checkbox"/>	<input type="checkbox"/>
16. Screening for Hepatitis C	<input type="checkbox"/>	<input type="checkbox"/>
17. Varicella vaccination accomplished if history for chickenpox, shingles and VCV vaccination negative	<input type="checkbox"/>	<input type="checkbox"/>
18. Pneumococcal vaccination accomplished	<input type="checkbox"/>	<input type="checkbox"/>
19. Prophylaxis against <i>Pneumocystis jiroveci</i> with cotrimoxazole if triple-immunosuppression including CsA or IFX.	<input type="checkbox"/>	<input type="checkbox"/>
20. Negative history and no clinical signs for malignancy	<input type="checkbox"/>	<input type="checkbox"/>
21. Patients instructed about food hygiene (raw eggs, unpasteurized milk products, uncooked meat/fish, raw vegetables)	<input type="checkbox"/>	<input type="checkbox"/>
22. Discontinuation of concomitant AZA/6-MP especially in young male patients.	<input type="checkbox"/>	<input type="checkbox"/>
23. Dermatological evaluation if increased risk for skin malignancy (high cumulative UV exposure, melanoma precursors, history of photochemotherapy, history of immunosuppressive therapy)	<input type="checkbox"/>	<input type="checkbox"/>

B. Checklist during maintenance therapy

Obligatory	Yes	No
1. No clinical signs of active infection (including reactivated TB)	<input type="checkbox"/>	<input type="checkbox"/>
2. Blood count and transaminases assessed at least every 4 months (transaminases $\leq 3 \times$ ULT)	<input type="checkbox"/>	<input type="checkbox"/>
3. In patients with unclear symptoms parasitic and fungal infection considered?	<input type="checkbox"/>	<input type="checkbox"/>
4. No history of infusion reactions	<input type="checkbox"/>	<input type="checkbox"/>
		→ 4 b
4.b Premedication administered, start at low infusion rate	<input type="checkbox"/>	<input type="checkbox"/>
5. Neurologic symptoms, patient referred immediately for appropriate management.	<input type="checkbox"/>	<input type="checkbox"/>

ULT: upper limit of normal.

Facultative	Yes	No
6. Regular gynaecological evaluation	<input type="checkbox"/>	<input type="checkbox"/>
7. Regular dermatological evaluation in high risk patients	<input type="checkbox"/>	<input type="checkbox"/>

B. Checklist during maintenance therapy (continued)

Facultative	Yes	No
8. Pre-travel consultation accomplished	<input type="checkbox"/>	<input type="checkbox"/>
9. Stool examination for bacterial pathogens, ova and parasites and complete blood count (eosinophilia) in patients returning after long term travels from developing countries	<input type="checkbox"/>	<input type="checkbox"/>

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