College voor zorgverzekeringen

Farmaco-therapeutisch en Farmaco-economisch plaatsbepaling van de dure geneesmiddelen met indicatie ziekte van Crohn naar aanleiding van opdrachtverlening
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'Infliximab, what we do and do not know'

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Gebaseerd op de formats van het
College voor zorgverzekeringen (CVZ)

Introductie

Dit format is bedoeld voor de indiening van een farmacotherapeutisch dossier voor een GVS aanvraag (1A of 1B) bij het College voor Zorgverzekeringen (CVZ). Voor alle indieningen zijn de procedures uit het procedureboekje van toepassing, beschikbaar via de CVZ website (www.cvz.nl).

Gebruik van het format is verplicht en de indeling dient zoveel mogelijk gevolgd te worden. Als dit niet mogelijk is dient u dit duidelijk toe te lichten. Een indiening dient efficiënt en informatief te zijn en dient derhalve niet meer dan 30 pagina's te bevatten (exclusief referenties).

Criteria voor indiening:

- All secties dienen ingevuld te worden. Wanneer een sectie niet van toepassing is dan dient NVT te worden ingevuld met een toelichting waarom de sectie niet van toepassing is;
- Het verwijderen van secties is NIET toegestaan;
- Het toevoegen van paragrafen, tabellen en figuren is wel toegestaan;
- Alle referenties in de tekst dienen correct te zijn opgenomen in de referentielijst;
- Alle relevante klinische studies van het te beoordelen middel en de vergelijkende behandeling(en) (gepubliceerd of in compacte analyseerbare vorm), incl. reviews/meta-analysen en relevante richtlijnen van de beroepsgroep dienen op papier toegevoegd te worden;
- De EPAR (op papier) dient onderdeel te zijn van het dossier;
- De 1B tekst (op papier) dient onderdeel te zijn van het dossier
- Overige referenties mogen op CD-rom worden aangeleverd.

Dossiers die niet voldoen aan bovenstaande criteria zullen niet in behandeling worden genomen door de Commissie Farmaceutische Hulp (CFH). Gebruik van de onderstaande checklist is aanbevolen om tot een volledig dossier te komen.

Checklist voor indiening

Wanneer een dossier wordt ingediend dient de registratiehouder de volgende punten te controleren:

- ❑ Ingevulde titel pagina
- ❑ Ingevulde koptekst en voettekst
- ❑ Opgemaakte inhoudsopgave
- ❑ Alle vereiste velden en tabellen zijn ingevuld
- ❑ Alle referenties zijn correct
- ❑ Alle referenties zijn toegevoegd aan het dossier
- ❑ Alle bijlagen zijn toegevoegd
- ❑ Bijgesloten EPAR
- ❑ Bijgesloten 1B tekst
- ❑ Bijgesloten klinische studies
- ❑ Bijgesloten richtlijnen

Inhoudsopgave

Separaat : Europese en Nederlandse Guidelines

Afkortingen

CD	Crohn's disease
Qol	quality of life
IS	immunosuppression
AZA	azathioprine
MP	mercaptopurine
MTX	methotrexate
IFX	infliximab, Remicade®
TNF-α	tumor necrosis fator-alpha
RA	reumatoid arthritis
UC	ulcerative colitis
ADA	adalimumab
IBDQ	inflammatory bowel disease questionnaire
ATI	antibodies to infliximab
HACA	human antichimeric antibodies
ANA	antinuclear antibodies
IBD	inflammatory bowel disease
AIR	acute infusion reactions
OR	odds ratio
95% CI	95% confidence interval
CMV	cytomegalovirus
HSTCL	hepatosplenic T cell lymphoma
EBV	Epstein-Barr virus

Samenvatting

Hier een samenvatting van de bevindingen in maximaal 750 woorden

Claim

Licht hier de claim met de betrekking tot de therapeutische waarde en de plaatsing op de bijlage toe.

In this review we would like to determine the efficiency, effectiveness and therapeutic value of IFX (Remicade®) in CD in the Dutch clinical practice. Since the last review written for CVZ, a substantial amount of studies and analysis of all sizes have been published. These studies served subjects like efficacy, quality of life (Qol), psychological and social impact and effects of therapeutic decisions on long-term effectiveness.

The therapeutic value and efficacy, which can be stratified regarding clinical manifestations (for example, fistulising disease), non-biological concomitant treatment and age (children, adolescents or adults), have proven to influence parameters such as effectiveness and cost-benefit ratio. More trials have provided us new and important information about treatment during pregnancy and the safety of the unborn child. Finally, the place of IFX in the pharmacological field has changed radically by introducing extramural biologicals, particularly Adalimumab (Humira). Together, these developments scream for a new and more extended review.

Inleiding

Beschrijf kort het geneesmiddel, de indicatie waarvoor vergoeding wordt aangevraagd, de aandoening en de standaard of gebruikelijke behandeling van de aandoening.

Infliximab (IFX, Remicade®), an intravenously administered chimeric (part-human, part-mouse) monoclonal immunoglobulin G1 antibody directed against tumour necrosis factor-alpha (TNF-a), was introduced in 1998. IFX is currently indicated for CD, fistulizing CD, Ulcerative Colitis (UC), ankylosing spondylitis, psoriatic arthritis and rheumatoid arthritis (RA)

Crohn's disease (CD) is a chronic, relapsing inflammatory disease that can affect every segment of the digestive tract. Many drugs have been used in the treatment of CD, none has, so far, been shown to modify the natural history of the disease or to maintain a stable remission over time. Steroids and immunosuppression (IS) with thiopurinic agents, such as azathioprine (AZA), mercatopurine (MP), or methotrexate (MTX) have been widely used. Resection of the inflamed bowel is the last step in the current therapeutic approach.

Methoden

Beschrijf kort de vergelijkende behandeling en welke klinische studies de belangrijkste zijn voor de bepaling van de therapeutische waarde.

An extensive literature search was conducted based on the IBD scientific literature depository present in the Erasmus MC in which all available literature was individually checked for aspects addressing IFX's safety, efficacy, QoL, economic value or other items deemed of interest in the context of this report. Subsequently, selected reports were distributed in the

study group and following discussion and written opinions by the senior members of the study group included for the preparation of this review by the junior members of the study group, vetted by the study group in total in used for final preparation of the report.

Therapeutische waarde

Beschrijf kort de belangrijkste uitkomstmaten op de vijf criteria; gunstige effecten, ongunstige effecten, ervaring, toepasbaarheid en gebruiksgemak van het geneesmiddel.

Beneficial effects: Clinical efficacy of IFX therapy is beyond doubt and its withdrawal seems unthinkable for current Dutch clinical practice or its acceptance with patients or society in general. An improved quality of life was demonstrated after IFX treatment.

Adverse effects: The most common adverse events reported during infliximab therapy include acute infusion-related reactions, infections and delayed hypersensitivity reactions. Infliximab is contraindicated in people with moderate or severe heart failure and active infections. Before treatment is started, people must be screened for active and inactive tuberculosis. The potential impact of IFX treatment on the development of infections, autoimmunity and malignancy must be monitored. Concerns have been raised regarding the risk of neoplastic disorders with the use of the biologic agents, and the general risk profile of these agents. Long-term safety is an important issue as IFX use and indications are rapidly increasing worldwide. It remains possible that rare IFX related fetal complications were not detected due to the sample size, retrospective analysis and reliance on spontaneous reporting

Experience: We have over 10 years experience with IFX. However, a lot of questions remain unanswered.

Applicability:

IFX is widely applicable within the registered indication.

Ease of Use:

IFX is an intramural drug. The drug is intravenously administered over a 2-h period

Conclusie

Clinical efficacy of IFX therapy is beyond doubt and its withdrawal seems unthinkable for current Dutch clinical practice or its acceptance with patients or society in general. There is good evidence that IFX is cost effective and it is felt as being so in the field in the Netherlands, but evidence clear evidence is complete. More research is needed in order to fill the gapes in today's knowledge.

1.0 Introduction

Crohn's disease (CD) is a chronic, relapsing inflammatory disease that can affect every segment of the digestive tract. CD primarily affects young adults. The highest incidence rates are reported from Northern Europe, the United Kingdom and North America, ranging from 6.6 to 15.6 cases per 100.000 person years [1]. The impact on physical, social as well as the emotional well-being of patients is substantial and the disease profoundly decreases the quality of life (Qol)[2]. Crohn's disease can be complicated by the development of strictures (narrowing of the intestine), obstructions, fistulae and perianal disease. Fistulae – abnormal connections between areas of the intestine or adjacent organs – develop in 17–43% of people with Crohn's disease. Perianal disease includes fissures, fistulae and abscesses. Other complications of Crohn's disease include acute dilation, perforation and massive haemorrhage of the gut, and carcinoma of the small bowel or colon.

Crohn's disease is not medically or surgically curable. Treatment aims to control manifestations of Crohn's disease to reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effects. Towards this aim, the armamentarium has been expanded with novel and more potent drugs. Although many drugs have been used in the treatment of CD, none has, so far, been shown to modify the natural history of the disease or to maintain a stable remission over time [4]. Population based studies show that using the conventional therapies only 42% of the patients with CD are symptom free at 2 years after initial diagnosis, and 12% after 10 years, while 10% of the patients have continuously active disease in 2 years and 1 % in 10 years [5]. Current treatment includes corticosteroids, immunosuppressants, TNF inhibitors, nutritional supplementation and dietary measures. Crohn's disease is typically treated in the short term (4–8 weeks) with corticosteroids. In severe active disease, hospital admission and intravenous administration of corticosteroids may be required. There is evidence that Crohn's disease in some people, despite a good initial response, becomes resistant to corticosteroids. Other people may become dependent on corticosteroid treatment, relapsing once the dose is reduced or
treatment is stopped. Since steroids are not useful in maintaining long-term remission, immunosuppression (IS) with thiopurinic agents, such as azathioprine (AZA), mercatopurine (MP), or methotrexate (MTX) are widely used, even though all have limited value for induction of response and can only benefit less then half of the patients who suffer from steroid dependency or resistance [6]. Between 50 and 80% of people with Crohn's disease will require surgery at some stage. The main reasons for surgery are strictures causing obstructive symptoms, lack of response to medical therapy, and complications such as fistulae and perianal disease. Resection of the inflamed bowel does not interrupt the progression of the disease [5]. Cosnes et al investigated the need for intestinal surgery from 1987 up to 2002. Although the 5 year cumulative probability of use of immunosuppressants increased from 0.13 to 0.56, the cumulative risk of intestinal surgery remained unchanged over time [7]. Infliximab (IFX, Remicade®), an intravenously administered chimeric (part-human, part-mouse) monoclonal immunoglobulin G1 antibody directed against tumour necrosis factor-alpha (TNF-a), was introduced in 1998 and has revolutionized the treatment of CD. IFX is currently indicated for CD, fistulizing CD, ulcerative colitis (UC), ankylosing spondylitis, psoriatic arthritis and rheumatoid arthritis (RA) [2, 4-6, 8-10]. [10]. In The Netherlands infliximab is administered as a second line therapy, find attached a summary of the current guidelines for

IBD treatment in The Netherlands. These Dutch guidelines are based on evidence from international published papers and reflect international guidelines on the treatment of crohn's disease such as the European CrohnColitis Organization guidelines (find attachted).

2. Methods

2.1 Vergelijkende behandeling

Voor het bepalen van de therapeutische waarde dient het geneesmiddel voor een bepaalde indicatie vergeleken te worden met de standaardbehandeling, of, indien niet aanwezig, de gebruikelijke behandeling. De standaardbehandeling is de behandeling die in de dagelijkse praktijk wordt gezien als de eerste keuze behandeling en waarvan de effectiviteit is bewezen. De standaardbehandeling voor een bepaald indicatiegebied kan bestaan uit meer dan één geneesmiddel of niet medicamenteuze behandeling. Geef aan welke vergelijkende behandeling relevant is en onderbouw deze keuze.

Although many drugs have been used in the treatment of CD, none has, so far, been shown to modify the natural history of the disease or to maintain a stable remission over time [4]. Population based studies show that using corticosteroids in combination with long-term thiopurines or methotrexate only 42% of the patients with CD are symptom free at 2 years after initial diagnosis, and 12% after 10 years, while 10% of the patients have continuously active disease in 2 years and 1 % in 10 years [5]. Since steroids are not useful in maintaining long-term remission, IS with thiopurinic agents, such as azathioprine (AZA), mercatopurine (MP), or methotrexate (MTX) have been widely used, even though all have limited value for induction of response and can only benefit less then half of the patients who suffer from steroid dependency or resistance [6]. Resection of the inflamed bowel does not interrupt the progression of the disease [5]. Apart from Infliximab also other anti-TNF medication is in use. In the Netherlands also Adalimumab is approved (*see GVS assessment on Adalimumab of. 24 september 2007*) and is perceived in the field, at least in the Netherlands to be equivalent and equipotent to IFX and good option after IFX failure [172]. Importantly though, no comparative studies have done and no knowledge as the relative potency of IFX vs Adalimumab is available. Another approved TNF medication, Etanercept, is ineffective in CD (not approved) and is considered even deleterious, patients treated with Etanercept for Rheumatoid Arthritis sometimes developing CD like symptoms as consequence of the Etanercept therapy, CD-like symptoms with subsequently are effectively managed with IFX [178]. Certoluzimab is not approved for CD in Europe but is used elsewhere and is generally perceived as inferior to either IFX or Adalimumab [179]. Thus with regard to the Dutch situation in CD, only IFX and Humira are relevant. The current review explicitly is limited to IFX and no attempt to assess Humira is made.

2.2 Literatuuronderzoek

Beschrijf de gebruikte databestanden, zoektermen en tijdsperiode van het uitgevoerde literatuuronderzoek.

Sources used:
Ovid Medliner, Ovid Old Medliner, Journals@Ovid full text, Your Journals@Ovid, Derwent Drug File, Biosis Previews, Embase

Search strings*:

#	keywords	# of hits
1	randomized controlled trial* OR controlled clinical trial* OR randomized OR meta analysis	358481
2	Infliximab OR Remicade OR anti-TNF	94253
3	Crohn's disease and/or fistulizing disease	2086378
4	Cost* OR quality of life OR QALY OR effectiveness R IBDQ	438002
5	1 AND 2 AND 3 AND 4	1443
6	5 (remove duplicates)	1083
7	6 (English language only)	1035
8	7 (from 2006 to current)	589

The search process identified 589 records.

Following review of the titles and abstracts, articles were selected. The results after screening are enclosed in this appendix.

Main reasons for exclusion during screening:

- Not related to one the products
- Not related to Crohn's disease

The extensive literature search was conducted based on the IBD scientific literature depository present in the Erasmus MC in which all available literature was individually checked for aspects addressing IFX's safety, efficacy, QoL, economic value or other items deemed of interest in the context of this report. Subsequently, selected reports were distributed in the study group and following discussion and written opinions by the senior members of the study group included for the preparation of this review by the junior members of the study group, vetted by the study group in total in used for final preparation of the report. Interestingly, we were not able to retrieve a "CFH beoordeling" for the use of IFX on morbus Crohn, probably it is not available in the public domain.

2.3 Relevante klinische trials

Hier kort aangeven welke relevante studies (fase II t/m IV) met betrekking tot het geneesmiddel zijn uitgevoerd. In de volgende paragrafen dienen de studies uitgebreid te worden toegelicht. Toevoegen van paragrafen is toegestaan. Daarnaast dient tabel 1 ingevuld te worden.

In total 9 clinical trails were selected as relevant for inclusion and of sufficient quality to meaningfully contribute to opination in adults. These are listed in table 1 (see supplementary material at the end of this review). Trails not included did not fulfil reporting criteria making results impossible to interpret, included patients also reported in other trails, included non-representative patient groups (for instance extensive co-morbidity), were not represented in literature before October 31, 2010, or were later withdrawn by the authors. A number of trails was also electively excluded because of a by the study-group perceived bias in reporting. Six randomised controlled trials (RCTs) that included licensed doses of infliximab met the criteria for inclusion in this review. These trials covered short treatment regimens that aimed to induce remission in people with active Crohn's disease (induction regimens) and longer-term regular dosing regimens that aimed to prevent relapse in people who had already responded to an induction regimen (maintenance regimens). The RCTs included people with moderate to severe Crohn's disease. Seven studies wholly or predominantly included adults with non-fistulising disease, two trials included adults with fistulae.(table 1). For IFX use in children, there were 8 trials selected and trails were selected for quality as described above. These are listed in table 2.

The outcomes reported in the clinical trials were mainly based on the Crohn's disease activity index (CDAI). The Pediatric CDAI (PCDAI) was reported in the paediatric studies. The inflammatory bowel disease questionnaire (IBDQ), a health-related quality-of-life measure, was also reported in some studies.
The CDAI is frequently used to assess disease severity. It is a composite of overall activity of Crohn's disease as assessed by clinicians, and has eight variables weighted according to their ability to predict disease activity. It gives a score ranging from 0 to over 600, based on a diary of symptoms kept by the patient for 1–7 days, and other measurements such as the patient's weight and haematocrit. A CDAI score of less than 150 is considered to be remission, a score greater than 220 is considered to define moderate to severe disease, and a score greater than 300 is considered to be severe disease. The paediatric CDAI (PCDAI) is an instrument similar to the CDAI but with less emphasis on subjectively reported symptoms and more emphasis on laboratory parameters of intestinal inflammation.
The Harvey-Bradshaw Index is another commonly used tool, which correlates well with CDAI. It is based on assessments of general wellbeing, abdominal pain, number of diarrhoeal stools per day, and the presence of abdominal mass and associated complications. Patients with a score of 8 to 9 or higher are considered to have severe disease.

2.4 Kort Studie methodologie

Beschrijf duidelijk de methodologie, studiepopulatie en uitkomstmaten (primair en secundair) van deze studie.

Argumentive literature study described above, a questionnaire study as to analyse the perceived economic value of IFX within the patient group, closed-end and opened interviewing of gastroenterologists in two peripheral hospitals on efficacy of IFX, guided panel discussion in ICC to obtain opinion spectrum in academic IBD specialists. Discussion with patients organisations based on provocative questioning, model calculation using Threda-software to obtain insight into economic value of IFX and underlying performance indicators.

3. Therapeutische waarde

De therapeutische waarde is de som van de waardering van alle voor de behandeling relevante eigenschappen van een geneesmiddel, die samen bepalend zijn voor de plaats van het middel binnen de therapie in vergelijking met andere beschikbare en aanbevolen behandelmogelijkheden. De therapeutische waarde wordt beoordeeld op de criteria gunstige effecten, ongunstige effecten, ervaring, toepasbaarheid en gebruiksgemak.

3.1 Clinical efficacy of IFX in adults with CD

3.1.1 IFX as induction therapy

An infusion of 5 mg/kg IFX can be given as induction treatment at week 0, 2 and 6. The efficacy to induce response and remission both in luminal disease and in fistulizing CD has been reported in several placebo controlled trials and has been confirmed in many open cohorts of patients throughout the world. Table 1 summarizes the results of prospective and retrospective studies on the outcome of IFX induction therapy [8-9, 11-14, 16-18]. Fifty – eight to eighty percent of the patients have an initial response to IFX [11-12, 19-20]. The trial of infliximab that mainly included people with non-fistulising disease studied a single-dose regimen. Participants were randomised to infliximab 5 mg/kg, 10 mg/kg, 20 mg/kg or placebo. Results were reported at 4 weeks. Infliximab at the licensed dose of 5 mg/kg achieved significant improvements in remission rate versus placebo. The rate ratio (RR) for remission (the rate of remission in the 5 mg/kg group divided by the rate of remission in the placebo group; remission defined as CDAI score below 150) was 12.04 (95% confidence interval [CI] 1.70 to 85.44). There were also significantly greater rates of 70-point reductions in CDAI (referred to below as response 70) in the infliximab 5 mg/kg group. [12]. In the larger ACCENT 1 trial [11], 58% of patients responded by week 2 and 27% achieved remission. A loading dose of three infusions of 5 mg/kg at 0, 2 and 6 weeks resulted in a significantly, but limited, higher increment of clinical response (from 59 to 69%, P=0.035) at week 10, compared to a single infusion [11]. Nevertheless, this finding justified the use of a three-dose induction scheme in CD. Overall, these studies demonstrated IFX to be effective in 58% to 80% of CD patients.

3.1.2. IFX as maintenance therapy

Clinical experience has shown that patients can relapse after a single infusion of IFX [11]. In a previous assessment of repeated administration of IFX (four infusions of 10 mg/kg every 8 weeks) in patients with CD retreatment with IFX maintained the clinical benefit up to 8 weeks after the last infusion in nearly all patients who responded to an initial dose of treatment. The interval for the prophylactic infusions of 8 weeks was chosen based on the pharmacokinetic properties of IFX [2]. Two studies of maintenance treatment in adults that mainly included people with non-fistulising disease were identified for inclusion. In one of these (ACCENT I, n = 573) all patients received a single infusion of 5 mg/kg infliximab and were then randomised to receive placebo, or infliximab at a dose of 5 mg/kg at weeks 2 and 6 and then every 8 weeks to week 54 (known as the 5 mg/kg group), or infliximab 5 mg/kg at weeks 2 and 6 and then 10 mg/kg every 8 weeks to week 54 (known as the 10 mg/kg group). [11]However, those whose disease initially responded but then worsened were allowed to cross over to treatment with a higher dose of infliximab at week 14. Those who crossed over from the placebo group were considered to have had episodic treatment, and those who crossed over from an active

treatment arm were considered to have disease that did not respond for most analyses. Results for ACCENT I demonstrated that infliximab improved the point prevalence of remission at weeks 30 and 54. At week 54 the point prevalence of remission RR for the infliximab 5 mg/kg group was 2.08 (95% CI 1.19 to 3.61), and the response 70 RR was 2.46 (95% CI 1.50 to 4.04).

The other infliximab trial (n = 73) recruited patients from one of the infliximab induction trials. Only those who responded to infliximab in the induction trial were eligible to enter this study. Participants were randomised to placebo or infliximab 10 mg/kg at 8-week intervals. Follow-up was for 48 weeks.

3.1.3. Loss of response

Patients may lose the obtained response to IFX. Almost one of every four patients in the study by Gonzalez et al. lost their response in a relatively short period of time, which is consistent with data obtained from randomized controlled studies [6, 11, 19]. In the ACCENT I study, patients using IFX had a median time to loss of response of 46 weeks (17->54)[11]. The management of these cases is not clearly stated in literature, but it seems that increasing the IFX dose or shortening the interval between doses may be rational alternatives [21]. Cessation of IFX after established remission for 12 months may result in relapse in up to 50% of patients [25].

3.1.4 IFX for fistulizing CD

Fistulas are a serious complication of CD and are difficult to treat. The incidence of fistulas in CD patients varies between 10 and 40% [20, 26-29]. Perianal fistulas, the most common variant, decrease the quality of life and increase the likelihood of total colectomy [19]. IFX was shown to be effective in two large placebo controlled trials for patients with perianal fistulizing disease. The study of infliximab induction treatment in fistulising disease compared infliximab at a dose of 5 mg/kg or 10 mg/kg with placebo. Follow-up extended to at least week 18. The primary outcome was a 50% reduction in the number of draining fistulae; the rate difference between the infliximab 5 mg/kg and placebo groups was 0.42 (95% CI 0.19 to 0.64). The secondary outcome was complete absence of fistulae; the rate difference between the infliximab 5 mg/kg and placebo groups was 0.42 (95% CI 0.21 to 0.63). Infliximab groups had statistically significant improvements in CDAI and perianal CDAI scores at week 2The larger ACCENT II [19] trial confirmed the beneficial effect of IFX on draining fistulas. All participants (282) received an induction course of three doses of infliximab 5 mg/kg and then responders and non-responders were randomised at week 14 to infliximab 5 mg/kg or placebo every 8 weeks for five doses. Patients were followed up for 54 weeks. After week 22 patients whose disease lost response could cross over to infliximab 5 mg/kg or 10 mg/kg. The primary outcome was time to loss of response (defined as a reappearance of a draining fistula, a change in therapy, a need for surgery, drop-out because of lack of efficacy, or worsening symptoms). Median time to loss of response after randomisation was 14 weeks for the placebo group and more than 40 weeks for the infliximab group.

3.1.5 IFX and concomitant treatment

The marketing authorization in Europe (the European "labelling") and the ECCO treatment guidelines have positioned IFX as second or third line immunosuppressive therapy in patients failing steroids and/or AZA [34]. The main rationale to use combined therapy in IBD was the intrinsic potential of IFX to induce anti-drug antibodies (immunogenicity). However, the use of concomitant IS medication is still questioned. Induction and maintenance therapy with MTX and IFX, although safe, has been shown to have no long-term advantage over IFX alone [35]. Similar findings on the lack of benefit of concomitant IS use have been noted for adalimumab [36] and certolizumab [37]. Apparently conflicting with these findings are the results from the SONIC trial, in which the combination of AZA and IFX was found to be superior to IFX monotherapy in achieving clinical response and mucosal healing in newly diagnosed CD patients. In this study, 508 patients with CD were randomized to receive AZA (2.5 mg/kg daily) and placebo, IFX 5 mg/kg (at 0, 2, 6 weeks and every 8 weeks thereafter) and placebo, or both AZA and IFX. At 26 weeks, steroid-free remission rates were significantly higher in patients receiving combination treatment compared to patients on IFX or AZA monotherapy (57% vs. 45% vs. 30%, respectively) [38]. The difference between the three groups persisted through one year of treatment. A course of steroids was allowed in all patients until week 12 to compensate for the slow onset of the therapeutic effect of AZA. Also, the total disappearance of mucosal ulcers was highest in the combined IFX and AZA group (44% IFX AZA vs. 19% AZA (P=0.001)). An important limitation of this study is that patients were immunosuppressive- and biologic-naïve and represent a different population compared to the earlier mentioned studies. The efficacy data of IFX treatment in CD patients clearly showed the synergic effect of concomitant IS treatment on IFX response [22-23, 38-39, 40-42]. There are several hypothesis on why concomitant IS treatment may lead to better efficacy to IFX. The first explanation is that IS reduce the risk of ATI formation. Earlier studies already showed that IS decreased the development of neutralizing ATI when this drug was used in an episodic, on-flare strategy, thereby probably contributing to a lower risk of losing response to the biologic [22-23, 35, 39-40, 43-44]. However, antibody formation still occurs in almost half of the patients treated with both IS and IFX [22]. Also, IFX serum levels were significantly higher in patients on concomitant IS therapy [22, 39, 43]. More recently it became clear that this protective effect is much less if at all present when patients are treated with IFX in a scheduled maintenance regimen [22-23, 39, 45].

Recently, a prospective open-label trial by van Assche et al [39] demonstrated that withdrawing IS from CD patients in remission on combined therapy for at least 6 months, did not affect efficacy over 2 years of follow up, but tended to decrease IFX trough levels. The trial indicated that the impact of withdrawing anti-metabolites in patients treated with scheduled IFX maintenance therapy had no or only limited risk of loss of efficacy, although IFX trough levels were generally lower after interruption of IS and this warrants further long term follow-up

IFX can be used as a bridge waiting for the delayed effect of AZA/6MP. An important point to consider in clinical practice however is, whether or not the bridge effect is holding with time; two different situations can be seen. In patients with previous failure to AZA/6MP a loss of efficacy was observed gradually, and at week 52 only 27% of the patients were still in remission off steroids in the IFX group. In such patients the bridge strategy thus is questionable. In contrast patients naïve for AZA/6MP at inclusion, despite the similar loss of

efficacy in time, more then 50% were always sin remission and off steroids at 1 year. Such patients probably would benefit from the bridge strategy [40]. In the Accent I study, the lowest incidence of infusion reactions occurred among patients receiving both steroids and IS, compared with patients only on IS or steroids [11]. In study by Farrell et al [43], patients receiving pre-infusion with hydrocortisone developed less ATIs than placebo-treated patients (p=0.06). However, this approach did not eliminate ATI formation or infusion reactions [43]. Many patients with CD receive IFX in an attempt to avoid corticosteroid side-effects, and, although rare, negative effects of administrating short –term intravenous or oral corticosteroid premedication exist [43].

The concomitant use of IS and pre-treatment with steroids reduce the risk of ATIs and of infusion reactions. Which of these strategies will optimally protect the patient is unclear.

3.1.6 IFX for extra intestinal manifestations

Extra-intestinal manifestations occur in up to 40% of patients with IBD. They include spondylarthritis (ankylosing sponylitis, sacroiliitis and peripheral arthropathy), peripheral arthritis, cutaneous manifestations (erythema nodosa, pyoderma gangrenosum), ocular inflammation (uveitis, sclera-conjunctivitis, episcleritis and scleritis), primary sclerosering cholangitis (PCS) and hypercoagulability [46, 47]. IFX seems efficacious for all systemic manifestations of IBD whether associated with CD or ulcerative colitis or even if there is no evidence of underlying IBD. The only placebo-controlled trial of IFX therapy for pyoderma gangrenosum showed short-term efficacy of IFX 5 mg/kg at 2 weeks in 6/13 (46%) of patients vs. 1/17 (6%) of placebo-treated patients (P = 0.025) [48]. IFX was found to be efficacious for the management of peristomal pyoderma gangrenosum a particularly disabling complication of CD or ulcerative colitis [49]. IFX is efficacious for treating uveitis [50-51]. The different joint disorders evolve parallel with the activity of the bowel disease. Although associated with IBD, they have a rather independent course. IFX relieves peripheral joint problems together with the bowel symptoms. Axial manifestations or spondylarthropathy associated with CD also respond well to IFX [52]. Moreover, both IFX and etanercept are very efficacious to improve disease activity, functional indices and quality of life in patients with active ankylosing spondylitis [53–56].

3.1.7 IFX and QoI

The impact on the physical, social as well as the emotional well being of patients is substantial and the disease decreases the QoI. Padierna et al found that 37.3% and 8.3% of CD patients suffer from anxiety and depression [57]. Common worries and concerns involve the uncertain nature of the disease reduced energy levels, medication adverse effects and the need for surgery or an ostomy bag. Although patients with CD who require surgery generally demonstrate the poorest quality of life, even relatively well patients with IBD exhibit a diminished QoI compared with non-IBD patients [31]. Gregor et al found the health utility scores of patients with CD to range from 0.3 to 0.7, which are similar to that of patients with severe angina or renal dialysis [58]. A significant short-term improvement in the Inflammatory Bowell Disease Questionnaire (IBDQ) was shown by several studies [16, 24, 47, 59-60]. Feagan et al concluded that maintenance treatment with IFX induced a significantly longer improvement in the QoL. Measurement of the QoL using the SF-36 resulted in a significant improvement as well [60]. Cadahia et al reported an overall improvement in the improvement in the physical domain of the SF-36 after four and ten weeks ($p<0.05$), as did Feagan et al after ten and 54 weeks [59-60]. The MCS did not significantly change in the trial by Cahadia et al [59]. Feagan et al only showed a significant increase in the MCS after 54 weeks in the 10 mg/kg IFX group, $p<0.05$ [60]. Overall, the individual scales of the SF-36 demonstrated greater improvement in scales relevant to the physical aspects of health as opposed to psychological measures.

The number of appropriate, high-quality articles is limited. Of all studies, only the RCT by Lichtenstein et al compared the use of IFX vs. placebo [31]. The other studies compared the effect of IFX within one study population or maintenance vs. induction treatment. Only two studies were not financially supported by the pharmaceutical industry [2, 16]. The results of both studies were in line with the studies supported by the manufacturer [16, 24, 31, 47, 59-60]. A clear conclusion can be made with respect to QoI. All studies describe a significant improvement in short – term and one study in long-term analysis.

3.1.8 The Netherlands specific aspects

Our own investigation as to the perceived value of IFX therapy supports the conclusions stated above. Both academic and peripheral gastroenterologists were unequivocally positive on both efficacy and effects on QoL of Infliximab, even when exposed to leading questioning prompting negative opinions on the medication. Also Dutch patients self-report a 97.8 % (*sic*; n=840) perceived improved QoL due to anti-TNF. The benefits of IFX treatment for CD extend beyond doubt to the Dutch setting.

3.2 Step-up or top-down IFX therapy

Patients with CD are more likely to have an inflammatory phenotype early on, in the course of CD. Nevertheless, the majority of patients with CD develop a disabling disease course leading to complications and surgery [61-62]. Especially young patients (<40 years) or patients with perianal lesions at diagnosis are at risk for complications. However, for an individual patient predicting a disabling disease course and the need for more advanced medical therapy has been difficult. Therefore, starting IS with the first or at least with the second course of corticosteroids has become general practice in young patients with CD. Treatment guidelines

generally recommend initial treatment with first-line agents, including mesalazine and systemic corticosteroids, following by AZA, with anti-TNF therapies reserved for patients in whom conventional therapies have failed. [38] A recently published clinical strategy trial from Belgium and the Netherlands randomized 133 patients with active CD naive to steroids and naive to AZA, to either a conventional step up strategy with full courses of steroids (prednisolone or budesonide) and introduction of AZA when they flared after tapering or became dependent on steroids [63] Patients in the top down arm received three infusions of IFX and were started on AZA at induction. From week 6, AZA was continued as a monotherapy and IFX was only administered upon flare. Until one year after the start of therapy, steroid free remission was more frequent in the early combined IS group (61.5% vs. 42.2%, difference 19.4% (P=0.05)). Also, the median time to relapse was longer in the early combined IS ('top down') group: 329.0 days vs. 174.5 days, P=0·03. The trial also confirmed that in patients who need corticosteroids to control their CD more than two thirds are treated with AZA after 2 years. As a caveat, it should be noted that this unblinded study is liable to the intrinsic observer bias associated with an open-label trial. The preliminary data from the Benelux step-up/top-down trial seem to suggest a role for IFX for bridging to IS. Induction therapy with IFX with maintenance with AZA resulted in a remission rate without steroids in 75% at 6 months vs. 41% for step-up therapy (P= 0.006) [64]. The details of this study are awaited for.
Dutch academic specialists strongly favour the step up protocol as standard treatment for newly diagnosed severe CD, but following leading questioning, it appeared however that peripheral specialists are more cautious.

3.3 Predictors of response to IFX

About thirty percent of patients do not respond to IFX for unknown reasons [12, 20-21]. Moreover, not all responders display a full response. It is important to identify reliable predictors for response to IFX in order to optimize the use of the drug and to gain insight in the differences in pathogenesis of different disease forms. It may also lead to improved cost-effectiveness [41-42]. Furthermore, identifying modifiable factors that are associated with a prolonged response could allow for optimization of response rates and duration [41]. The mean duration of response is 2-3 months [9, 18, 20]. Patients with biologically active inflammation as witnessed by increased CRP have the best chance of responding to IFX therapy [21, 65]. Orlando et al. claimed, no previous surgery and three infusions predicted a good response for luminal disease, whereas for fistulizing disease no variables were related to a good response despite a favorable trend of response was observed for perianal fistulas. (p=0.07) [33]. Parsi et al [41], showed that non-smoking and IS appears to be associated with a higher rate and a longer time of response to IFX. Rutgeerts et al [21], in a randomized placebo-controlled trial of 73 patients with inflammatory CD, showed a longer duration of response for patients on concurrent IS use (P = 0.17). Although this difference did not reach statistical significance, a relationship between concurrent IS use and longer duration of response was suggested. Similarly, in a study from the University of Chicago involving 129 patients with either inflammatory or fistulous CD, there was a higher response and remission rate for patients on concurrent therapy with 6-MP or AZA, but again this difference did not reach statistical significance [9]. A study by Farrell et al [18] however, did not find an improvement in response to IFX in patients on concurrent IS therapy. Vermeire et al [42], identified young age, site of disease (colitis) and concomitant IS as an independent variables favouring a short-

term responsiveness to IFX, whereas previous abdominal surgery and isolated ileitis were associated with poor response. The discrepancies in these study results may be due to different definitions of response, different patient populations, or different lengths of IS therapy. The only clinical, biological and genetic risk factors, having a better response to IFX therapy, reported in at least two independent randomized controlled trials or large cohort studies are non-stricturing disease, pure colonic disease [41, 66] and concomitant IS [41, 66]. The Odds ratio to respond when patients are taking IS was 3 (95%).

3.4 Immunogenicity

3.4.1 Antibodies to IFX (ATI)

IFX is a chimeric antibody and may be associated with the formation of ATI formerly called human antichimeric antibodies (HACA). The formation of antibodies to IFX may lead to infusion reactions, loss of response and serum sickness-like delayed infusion reactions [8, 10, 43]. In general, it can be stated that ATI interfere with the safety and efficacy of the drug. Immunogenicity leads to clinical problems especially when IFX is administered episodically. In the episodic re-treatment arm of the Accent I study [23], the cumulative incidence of ATI amounted to 30% through 72 weeks, which was significantly higher than the 10% (5mg/kg) and 7% (10mg/kg) in the group of patients treated with systematic treatment every 8 weeks. In the episodic treatment arm, there was a more rapid reduction in serum IFX concentrations from post infusion peak levels in patients with ATI, and a reduction in the magnitude and duration of clinical response. The presence of ATI was associated with a 12% increase in infusion reactions. Overall patients receiving IS had a lower incidence of ATI through the groups (10% vs. 18%) than patients not receiving IS. However, in the overall populations of the trial similar proportions of antibody-positive, -negative and inconclusive patients achieved clinical response (64%, 62% and 65%) and clinical remission (41%, 39% and 48%) at 54 weeks [23]. Baert et al [44] detected ATI in 38 of 125 (61%) patients and Farrell et al [43] reported ATI in 19 of 53 patients (36%). In these two studies was clearly demonstrated that the formation of ATI was associated with the occurrence of infusion reactions, lower post infusion IFX serum levels and with a shortened duration of response. The formation of ATI was decreased by concomitant therapy with IS. Baert et al [44] also found IFX concentrations were significantly lower at four weeks among patients who had had an infusion reaction than among patients who had never had an infusion reaction ($P<0.001$).

Vermeire et al [22] confirmed this finding and found in patients who developed ATI > 8µg/ml during follow-up, the IFX levels 4 weeks after the first infusion were retrospectively found to be significantly lower. This suggests, IFX levels at week 4 can be used as a predictor of response, ATI formation and infusion reactions. A trough level of < 4µg/ml after the first infusion had a positive predictive value of 81% to detect development of High ATIs (> 8µg/ml) during the course of treatment, and a trough level of < 2.5 µg/ml measured 4 weeks after the first infusion had a PPV of 86% to detect later development of high ATIs [22]. In contrast, trough levels of > 15 µg/ml measured 4 weeks after the first infusion were 80% predictive for the absence of ATIs during later follow-up, and trough levels of > 20µg/ml had a negative predictive value of 95% for developing ATIs during follow-up [21]. This means the concentration of IFX measured early after the first infusion of IFX (4 weeks) might be a good prognostic parameter for developing immunogenicity. A prospective controlled trial with will be needed to confirm this.

3.4.2 Antinuclear antibody (ANA)

ANA formation has been reported in 56% of CD patients treated with IFX [64]. The clinical relevance of ANA induction by anti-TNF agents is unclear, and lupus like disease has been reported in patients treated with all anti-TNF agents. In the study by Vermeire et al. [68] 2 patients developed Drug induced Lupus erythematodes, with anti-histone and anti-dsDNA antibodies, but without major organ damage [68]. In clinical trials and post-marketing safety cohorts the prevalence of drug related lupus with IFX has been between 0.2 and 0.6% [69]. Drug related lupus should be suspected in patients with IBD treated with anti-TNF agents who present with arthralgias, myalgias, serositis, facial rash and high ANA titers (particularly anti dsDNA). Occurrence of these symptoms in combination with high ANA titers often necessitates interruption of anti-TNF therapy which usually results in complete resolution of symptoms. However, the symptoms will recur when a patient are exposed to the same anti-TNF again [70]. It is currently unclear if switching to a second anti-TNF is a valuable option in patients with positive ANA and symptoms suggestive of drug related lupus.

3.4.3 Infusion reactions

Since IFX is infused intravenous, some patients experience, moderate acute infusion reactions characterized by headache, dizziness, nausea, flushing, chest pain dyspnoe, pruritis, asthenia, myalgia, arthralgia and gastrointestinal symptoms [4-6,8,10,43,68]. Acute infusion reactions (AIR) occur during or within one hour after infusion. AIR are generally mild to moderate, but may preclude further treatment and often herald loss of efficacy since they are associated with ATI induction [69]. Severe reactions with anaphylaxis on the contrary are exceedingly rare and are allergic, IgE mediated phenomena. Delayed infusion reactions occur usually in patients with a longer interval between infusions and are associated with rapid clearance of the drug. In the ACCENT I trial 4.5% of the IFX and 2.7% of the placebo infusions were associated with an infusion reaction. Also, 2.4% of the patients (14/573) met the definition of a delayed hypersensitivity reaction [11]. In the cohort of the study by Baert et al [44] a total of 27% of patients developed infusion reactions with episodic, on-flare IFX therapy. In a recent safety cohort reported by Fidder et al 115/682 or 17% of IBD patients developed an AIR and 7% a delayed-type hypersensitivity reaction. Both acute and delayed reactions occurred early on in the treatment (after a median of 2 to 3 infusions) and were linked to episodic therapy and the absence of induction therapy in a multivariate analysis [69].

Serum sickness-like reactions were defined clinically as the occurrence of at least one of the following cluster of features occurring 1-14 days after reinfusion of IFX: myalgia, artralgias, fever or rash [71]. The infusion reaction can be life threatening and require treatment with epinephrine. Severe anaphylactic or anaphylactic-like reactions with clinical symptoms including hypotension, laryngeal/pharyngeal edema and severe bronchospasm have already been reported during IFX infusion [71]. This underscores the fact that clinicians should be prepared to manage patients experiencing severe infusion reactions. Table 2 summarizes the results of prospective and retrospective studies on the frequency of acute infusion reactions, and presence of auto-antibodies in CD patients treated with IFX.

3.5. IFX safety in adult CD

Given that this agent neutralizes TNF-alpha, a key cytokine in host immune surveillance, the potential impact of IFX treatment on the development of infections, autoimmunity and malignancy must be monitored [4,68]. Concerns have been raised regarding the risk of neoplastic disorders with the use of the biologic agents, and the general risk profile of these agents. Long-term safety is an important issue as IFX use and indications are rapidly increasing worldwide.

3.5.1 Infections

Anti-TNF agents such as IFX have immunomodulatory properties. Even if ex vivo experiments have shown that human lymphocyte function is not affected by IFX recent experience has revealed a limited but real risk of serious infections. Case series have pointed out opportunistic infections occurring in IFX-treated patients [62]. The infections most frequently reported in clinical trials of anti– TNF-α agents were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis), but these did not occur significantly more frequently than in placebo-treated patients [12, 19, 21]. However, more serious infections, including pneumonia, sepsis, disseminated tuberculosis (TB), invasive fungal infections (histoplasmosis or coccidioidomycosis), and other opportunistic infections (pneumocystosis or listeriosis) have been reported after anti–TNF-α agent use [71-74]. Invasive opportunistic fungal infections that have been reported following anti–TNF-α treatment include histoplasmosis [71-72], coccidioidomycosis, systemic candidiasis, pneumocystis jiroveci (carinii) pneumonia, invasive pulmonary aspergillosis, disseminated sporotrichosis, nocardiasis [19], and cryptococcosis [72]. Viral infections, including herpes simplex, primary varicella infection, herpes zoster, and cytomegalovirus (CMV) infection, have been reported following anti–TNF-a therapy [8, 72]. In some cases, such as disseminated cytomegalovirus or varicella infection, these have been life-threatening [19, 72]

Since becoming widely available, reactivation of latent tuberculosis was reported to be associated with IFX use [11, 74]. A randomized trial of IFX vs placebo in rheumatoid arthritis patients with co-morbidities showed that serious infections were 3 times more likely to occur in rheumatoid arthritis patients treated with IFX 10 mg/kg compared with placebo-treated patients [72, 75]. Occurrence of intracellular and granulomatous infections, such as tuberculosis, histoplasmosis or CMV are now recognized to be a class effect of all anti-TNF agents [76-77]. Most patients with IBD receive a combined immunomodulator regimen also containing purine analogues, MTX or steroids. Also, in a recent safety analysis comparing an unselected single center cohort of IFX-treated patients with those on traditional therapy including steroids and anti-metabolites, the concomitant use of systemic steroids inferred a risk of serious infections (OR 2.7) [69]. The large (more than 10,000 patient-years as of August, 2005) TREAT registry, which follows North American patients started either on IFX or on alternative immunomodulatory treatment, revealed that the risk of serious infections in IFX-treated patients is mainly linked to concomitant use of systemic steroids [19,78]. Toruner et al [79] concluded, IS especially when used in combination, and older age, are associated with increased risk of opportunistic infections. In univariate analysis, use of corticosteroids (OR, 3.4; 95% CI, 1.8 – 6.2), AZA/ 6MP (OR, 3.1; 95% CI, 1.7– 5.5), and IFX (OR, 4.4; 95% CI, 1.2–17.1) were associated individually with significantly increased odds for opportunistic infection. Multivariate analysis indicated that use of any one of these drugs yielded an OR of

2.9 (95% CI, 1.5–5.3), whereas use of 2 or 3 of these drugs yielded an OR of 14.5 (95% CI, 4.9 – 43) for opportunistic infection. The relative risk of opportunistic infection was greatest in IBD patients seen at older than 50 years of age (OR, 3.0; relative to those 24 years or younger). No patient died from opportunistic infection [79] .

Abscesses (perianal, peristomal [20, 74], and abdominal [12, 19, 71]) are another serious complication. Despite the theory that persistent fistula tracks may lead to abscesses, proved by Present et al [20]. Sands et al showed that abscess development in patients with fistulising CD is not dependent on cumulative IFX exposure [72].

Part of the difficulty in determining causality is that many of the serious infections in patients treated with TNF alpha have occurred in patients on concomitant IS or corticosteroids that in addition to their underlying CD could predisposes them to infections. It also remains unclear whether the increased risk of infections in these immune compromised patients is caused by the underlying systemic chronic disease or the risk can be attributed solely to the use of biologic agents. A third point to be examined is the whether or not there is a causal relationship between persistent fistula tracks leading to abscesses in IFX treated patients.

3.5.2 Neoplasia

The risk of malignancy in patients exposed to IFX is controversial. Due to TNF-α's role as cytolytic factor in in-vitro and in-vivo models of tumor surveillance, there has been a concern that anti-TNF-α therapy might increase the likelihood of tumor development [80]. In contrast to clinical trial data with IFX and ADA in rheumatoid arthritis, A meta-analysis of placebo-controlled trials of anti-TNF therapies for CD (including IFX, ADA, certolizumab, etanercept, onercept, and CDP571) did not observe an increased risk of cancer among patients treated with anti-TNF therapy compared to placebo [77].

In a study by Colombel et al [71], who studied 500 CD patients for a median of 17 (range, 0-48) months with a median of 3 IFX infusions, 1.8% of the patients developed neoplasia [71]. In an age, sex, and IS matched control analysis at several Italian sites, Biancone et al found no increase of malignancy with IFX compared to standard therapy in 404 patients with IBD patients (RR1.4) [81]. Similar effort comparing a cohort of IFX exposed patients from a large single center experience with long term follow up (3775 patient-years in the IFX group) found no increased malignancy risk in anti-TNF treated patients as compared to controls [69]. Caviglia et al [4], reported malignancy in 6% of the patients. However, this study did not include a control group and consisted of a rather heterogeneous and relatively small population, which makes it difficult to establish a direct cause effect relationship between anti-TNF alpha and the increased risk of developing malignancies [4]. The number of available data remains relatively small. Only few studies were powered to detect a causal relationship between anti-TNF-α therapy and a rare event such as cancer, partly because patients were also using IS drugs. Animal data suggest that suppression of TNF may actually protect against tumor development [80].

3.5.3 Lymphoma

The discussion on the malignancy risk of anti-TNF agents in IBD has recently focused on lymphoma. In contrast to longstanding rheumatoid arthritis, IBD itself does not infer a specific risk of lymphoma [82]. However it is well known that patients with long-standing IBD treated with immunomodulatory drugs may be more susceptible to developing lymph proliferative disease [72-73, 83]. In a Swedish cohort of 217 residents of Stockholm County with CD treated with IFX, Ljung et al [84] identified three patients who developed lymphoma (of which two were fatal). The overall annual incidence of lymphoma was 1.5% in this cohort, compared with the overall population based value of 0.015% in the background Swedish population. One of the three patients had been on concomitant AZA [84], which is likely associated with a threefold elevation in risk of lymphoma in IBD [72]. In a meta-analysis of the available literature for the 8905 patients (21,178 patient-years) the observed rate of NH lymphoma was 3.2× higher than expected [85]. More reassuring results were noted in the large TREAT registry. Over 6000 CD patients, approximately half of whom have received IFX have been followed for an average of 1.9 years [31]. The incidence rate of lymphoma in the cohort who had received IFX was 0.62 cases per 1000 person-years, versus 0.57 cases per 1000 in the group not receiving IFX. Considering the effect on lymphoma risk from other forms of IS, it seems to be biologically plausible that anti–TNF-a therapy is associated with an increased relative risk of lymphoma. The highest estimate of the absolute risk is 1.5% annually [31], but this is an outlier, and most other estimates are in the range of 0.6 to 2 cases per 1000 person-years. The risk ranges from 1 case per 500 person-years to 1 per 1600 person-years.

Colombel et al states their data from a large treated population generally concurs with the conclusion that causal association between IFX and risk of malignant disease is unlikely [71]. Biancone et al found no association [80]. These findings may be related to the small sample size, it should be noted that the frequency of NHL shows wide variations in CD, and has also been reported to be uncommon.[80] There have been at least 16 cases of hepatosplenic T-cell lymphoma (HSTCL) occurring in the setting of combined IFX and thiopurine therapy [86]. The HSTCL occurred predominantly in a younger population (age range 12– 40 years, average age 23) and 15 of the 16 were male [73, 75, 86-87]. There have been at least 9 additional cases reported among patients treated only with thiopurine therapy [87]. HSTCL occurring in the setting of IBD in the absence of IS therapy have not been reported to our knowledge. The reports of 16 cases of a rare lymphoma in recent years and in young males on anti-TNF therapy suggest an increased evidence, but it is unclear at present whether the risk is particularly associated with combination therapy rather than with anti-TNF monotherapy or thiopurine monotherapy. We must point out that population based studies showed CD patients might have a generally increased risk at non-Hodgkin lymphoma's and squamous skin-cancers [11, 71, 83]. Because of the inconsistent findings in different studies and the failure to prove a causal relationship between IFX and the development of lymphoid or non-lymphoid cancers, further investigation, regarding large controlled studies with a long follow-up, is necessary.

3.5.4 Pregnancy

In the relatively young population affected by IBD questions about pregnancies and fertility are very relevant. In women, the key to a healthy pregnancy is adequate control of disease activity throughout the pregnancy. Women with active CD have poorer pregnancy outcome [31, 88]. IFX is listed as a pregnancy category B mediation and the product label states that "It is not known whether IFX can cause fetal harm when administered to a pregnant women" [10]. In murine models, no evidence of embryotoxicity or teratogenicity has been observed. However, anti-TNF antibodies are species-specific and limited information is available regarding pregnancy outcome in humans [89]. The safety of IFX beyond the first trimester is unknown because IgG subclasses are readily passed into the fetus during the second and third trimester [90]. Case reports and studies with a low number of patients did not show high rates of premature birth, miscarriages, congenital malformations, intrauterine growth retardation or small for gestational age parameters [31, 90-93]. In one case report, the mother received IFX during the conception period and first trimester, had active disease throughout and was treated with AZA, metronidazole and mesalazine as well. The pregnancy ended in premature birth at 24 weeks and death of the infant 3 days later of intracerebral and intrapulmonary bleeding [94]. In a study by Lichtenstein et al [31], of the 5807 patients enrolled, 66 pregnancies were reported, 36 with prior INF exposure. Foetal malformations have not occurred in any of the pregnancies. The rates of miscarriage (11.1% vs. 7.1%, P ¼ 0.53) and neonatal complications (8.3% vs. 7.1%, P=0.78) are not significantly different between INF-treated and INF-naive patients, respectively. Katz et al [95]. Reported data extracted from the IFX post marketing surveillance database regarding exposure to IFX before or during pregnancy in women with RA and CD. No increased risk of adverse events was detected. The results of pregnancy outcome were similar to those expected for the general U.S. population of pregnant women or pregnant women with CD not exposed to IFX [95]. These data suggest that IFX exposure during pregnancy results in outcomes, that do not differ from those in the

U.S. population of pregnant women and pregnant women with CD not exposed to IFX. The incidences of live births, miscarriages and therapeutic terminations were consistent with those observed in a national cohort of healthy women. It also remains possible that rare IFX related fetal complications were not detected due to the sample size, retrospective analysis and reliance on spontaneous reporting [31, 94]. Mahadevan et al suggest that the benefits of IFX in achieving response and maintaining remission in mothers with CD may outweigh the risk to the fetus of exposure to the drug [93]. A case report has shown that clinically significant IFX levels can be detected in the offspring of mothers who received IFX infusion. Monoclonal IgG1 antibodies didn't cross the placental barrier in early pregnancy but did appear in the serum of the newborn baby when administered in the last trimester. High IFX levels in the serum of the infant were likely to be due to placental transfer (IgG1 antibodies cross the placenta barrier in the 2nd and 3rd trimesters) and not breastfeeding, as IFX was not detected in the breast milk [96].

3.5.5 Miscellaneous

IFX and other agents that inhibit TNF-α have been associated with new onset or exacerbation of clinical symptoms or radiographic evidence of central nervous system demyelinating disorders, including MS and optic neuritis [19, 72]. Although there is evidence to suggest that demyelinating diseases occur more commonly in patients with IBD than among those without IBD [97], the temporal relationship of these events to initiation of anti–TNF-α therapy, and the improvement or resolution of symptoms following cessation of therapy, suggests a causative relationship. A history of demyelinating disease or optic neuritis constitutes a contraindication for the initiation of anti-TNF therapy, and patients developing these disorders with anti-TNF therapy should be permanently discontinued [97]. Worsening of severe congestive heart failure (NYHA class III–IV) is a class effect of anti-TNF agents and advanced cardiac failure constitutes a contraindication for these therapies [98]. Eczematous skin lesions are an emerging observation in patients treated with anti-TNF agents in a maintenance schedule. A recent analysis from a large single center experience found skin lesions ranging from dry itchy skin to psoriasis like eczema and palmo-plantar pustulosis in up to 20% of patients, more often in women (OR 1.9, 95% CI 1.24-2.85) [69]. Most patients can be helped with topical therapy.

3.6 IFX treatment in pediatric CD

CD presents before the age of eighteen years in up to 30% of all patients [99]. There seems to be a worldwide trend toward increasing incidence rates of pediatric CD [100]. In The Netherlands, the incidence of pediatric CD between 1999–2001 was estimated to be 2.1/100.000 children [101].

Unique to pediatric-onset disease is the potential for linear growth impairment and delay in puberty as a complication of undertreated inflammation. As among adults, the phenotypic spectrum of chronic CD is wide. Nevertheless, there are some specific demographic and phenotypic differences that characterize early- versus later-onset disease. For instance, CD occurring prior to puberty affects a preponderance of males, whereas adult females are more commonly affected; and, the majority of pediatric CD patients has ileocolonic or colonic disease, whereas adults more often present with terminal ileal disease without colonic involvement. The treatment paradigm for pediatric CD is quite similar to adult treatment, with

induction and maintenance of remission as main treatment goals. In children, special considerations in treatment are needed regarding optimal growth and development [102].
IFX has been approved by the US Food and Drug Administration (FDA) for the treatment of pediatric CD in May 2006 [103], fourteen years after its first use in a pediatric CD patient [104]. In March 2007, the European Medicines Agency (EMA) also approved IFX for the treatment of active CD in pediatric patients aged 6 – 17 years who do not respond to conventional therapy. IFX is the only anti-TNF drug approved for the treatment of pediatric CD.

3.7 Clinical efficacy of IFX in pediatric CD

3.7.1. IFX as induction therapy in pediatric CD

Table 2 summarizes the results of the first prospective and retrospective studies on the outcome of IFX induction therapy [105-112]. It is somewhat difficult to compare these results because of different infusion schedules, different definitions for response and remission, and variable timing of evaluating treatment response. Overall, these first studies demonstrated that IFX was very effective in the majority of pediatric CD patients, but relapse of disease was common after discontinuation of IFX treatment (despite continuous use of thiopurines or MTX). Furthermore, IFX induction proved to be successful in achieving mucosal healing [107, 110].

3.7.2 IFX as maintenance therapy in pediatric CD

The REACH study was the first, randomized trial that evaluated IFX maintenance treatment in pediatric patients with moderately to severely active CD [113]. At baseline, 112 patients (age 6 to 17 years) on concomitant IS received an induction regimen of 5 mg/kg IFX at weeks 0, 2 and 6. At week 10, 88% of patients had responded to induction with IFX, defined as decrease from baseline in the Pediatric Crohn's Disease Activity Index (PCDAI) of at least 15 points, with a total PCDAI score of 30 or less. One hundred three patients at week 10 were randomized to receive IFX maintenance treatment every eight weeks (n=52) or every twelve weeks (n=51). At the endpoint visit of 54 weeks, 29 of 52 patients (56%) in the two-month interval group were in clinical remission (PCDAI ≤ 10) and not requiring dose adjustments compared to 12 of 51 patients (24%) in the three-month interval group ($p<0.001$). Thirty-two patients (31%) crossed over during the study due to loss of response, which was successful in 75%. Allowing for dose intensification in case of relapse, remission rates at week 54 were also superior with every eight week dosing compared to every twelve week dosing (71% vs. 47%, $p=0.02$). In conclusion, the REACH study demonstrated that maintenance therapy every eight weeks was superior to every twelve weeks in maintaining clinical response and remission in pediatric CD.

A second randomized, open label study showed that scheduled IFX maintenance treatment every eight weeks was more appropriate for disease control compared to episodic IFX treatment [114]. Forty patients (median age 14.0 years) on concomitant IS received an induction regimen of 5 mg/kg IFX at weeks 0, 2 and 6. At week 10, 34 of 40 patients (85%) were in clinical remission (Harvey-Bradshaw Index (HBI) < 5 or complete fistula closure). Patients were randomized at week 10 to receive scheduled IFX infusions every eight weeks (n=18) or IFX infusions on demand (n=13). Endpoint evaluation at week 60 showed complete clinical remission in 83% of patients (15/18) on scheduled maintenance treatment compared to 61% of patients (8/13) on episodic treatment ($p<0.01$).

Furthermore, several observational studies have been published on the efficacy of repeated use of IFX in pediatric CD. The first long-term results came from a Dutch cohort and showed that IFX was effective in 16 of 30 patients (53%) after a mean follow-up of 25 months. The majority of pediatric CD patients, who were unresponsive to IFX therapy (8/14), underwent bowel resection [115]. Wewer et al introduced the term IFX dependency as an analogue to steroid dependency. Ninety days after intended cessation of IFX therapy, 10 of 24 patients (42%) became IFX dependent, indicating that repeated IFX infusions were needed to maintain initial clinical response [116]. Duricova et al found similar results after a follow-up ranging from 3 to 75 months: prolonged response was seen in 22%, IFX dependency in 66%, and no response in 12% of pediatric CD patients [117]. Wynands et al demonstrated that repeated infusions and dose adjustments were required in a substantial number of children to maintain clinical remission [118]. Eleven of 20 patients (55%) remained in clinical remission (HBI < 5) at twelve months of scheduled IFX maintenance therapy, whereas eight patients (40%) required dose adjustments because of loss of response. When IFX therapy was stopped after twelve months, eight of the eleven patients (73%) in clinical remission experienced relapse within the following year despite continued immunomodulator therapy. Recently, Sinitsky et al described treatment outcome in sixteen pediatric CD patients who were all treated with a three-dose induction scheme followed by scheduled IFX infusions. At one year, ten of twelve patients (83%) were in clinical remission (PCDAI < 15), but seven of these twelve patients had relapsed at some point within the first year [119].

Only three pediatric studies have reported on the efficacy of IFX after more than two years of treatment. De Ridder et al evaluated treatment outcome in 66 pediatric CD patients (age 8 – 18 years) after a mean follow-up of 41 months. Prolonged response was seen in 15% of patients, 56% were IFX dependent, while 29% eventually lost response to IFX. Twenty-six patients (39%) needed surgery despite the use of IFX. Dose adjustments were frequently needed to maintain clinical response (23% increase of dosage, 38% shortening of the interval between two infusions) [120]. A subsequent study from the same group described treatment outcome in an expanded cohort of pediatric CD patients (n=152). Kaplan-Meier analysis showed that the cumulative probability of losing response to IFX in patients who initially required repeated infusions, was 13% (±3%), 40% (±6%), and 50% (±9%) after 1, 3 and 5 years, respectively. Seventy-four patients (49%) needed one or two dosing adjustments, with a median time to any adjustment of six months [121]. Recently, Hyams et al reported on the long-term outcome in 128 pediatric CD patients on IFX maintenance treatment who had at least one year follow-up after initiation of IFX. The likelihood of continuing IFX at 1, 2 and 3 years was 93% (±2%), 78% (±4%) and 67% (±5%), respectively. Reasons for discontinuing IFX treatment were loss of response, allergy or elective discontinuation. Dosing adjustments at any time during follow-up were required in 49% of patients after a median period of nine months. Inactive disease that did not require concomitant corticosteroids in the preceding three months or surgery in the previous year, was seen in 54%, 67%, and 57% of patients at 1, 2, and 3 years, respectively [122].

Taken together, IFX has proven to be an effective maintenance therapy for pediatric CD, but a substantial number of patients loses their initial response and requires dose adjustments to maintain clinical response. Current (inter)national treatment guidelines recommend a three-dose induction scheme at week 0, 2 and 6, followed by scheduled maintenance treatment every eight weeks. Dose escalation or reduction in dose interval may be required to maintain remission in the long-term [123-124].

3.7.3 IFX for fistulizing pediatric CD

Although the presence of perianal disease (in combination with luminal disease) is often an indication to start IFX therapy, data on the efficacy of IFX in children with fistulizing CD are based on a small number of patients. Recently, Crandall et al performed post hoc analyses on the effect of IFX upon concurrent perianal disease in a subpopulation of 31 CD patients of the REACH study (38%) [125]. Two weeks after a single IFX infusion, 9 of 22 CD patients with perianal disease (41%) attained partial or complete response. Partial response was defined as an initial perirectal subscore of 10 (active fistula, drainage, tenderness or abscess) decreasing to 5 (1 – 2 indolent fistula, scant drainage, no tenderness). Complete response was defined as initial perirectal subscore of 5 or 10 decreasing to 0 (no symptoms or asymptomatic tags). At week 54, complete response was achieved in fifteen patients (68%), and partial response in one patient (5%). In addition, nine patients developed perianal signs and symptoms during IFX treatment: seven had complete response and two had no response at week 54.

Furthermore, five other pediatric studies have reported on the beneficial effect of IFX on perianal disease. In a French study, all perianal fistulas (n=12) were closed three months after a three-dose induction scheme [108]. Analyses from Italy demonstrated that 54% of patients (7/13) had complete closure of fistulas eighteen weeks after the first IFX infusion, 23% had a partial response (3/13), and 23% minimal response (3/13) [109]. Two studies from The

Netherlands also showed good clinical response with closure or drainage cessation in nine of sixteen patients (56%) with fistulas [115]. Additionally, prolonged response occurred significantly more often in patients with fistulizing disease compared to those without fistulas [120]. Finally, a recent study showed complete fistula closure after a three-dose induction scheme in nine of thirteen children (69%) with fistulizing disease [114]. IFX for treatment of enterovesicular fistulas in children has been described in two case series [126-127]. In total, eight children received a three-dose induction schedule with a variable outcome.
Overall, the reported data suggest that IFX is effective in the treatment of children and adolescents with fistulizing disease.

3.7.4 IFX and concomitant treatment in pediatric CD

Concomitant use of corticosteroids can be another (indirect) measure of evaluating the efficacy of IFX. Several studies have demonstrated short-term corticosteroid-sparing effects of IFX [105, 108, 110-111, 113, 128]. Furthermore, a recent American study showed that IFX was also associated with prolonged corticosteroid withdrawal over a three-year period. By 1, 2, and 3 years, less than 10% of patients continuing on IFX maintenance treatment were receiving corticosteroids [122].
Until recently, immunosuppressive therapy with thiopurines or MTX was usually continued during IFX maintenance therapy. The main rationale for this combined treatment was to improve short- and long-term clinical outcomes by preventing the formation of ATI, and achieving higher IFX serum levels. With the occurrence of HSTCL in predominantly young patients on combination therapy, many pediatric gastroenterologists converted to IFX monotherapy or combined therapy with MTX. To date, no pediatric studies have evaluated the response to IFX in relation to immunomodulator use.

3.7.5 IFX for extraintestinal manifestations in pediatric CD

Approximately 30% of children with CD will develop at least one extraintestinal manifestation after diagnosis, such as musculoskeletal, dermatological, opthalmologic and/or hepatobiliary manifestations [129-130]. IFX treatment for children with extraintestinal symptoms has only been described in case reports and small case series [131-138].

3.7.6 IFX and growth retardation

Growth retardation is a common complication of pediatric CD, and restoration of normal growth is considered a marker of therapeutic success [139]. The effect of IFX on linear growth was the primary outcome in only one study [140]. Both height velocity and height for age SDS improved significantly during median IFX therapy of 26 months, provided patients were treated prior to or in early puberty.

The REACH study also reported on the positive effect of IFX on linear growth [113]. Mean baseline height for age SDS of patients with at least one year delay in bone age improved significantly at both week 30 (mean improvement in SDS of 0.3) and week 54 (mean improvement in SDS of 0.5). Significant increases in mean height for age SDS or height velocity SDS were also observed in three other studies [108, 110, 114]. In contrast, three retrospective studies found no significant improvement of growth, but details on pubertal status were not available in these patients [116, 119, 141].

Thayu et al demonstrated that IFX induction therapy was also associated with improvement in biomarkers of bone formation. Serum bone-specific alkaline phophatase (BSAP), N-terminal propeptide of type 1 collagen (P1NP), urine C-telopeptide of collagen cross-links (CTX-1), and deoxypyrodinoline increased significantly during induction, and were associated with increases in height for age SDS at 54 weeks [142].

3.7.7 IFX and Qol in pediatric CD

To our knowledge, Qol of pediatric CD patients treated with IFX was only assessed in the REACH study [113]. A subset of 76 patients (68%) filled in the IMPACT III Questionnaire, a validated questionnaire in patients ranging in age from 10 – 17 years in North America. Response to IFX was associated with improved Qol. The mean IMPACT III scores at week 10, 30 and 54 improved significantly from baseline.

3.8 Step-up or top-down IFX therapy in pediatric CD

The great majority of CD patients included in pediatric studies on IFX were treated according to a step-up strategy, indicating that conventional treatment had failed before IFX therapy was initiated (steroid dependency, steroid resistance, intolerance or insufficient response to IS). However, it could be more effective to use IFX early in the disease course, because the early stages of immune-mediated disease may be more susceptible to immunomodulation [143, 144], which may alter the natural history of CD. Moreover, since the accumulation of tissue damage is a key factor of IBD and often leads to stenoses and/or fistulas, irreversible destruction of the digestive tract requiring surgery might be prevented.

Experience with a top-down approach is limited in pediatric CD. In two case reports, IFX was used as first-line therapy in a fourteen-year old boy and twelve-year old girl. An impressive clinical improvement was seen after two IFX infusions, and they were still in clinical remission on combination therapy of 6-MP and Asacol after five months, and thiopurine monotherapy after seven months, respectively [145, 146]. Recently, a South Korean study retrospectively compared three treatment strategies in 36 newly diagnosed pediatric CD patients with a minimal follow-up of two years [147]. Group A (n=10) received induction treatment with oral prednisolone and mesalamine maintenance treatment; group B (n=13) was treated with oral prednisolone and AZA; and group C (n=13) received induction with IFX, followed by IFX and AZA maintenance treatment for one year, and AZA monotherapy after that year. At one year

follow-up, there were significant differences in relapse rates between group A and C (80% vs. 23%, p=0.012), and group B and C (62% vs. 23%, p=0.047). Relapse was defined by a PCDAI score > 10. After two years, relapse rates were 90%, 77% and 39% in group A, B, and C, respectively. This study was limited by the small number of patients, retrospective data collection, and potential biased assessment of treatment efficacy.

Although these limited data support the view that early use of potent immunosuppressive therapy can change disease course, they need to be confirmed in large, prospective trials to determine the benefit-risk ratio of this approach, as there are concerns about potential dangerous long-term side effects of IFX.

3.9 Predictors of response to IFX in pediatric CD

Although IFX is effective for the majority of pediatric CD patients, about 5 – 15% of patients does not benefit from induction therapy (primary nonresponders) [108, 113-114, 118], while other patients eventually lose their initial therapeutic response [118, 120]. This interindividual variation in response is likely to be caused by multiple host factors, such as disease and immune phenotype, and genetic background.

In children, episodic treatment has been associated with higher relapse rates compared to scheduled maintenance treatment [114]. Other clear risk factors have not yet been identified, although some interesting data have emerged. Two studies have suggested that IFX was more effective when therapy was initiated early in the disease course [106, 109], but three other studies failed to demonstrate this association [108, 111, 120]. Duricova et al found that stricturing/penetrating disease behaviour and intestinal surgery prior to IFX treatment were significantly associated with treatment failure. No associations were found between genetic polymorphisms (TNF-308 A>G, TNF-857 C>T, Casp9 93 C>T, FasL-844 C>T, LTA 252 C>T and CARD15) and treatment outcome [117]. A recent study by Dubinsky et al found six known susceptibility loci that were associated with primary nonresponse, as well as pANCA (perinuclear antineutrophil cytoplasmic antibodies) positivity [148].

To conclude, it is important to find good predictors of (non)response to select the most suitable patients for IFX treatment, which will prevent exposure and toxicity in patients who will not benefit from IFX.

3.10 Immunogenicity in pediatric CD

In three small, pediatric studies, ATI were detected in about one third of patients [118, 149, 150], which is in contrast to the presence of ATI observed in the REACH study (3%) [113]. However, this test result should be interpreted with caution, as the majority of patients (77%) had inconclusive test results for ATI due to detection of IFX in the serum. The presence of ATI was found to be associated with an increased risk of infusion reactions and shortened duration of response [118, 149, 150]. Furthermore, Miele et al also showed that concomitant use of thiopurines or MTX had a protective role against development of ATI; there was a trend towards a lower prevalence of ATI formation in patients younger than fourteen years of age; and, in contrast to adults, the interval between IFX infusions did not influence the formation of ATI in children with CD [149]. Candon et al demonstrated that the prevalence of ATI in patients treated with a single infusion was significantly higher than those treated with three consecutive infusions (78% vs. 16%, p=0.003) [150].

Pooling of seventeen pediatric studies showed acute infusion reactions in 154 of 1040 patients (15%) and in 209 of 6464 infusions (3%) [105, 107-109, 111, 113-114, 116, 118, 120 128, 149-154]. The rate of infusion reactions per patient varied from 0 – 39%. Most reactions were mild and responded rapidly to treatment, temporarily stopping the infusion and/or reducing the flow rate of the infusion. Jacobstein et al showed that use of premedication (antihistamines, antipyretics, or corticosteroids) did not seem to prevent the development of acute infusion reactions. Once an infusion reaction had occurred, premedication tended to reduce subsequent reactions [153]. Delayed hypersensitivity reactions occurred in 2 – 8% of patients [111, 114, 116, 151-152]. Female gender, the use of IS for less than four months, and previous infusion reactions have been identified as possible risk factors for subsequent infusion reactions [151-152]. Kugathasan et al observed a significant difference in the rate of severe systemic reactions in adult (11/52, 21%) and pediatric patients (1/34, 3%, p<0.02). Delayed systemic reactions were not seen in patients younger than seventeen years of age. They concluded that episodic IFX retreatment, specifically a distant second infusion, was associated with high rates of severe systemic reaction in adults, but not in children [154].

Formation of autoimmune antibodies has been described in pediatric CD patients treated with IFX. Positive antinuclear antibodies, without any clinical symptoms, were detected in 20 – 29% of patients [108, 113-114]. The incidence of formation of antibodies to double stranded DNA varied from 0 – 10% of patients [107-108, 113]. Development of a systemic lupus erythematosus-like syndrome is rare in the pediatric population, and has been described in case reports only [155-156]. Another autoimmune disorder that has been described sporadically in pediatric CD patients on IFX, is vasculitis (Henoch-Schönlein purpura, vasculitis of the fifth finger) [111, 119].

3.11 IFX safety in pediatric CD

Pooling of pediatric studies shows serious or unusual infections in 34 of 1031 patients (3.3%): sepsis (n=4), Listeria monocytogenes meningitis (n=1), herpes zoster infections (n=9), pneumonia (n=4), abscess (n=11), cutaneous tinea infections (n=3), Pseudomonas infection of a gastrostomy site (n=1), and in one patient appendicitis and pancreatitis [105-120, 122, 128, 151]. Furthermore, several case reports have reported on serious or unusual infections in pediatric patients treated with IFX (Epstein-Barr virus (EBV) associated hemophagocytic

lymphohistiocytosis, opportunistic fungal skin infection with Pityrosporum folliculitis, flare-up of an intramyocardial inflammatory process, fatal case of disseminated CMV) [157-160].
Beside this latter case, another two deaths during IFX treatment were reported in pediatric literature. One of the patients with sepsis died after the fifth IFX infusion [115]. This patient was malnourished, had undergone multiple surgical procedures, and was leucopenic as a consequence of AZA therapy. The sepsis may have originated from an abscess located near a stenosis in the colon. The other patient was reported by Hyams et al: an 11-year old male suffered from cardiac arrest secondary to cardiac arrhythmia associated with a long QT interval. The patient had previously suffered a near sudden death from arrhythmia before being diagnosed with CD [122].
Another important issue in the management of IFX administration is a potential increased risk of malignancies. In pediatric literature, one case of a bowel-associated Hodgkin's lymphoma has been described in a fifteen-year old female patient who was treated with 6-MP and eight infusions IFX [122]. Lee described a case of undifferentiated leiomyosarcoma from the umbilicus with liver and lung metastases in a six-year old boy, eighteen months after IFX induction therapy [161]. Indirect observations between IFX and childhood malignancies were assumed in a study by Cezard et al [108]. Increased EBV polymerase chain reactions occurred in eight of 21 patients (38%) and returned to normal after IFX was stopped. Authors suggested that retreatment with IFX may lead to an increased risk of developing EBV-induced lymphoma. In 2005, Thayu et al reported on the first pediatric IBD patient with HSTCL who had been treated with 6-MP in combination with IFX [162]. According to recent data from Centocor, the number of reported HSTCL cases under combination therapy has increased to eighteen (data on file, Centocor).
IFX treatment has been associated with rare cases of neurological disorders in adults, such as optic neuritis, seizures, and demyelinating disorders. In children, one case of posterior reversible encephalopathy syndrome following the first IFX infusion has been described in a fifteen-year old boy with CD [163]. Another case report described a sixteen-year old CD patient who developed complex regional pain syndrome type I after his first IFX infusion [164]. To our knowledge, no other neurological disorders have been reported in pediatric patients. Worsening of severe congestive failure has never been reported in children as far as we know.

Dermatological symptoms such as eczema, or psoriasiform lesions, are an emerging observation in pediatric patients treated with IFX. Two case reports reported on a new-onset psoriasiform skin rash in pediatric patients treated with IFX [165, 166].
In conclusion, severe adverse events of IFX treatment are reported in low frequency, but they may be severe and even fatal. In 2010, Centocor (manufacturer of IFX) has initiated a prospective long-term observational registry of pediatric CD patients in Europe and North-America. This registry intends to collect information on all serious adverse events associated with IFX, as well as other medical therapies for CD.

4. Farmaco-economic analysis

4.1.1 Costs analysis for the Netherlands

The Netherlands spent 57.5 billion euro on healthcare in 2003 [167]. According to the Organization for Economic Co-operation and Development (OECD) in 2001, € 18222 million were spent on curative care in The Netherlands [168]. Of the total spent on curative care, 69% was provided in hospitals. General health has improved in the OECD countries, accompanied by increased healthcare costs [169]. In 1970 five percent of the General National Product in The Netherlands was spent on healthcare and this percentage increased in 2003 to 8.8% [167]. Today, the increased government expenses on healthcare are larger than the economic growth. Several factors are responsible for this phenomenon. An important factor is the higher drug costs. Since 1977 there has been a five percent annual growth in drug expenses. In 2005, 0.2% (119 million euro's) of the total healthcare budget of The Netherlands was spent on patients with IBD. For CD, 31% of costs were attributable to hospitalization, 33% to outpatient care, and 35% to pharmaceutical claims.

IFX costs €672,61 per bottle of 100 mg [170]. With an average body weight of 70 kg, the costs are € 2690 per infusion (350 mg, four bottles). In the induction period, the infusion frequency is higher. For these first three infusions at week zero, two and six, the costs are €8071 per patient. For maintenance treatment with IFX, the frequency of administration is once every 8 weeks. This amounts to € 17488 per patient per year. The average costs of IFX treatment, per year, in the first five years of treatment are € 18564 per patient. A recent study stated there are 34268 patients in the Netherlands are diagnosed with CD [171]. In the Netherlands, 70% of CD patients will eventually be in need of some sort of CD related surgery. Today, all patients eligible for surgery receive anti-TNF agents before surgery. We can therefore say that it is reasonable to expect that 70% of patients will use IFX or a similar biological at least once. Episodic treatment is very rare; almost all patients receive maintenance treatment [172]. Once diagnosed, patients will remain ill for the rest of their lives. Assuming the disease duration is 70 years, 1% of all CD patients will need to start IFX In first 5 years of treatment, these 342 patients cost € 6.348.888 of IFX treatment per year (a theoretical calculation). In a five year time period, 1700 patients will be eligible for IFX treatment.

4.1.2 Costs analysis - general

Schering-Plough carried out three analyses comparing IFX with standard care in adults with severe active CD, in fistulizing disease and in children and young people. The analyses used a Markov model with states representing progression over a 5-year period. For fistulizing disease the same basic model was expanded to include health states relating to fistulae. The model considered two IFX dosing schedules: maintenance treatment and IFX clinical discretion (ICD). ICD approximates episodic treatment: an induction dose of 5 mg/kg at week 0, and 5 mg/kg thereafter according to clinical discretion. The definition didn't guarantee episodic treatment or rule out maintenance treatment. Maintenance was modeled as 5 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter. The base-case incremental cost-effectiveness ratios (ICERs) for severe active CD for maintenance treatment compared with standard care was € 30.025,51 per QALY gained. For ICD treatment, IFX dominated standard care (that is, IFX was more effective and less expensive than standard care). When maintenance treatment was compared

with ICD the ICER was € 530180 per QALY gained. In fistulizing disease the ICER was € 34780 per QALY gained, and for pediatric patients the ICER was € 16102 per QALY gained, both for maintenance treatment compared with standard care. Sensitivity analysis suggested that the results were most sensitive to changes in the average weight used for patients. When this was increased from 60 kg to 70 kg, it caused the ICERs to increase to over € 34775 per QALY gained in all adult analyses [173].

4.1.3 Cost analysis – patient and physicians

To assess perceived economic value to the patient population, 68 patients were challenged to indicate whether they would be prepared to pay on top of existing health care costs for IFX out of their own pocket. Maybe unsurprising, in general this evoked irritated opinions, people generally finding that current health care costs are very high already and 13,8 % of patients would refuse to do so, whether 10,2 % of patient professed not to harbor any opinion on this issue. All other patients however would be prepared to pay, although 45,5 % of patients indicated that they would only be prepared to pay Euro 250, - or less. Nevertheless, current health costs have not saturated yet the desire of patients to pay for IFX therapy. The reverse question (would you like to have lower health care-costs in return for none-reimbursement of IFX therapy was unfortunately not asked.

Within Dutch specialists whether academic or peripheral the economic efficacy of IFX therapy was not in doubt, even when prompted to express negative opinions in this respect by leading questioning. Threda analysis shows that IFX is independent performance indicator for the quality of Dutch Health care.

4.2 Cost-effectiveness of IFX maintenance treatment.

In general, CD has an expensive course of disease, since diagnosis is at an early age and life expectancy is normal. A cost/utility analysis of different medical treatment options for perianal fistulae in CD showed that interventions involving IFX were effective but expensive, with a cost of more than € 251491 for each quality adjusted life-year gained [174]. However, 2 studies have suggested that treatment with IFX leads to decreases in use of health care resources and in overall direct medical costs [175-176]. Although the efficacy of IFX treatment in CD patients is proven, prescription of IFX is hampered in daily practice due to its costs (the Netherlands: up to € 17500 yearly) and the funding system (such as in the Netherlands, Belgium, Canada and the USA) [2]. Annual direct medical costs for CD patients are predominantly caused by surgery and other inpatient services, such as hospitalization, resulting in 81% of the costs, whereas medications only account for 10% of the costs [2,174-175]. In order to increase the chance of achieving sustained CDAI remission, patients need to be maintained on IFX therapy every 8 weeks after the induction, as designed in the ACCENT I trial [11]. This increases the direct drug costs, compared with the strategy of episodically re-treating patients with IFX as they flare. However, this increase can potentially be offset by reductions in hospitalization and surgeries/procedures in patients who achieve sustained remission. Furthermore, the improvement in employment status and Qol in these patients will eventually translate into increased productivity and decreased caregiver burden which will in turn reduce the indirect and total cost of caring for the disease. However, most IFX studies have been done with patients who suffer from moderate to severe CD. These patients are responsible for the majority of the costs of care and have the greatest burden of disease [74]. This is not a problem when the step-up approach is used. If we switch to a top-down approach, research to the cost-effectiveness in patients with mild to moderate disease should be done. A shortcoming in the current studies is the lack of an appropriate control group, with comparable disease activity. The likelihood that patients, treated with IFX, are the sickest group also would be the ones, most likely to fail therapy and to accrue additional healthcare use and its associated costs, suggests that the overall impact of the drug may have been underestimated by studies. A study by Lichtenstein et al showed that adults with CD miss more work than do adults without the disease [74]. Another finding emerging from this study, was that both the number of the hospitalizations and the number of surgeries decreased as the percentage of time in CDAI remission increased ($p < 0.01$ and $p < 0.05$ respectively) [74]. In a retrospective study by Rubenstein et al [107], including 79 patients. a decrease was seen in the annual incidence of all surgeries (38%, $p < 0.01$), gastrointestinal (GI) surgeries (18%, $p < 0.05$), endoscopies (43%, $p < 0.01$), ER visits (66%, $p < 0.05$), all outpatient visits (16%, $p < 0.05$), outpatient GI visits (20%, $p < 0.01$), all radiologic examinations (12%, $p < 0.01$), and non-plain films (13%, $p < 0.01$) [175]. Remission of CD increases employment and is associated with a reduced number of hospitalization and operations, as well as a normalized Qol [2,74]. Because IFX can induce and sustain remission in most patients with refractory and fistulizing CD, this strategy could be cost-effective despite its costs [2]. A recent study by Sprakes et al showed, IFX use resulted in CD–related cost savings and hospital resource use. The reduction in CD related costs was significant in the 12 months following IFX therapy ($p < 0,001$). However, this was not sufficient to cover the cost of therapy. In order to be more cost-effective, they state only patients who are likely to do well on IFX should be selected for this treatment. This may reduce overall costs to the health service [177].

4.3 Cost-effectiveness of IFX treatment - conclusion.

Although IFX treatment is widely perceived to be cost effective, the statement that IFX use is cost-effective is premature. The available studies do not provide the empirical evidence for this assumption: costs were not calculated and cost-effectiveness ratios were not constructed. Additional research is needed to evaluate the impact of currently available therapies on the Qol in IBD patients. Mathematical models have predicted an overall savings of health care costs with the introduction of this agent. Ongoing cost analyses will determine the true impact of IFX upon the cost of care for patients with CD.

5. Recommendations for further research

5.1 Optimizing therapy starts with selecting the ideal patient

In clinical trials and also in open-label experience about 30% of patients with IBD have failed to respond to IFX and clear predictors of response could improve the benefit to risk ratio of anti-TNF therapy. Unfortunately, the prime candidate responder to IFX still needs to be profiled. It is mandatory to continue to search for clinical parameters that can identify those patients who are more likely to benefit from current or new treatments. In this respect, studies on genetic polymorphisms, serological markers, and cytokine profiles could ad more insight to the problem and could improve the understanding in the mechanism of action of drugs. More importantly the insights derived from such studies would enable practitioners to better serve patients with CD by offering them a more efficacious, individually tailored therapeutic management.

5.2 Safety

Short- and long-term IFX treatment is generally well tolerated. However, clinicians must be vigilant for the occurrence of infrequent but serious events, including serum sickness like reaction, opportunistic reaction and sepsis, and auto-immune disorders. Caution is required when prescribing the drug in children, pregnant women and elderly patients. In chidren and adolescents, safety issues are even more crucial, because of the life expectancy of many decades. Moreover, the HSTCL occurs specifically in the young patients. Elderly often present with co morbidity. [6, 71] Only a prospective pregnancy registry of IBD patients will adequately differentiate between the effects of disease activity and medication use on adverse pregnancy outcome

5.3 Concomitant therapy

Despite the ten years of experience with IFX in the clinical practice not all controversies have been solved. The concomitant use of IS and pre-treatment with steroids reduce the risk of ATIs and of infusion reactions. Which of these strategies will optimally protect the patient is unclear. It also remains unclear if the benefit of concomitant IS therapy is a result of the decreased immunogenicity, selection of patients with a inflammatory phenotype or synergistic activity. More research is needed, to find out which of the theories regarding IS therapy is true and which concomitant treatment results in the highest benefit for the patient. Selecting patients with a high a priori likelihood of response to biological agents also improves the benefit to risk profile.

5.4 Conception and pregnancy

Small series of women who gave birth to a child after having been exposed to IFX during pregnancy do not show excess pregnancy or peri-partum complications. It also remains possible that rare IFX related fetal complications were not detected due to the sample size, retrospective analysis and reliance on spontaneous reporting [31, 94]. Low maternal IFX levels at birth are associated with shorter IFX exposure times in the newborn. Adjustment of dosing intervals should be considered in the third trimester to minimize exposure to the infant. How and when these adjustments should be administered, is unclear. Follow-up of larger numbers of pregnant women exposed to IFX will be necessary to definitely exclude any fetal risks.

5.5 IFX and vaccination

Based on available data, the benefits of IFX use in keeping the mother's disease under control may outweigh the unknown risk to the fetus of exposure to drug. IgG1 antibodies cross the placenta barrier in the 2nd and 3rd trimesters. IFX is detectable in infants up to 6 months from birth. There is nothing known about the effect of IFX in exposed infants on their vaccination status. In the Netherlands, infants receive their first vaccination at the age of 2 months. Their immune status is not determined afterwards. It might be possible, that these children are not fully protected and therefore at risk for serious infections. Since there is no data available yet, using IFX in the second and third trimester is a very complex decision for the mother and the treating doctor. Further studies arte needed to determine the implications of infant IFX exposure on vaccination status and immune status development.

5.6 Head to head comparison with other biologics in order to see which anti-TNF is more effective and cost-effective

It is widely recognized that the choice between IFX (Remicade) or ADA (Humira) is relevant for anti-TNF-naïve CD and that a significant number of patients will benefit and costs would be reduced if an optimal choice is made and guidelines need urgently to be optimized. The two pharmaceutical industries involved (MSD for Remicade and Abbott for Humira) are for obvious reasons afraid of a head-to-head comparison of the two medications, but for decision makers such a trail would allow the design of more cost-effective care of CD patients. Especially, in view of the large economic costs associated with CD, it is easy to envision how even moderate differences in efficacy can have big economic and social impact. The question as to whether ADA or IFX is more cost-effective is highly timely in view of the recent decision of the Dutch Health Ministry to place the cost burden associated with both IFX and ADA therapy on intramural funds. This will stimulate hospitals to pursue a long-term cost-effective strategy with respect providing anti-TNF therapy (until this year, Humira was considered an extramural medication, so reimbursed by the insurer, whereas IFX was paid from intramural funds) and thus also from this angle information as to the comparative cost-efficacy of IFX and Humira is highly relevant. Therefore to compare efficacy of ADA and IFX a head-to-head study is warranted, both looking first line therapy as well as following failure of the primary initiated anti-TNF medication. The results should allow rational funding decisions and definition of evidence-based guidelines with respect to the clinical use of IFX and ADA in CD.

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Bijlagen

Table 1. Studies on the efficacy of Infliximab therapy in adult Crohn's disease

Study	N	Age (yr)	Infliximab	Treatment outcome	Follow-up
Hanauer et al. [11] ACCENT I.	573	28-46	All: a single infusion of IFX. at wk 2 and 6, and every 8 weeks thereafter: I: infusion placebo II: infusion IFX 5mg/kg III: infusion IFX 5 mg/kg at week 2 and 6. 10mg/kg every 8 weeks thereafter	58% responded to a single of IFX within 2 weeks.	54 wk
Targan et al [12]	108	37.6y	1 infusion, 5, 10 or 20 mg/kg	12wk after diagnosis, one third of the CD patients achieved remission. As compared with 4 percent of patients given placebo (p=0,005)	12 wk
Martimore [13]	57	18-76	1 infusion 5mg/kg or 5mg/kg at week 0,2 and 6.	89% clinical response 52% (30pt) remission at 4 weeks. Of which 10 pt had remission > 12 wkn. 42% of fistulae closed.	4-70 wk
Hommes et al.[14]	71	17-59	As many infusions as needed. 5mg/kg.	81% of luminal CD patients responded. 87% patients with fistulous CD responded.	52 wk
Van Balkom [16]	56	L 31.3 y F 33.4 y	L one infusion 5 mg/kg F infusion at week 0,2,6 5mg/kg.	L: 4 wk, the mean total and dimensional inflammatory bowel disease questionnaire scores improved compared to baseline (P < 0.001). F: at week 6, all scores changed from baseline (P < 0.05).	10 wk.
Ardizzone [17]	63	Mean 33	5mg/kg at week 0,2 and 6.	Luminal: wk 2: 42,5% response, 31,3 % remission wk 10: 80,6% response, 71% remission and off steroids fistulizing: wk 10: 46,9% complete response, 25% partial response, 28,1% no response	10 wk.
Farrell [18]	100	15-84	5mg/kg	60% of patient with active disease experienced ≥ 50% reduction of their HBI at week 2. 69% of patients with	6 mo.

				fistulous disease experienced ≥ 50% reduction of their PDAI at week 2.	

Table 2 Studies on the efficacy of infliximab induction therapy in pediatric Crohn's disease

Study	N	Age (yr)	Infliximab	Treatment outcome	Follow-up
Hyams et al (105)	19	9 – 19	1 to 3 infusions (5 mg/kg)	Wk 12: significant decrease in PCDAI	12 wk
Kugathasan et al (106)	15	6 – 18	1 infusion (5 mg/kg)	Wk 4: 94% response Wk 10: 67% remission Wk 52: 21% prolonged response	52 wk
Baldassano et al (107)	21	11 – 17	1 infusion (1, 5 or 10 mg/kg)	100% response, 48% remission at some point during study	12 wk
Cezard et al (108)	21	11 - 17	3 infusions (5 mg/kg on days 0, 15 and 45)	Day 45: 90% remission Wk 52: 10% prolonged response	52 wk
Lionetti et al (109)	22	3 – 18	mean 3.3 infusions with an interval range from 2 - 12 wk	Wk 18: significant decrease in PCDAI	18 wk
Borrelli et al (110)	18	6 – 18	3 infusions (5 mg/kg on wk 0, 2 and 6)	Wk 8: 56% remission	26 wk
Lamireau et al (111)	88	3 – 18	median 4 infusions	Day 90: 34% remission, 53% improvement in symptoms, 13% relapse	13 wk
Afzal et al (112)	24	1 – 14	3 infusions (5 mg/kg on wk 0, 2 and 6)	After induction: 71% clinical remission 82% relapse within 4 mo of 3rd infusion	Mean 2.1 yr

Biographies:

Prof. Dr. Maikel P. Peppelenbosch,
Maikel Petrus Peppelenbosch werd geboren op 20 juli 1967 in Utrecht. In 1985 behaalde hij zijn VWO diploma aan het Herman Jordan Lyceum in Zeist. Hij studeerde medische biologie aan de Universiteit Utrecht en promoveerde daar in 1994 (cum laude). Daarna werd hij postdoc, eerst aan de UU, daarna aan het Ludwig Institute for Cancer Research in Londen. In 1996 werd hij senior-onderzoeker bij het instituut voor biotechnologie in Gent. Vanaf 1997 was hij als onderzoeksleider werkzaam in het Academisch Medisch Centrum in Amsterdam. In 2004 werd bij benoemd tot hoogleraar cell biologie en hoofd van de immunologie en cellbiologie afdeling van het Universitair Medisch Centrum Groningen, verbonden aan de Universiteit van Groningen. In oktober 2009 werd hij Hoogleraar experimentele gastro-enterologie aan het laboratorium van de Maag-, Darm- en Leverziekten van het ErasmusMC, het universitaire medische centrum in Rotterdam.

Dr. C. Janneke van der Woude
Christien Janneke van der Woude werd geboren op 4 maart 1966 in Groningen. Zij behaalde haar artsenbul aan de Vrije Universiteit van Amsterdam en deed haar MDL opleiding in het Universitair Medisch Centrum Groningen. Zij promoveerde in 2004 aan de Universiteit van Groningen op het proefschrift "Apoptosis in (pre-) malignant lesions in the gastro-intestinal tract". Sinds 2001 is ze als staflid verbonden aan de Maag-, Darm- en Leverafdeling van het Erasmus MC te Rotterdam. In het Erasmus MC geeft zij de leiding aan de klinische IBD unit, daarnaast verricht zij onderzoek naar diverse aspecten van inflammatoire darmaandoeningen, in nauwe samenwerking met de afdelingen kinder-Maag-Darm-Leverziekten, pathologie, psychologie en interne geneeskunde. In breder verband houdt zij zich binnen Nederland bezig met onderzoeksprojecten in het kader van een samenwerkingsinitiatief op het gebied van Crohn en Colitis (ICC) waar ze voorzitter is. Bij dit initiatief zijn alle IBD-units van de Nederlandse academische medische centra betrokken. Janneke van der Woude is bestuurslid van de European Crohn's en Colitis Organization. Tevens is zij consultant voor Abbott betrefftende het adalimumab beleid in Nederland en voor Schering-plough (MSD) betreffende het infliximab beleid in Nederland

Dr. Lissy de Ridder
Lissy de Ridder werd geboren op 28 mei 1969. Zij studeerde geneeskunde aan de Universiteit van Amsterdam. Haar opleiding tot kinderarts deed ze in het Academisch Medisch Centrum Amsterdam. Zij promoveerde in 2007 aan de Universiteit van Amsterdam op het proefschrift "Pediatric inflammatory bowel disease: scoping the future. Genetics, diagnostics and therapeutics". Na omzwervingen door het hele land, landde ze in september 2007 als staflid op de Maag-, Darm- en Leverafdeling van het Erasmus MC-Sophia kinderziekenhuis te Rotterdam. Zij verricht wetenschappelijk onderzoek naar alIerlei aspecten van IBD op de kinderleeftijd en zit in diverse (inter)nationale samenwerkingsverbanden zoals de Europese pediatrische IBD werkgroep, de Nederlandse werkgroep IBD bij kinderen en is voorzitter van de klinische studiegroep `gastroenterologie, hepatologie en voeding van het "medicine children research network" (MCRN). Naast de behandeling van kinderen met IBD en het onderzoek houdt zij zich ook bezig met het begeleiden van artsen in opleiding, promovendi en studenten geneeskunde.

Drs. Veerle J.A.A. Nuij
Veerle Johanna Andrea Antonia Nuij werd geboren op 1 februari 1988 in Groningen. In 2006 behaalde zij haar diploma Gymnasium aan het Stedelijk Gymnasium te Breda. In datzelfde jaar ging zij geneeskunde studeren aan de Erasmus Universiteit in Rotterdam. In 2008 werd ze na een meeloopdag geprikkeld om wetenschappelijk onderzoek te doen. Vanaf maart 2008 tot en met april 2010 ondersteunde zij naast haar studie Dr. J.E. Baars met het verzamelen en invoeren van data ten behoeve van het promotie traject van Dr. Baars. In september 2010 behaalde zij haar doctoraalexamen. Sinds 1 oktober 2010 is zij werkzaam als arts-onderzoeker in het Erasmus Medisch Centrum in Rotterdam, onder leiding van Prof. Dr. E.J. Kuiper (afdelingshoofd) en Dr. C.J. van der Woude.

Drs. Charlotte I. de Bie
Charlotte Irene de Bie werd geboren op 7 december 1984 in Gorinchem. In 2002 behaalde zij haar Gymnasium diploma aan het Gymnasium Camphusianum in dezelfde plaats. In datzelfde jaar ging zij geneeskunde studeren aan de Erasmus Universiteit in Rotterdam en in 2008 studeerde zij af als arts. Na haar artsexamen heeft ze enkele maanden gewerkt als arts-assistent kindergeneeskunde in het Maasstadziekenhuis te Rotterdam. Sinds 1 juni 2010 is zij werkzaam als arts-onderzoeker in het Erasmus Medisch Centrum in Rotterdam, onder leiding van Dr. L. de Ridder en Dr. J.C. Escher.

EFM software bv.

Sinds 1994 is EFM gespecialiseerd in balanced scorecard analyses en KPI's (key performance indicators). EFM Software is Gold Certified partner van Microsoft; het hoogste niveau. EFM gebruikt steeds de laatste technologie en volgt standaarden op de voet. Het resultaat: gecertificeerde producten die toegankelijk en zeer gebruiksvriendelijk zijn. Meer dan 15 mensen werken vanuit het hart van Rotterdam aan de ontwikkeling, training, implementatie en het onderhoud van het analyse arsenaal. Meer dan 500 organisaties, waaronder Nuts-Ohra, Rivas zorggroep, GGZ Midden-Brabant, en Attent Zorggroep gebruiken EFM voor management informatie en analyse.

SAMENVATTING RICHTLIJN DIAGNOSTIEK EN BEHANDELING VAN INFLAMMATOIRE DARMZIEKTEN BIJ VOLWASSENEN

INITIATIEF:

- Nederlandse Vereniging van Maag-Darm-Leverartsen, voorheen Nederlands Genootschap voor Maag-, Darm- en Leverartsen

ORGANISATIE:

- Kwaliteitsinstituut voor de Gezondheidszorg CBO

IN SAMENWERKING MET:

- Nederlands Huisartsen Genootschap
- Nederlands Instituut van Psychologen
- Nederlandsche Internisten Vereeniging
- Nederlandse Vereniging van Diëtisten
- Nederlandse Vereniging van Ziekenhuisapothekers
- Nederlandse Vereniging voor Arbeids en Bedrijfsgeneeskunde
- Nederlandse Vereniging voor Heelkunde
- Nederlandse Vereniging voor Obstetrie en Gynaecologie
- Nederlandse Vereniging voor Pathologie
- Nederlandse Vereniging voor Radiologie
- Verpleegkundigen & Verzorgenden Nederland

Nederlandse Vereniging van Maag-Darm-Leverartsen MDL

Inleiding

Doelgroep Richtlijn

Inflammatory Bowel Diseases (IBD) betreft een groep ideopathische, chronisch inflammatoire darmaandoeningen waarvan de oorzaak tot op heden niet bekend is. en waartoe colitis ulcerosa (CU) en de ziekte van Crohn (ZvC) gerekend worden. Bij ongeveer 10% van de IBD-patiënten kan de diagnose CU of de ZvC niet met zekerheid gesteld worden en is er sprake van niet-classificeerbare colitis. De incidentie van IBD, in het bijzonder van de ZvC, neemt de laatste decennia toe. De voorliggende samenvatting van de richtlijn IBD is geschreven voor alle zorgverleners die met regelmaat betrokken zijn bij diagnostiek naar en behandeling van IBD. Te denken valt aan MDL-artsen, die veelal de spil vormen in een multidisciplinair team dat verder -in willekeurige volgorde- bestaat uit een chirurg, kinderarts, huisarts, gynaecoloog, (klinisch) psycholoog, radiodiagnost, reumatoloog, diëtist, IBD-verpleegkundige en meer.

Samenstelling

In opdracht van de Orde van Medisch Specialisten en het MDL-genootschap (thans VvMDL-artsen) is de werkgroep IBD gevormd door het CBO uit vertegenwoordigers van allerlei bij IBD-behandeling betrokken disciplines en vertegenwoordigers van de patiëntenvereniging (CCUVN).

Gehanteerde methode

De richtlijn is tot stand gekomen door methodisch gebruik te maken van wetenschappelijk bewijs (conform Evidence-based Richtlijnontwikkeling, onder redactie van JJE van Everdingen *et al.*; Bohn Stafleu Van Loghum, Houten, 2004).

De tekst van deze richtlijn is weergegeven in 4 onderdelen: 1. diagnostiek, 2. therapie, 3. extra-intestinale verschijnselen & complicaties, 4. zorgorganisatie

1. Diagnostiek

Vaststellen van IBD

IBD wordt aan de hand van ziektelokalisatie en het beloop van het ontstekingsproces in verschillende fenotypes onderverdeeld. De symptomen bij eerste presentatie zijn vooral afhankelijk van de ziektelokalisatie en ernst van de ziekte en niet zo zeer van de diagnose ZvC of CU. Tot op heden bestaat er geen test waarmee met zekerheid onderscheid gemaakt kan worden tussen deze twee ziektes. Daarom berust de diagnosestelling op een combinatie van klinische bevindingen en uitkomsten van biochemisch, radiologisch, endoscopisch en histologisch onderzoek. Symptomen van het prikkelbaar darmsyndroom en IBD vertonen overlap hetgeen het stellen van de juiste diagnose moeilijk kan maken . Verdenking op IBD wordt versterkt door aanwezigheid van bloedverlies, perianale afwijkingen, een positieve familieanamnese en tekenen van ontsteking. Bij patiënten in de eerstelijns zorg die op basis van anamnese en onderzoek verdacht worden van een chronisch inflammatoire darmziekte is doorverwijzing naar een specialist voor aanvullend onderzoek aangewezen.

Ileocoloscopie met het nemen van biopten is het belangrijkste om de diagnose ZvC of CU te stellen. Histopathologische criteria zoals continuïteit van ontsteking, cryptabcessen, granuloomvorming, betrokkenheid van verschillende darmsegmenten en tekenen van chroniciteit van ontsteking ondersteunen de diagnosestelling in belangrijke mate. Microbieel

onderzoek speelt een belangrijke rol bij de differentiaal diagnostiek en bij het vaststellen van een opvlamming van IBD, namelijk ter uitsluiting van microbiële enteritis.
Bij patiënten met de ZvC bij wie de diagnose met behulp van ileocoloscopie is vastgesteld, is aanvullend dunne darm onderzoek aangewezen om de uitbreiding van ziekte vast te stellen. Wat de meest geschikte modaliteit voor dit aanvullend beeldvormend onderzoek is, hangt onder andere af van lokale beschikbaarheid en expertise. MRI, echografie, scintigrafie en CT kunnen alle van waarde zijn, waarbij CT-scanning de laagste sensitiviteit en specificiteit heeft wanneer het uitgedrukt wordt in een score per ziek darmsegment. Ook een enteroclyse van de dunne darm of klassieke dunnedarmfoto levert adequate diagnostische informatie. Videocapsule onderzoek is sensitief, maar niet zeer specifiek en de plaats van deze modaliteit in de diagnostiek is niet afgebakend.

Tabel 1; Montreal classificatie

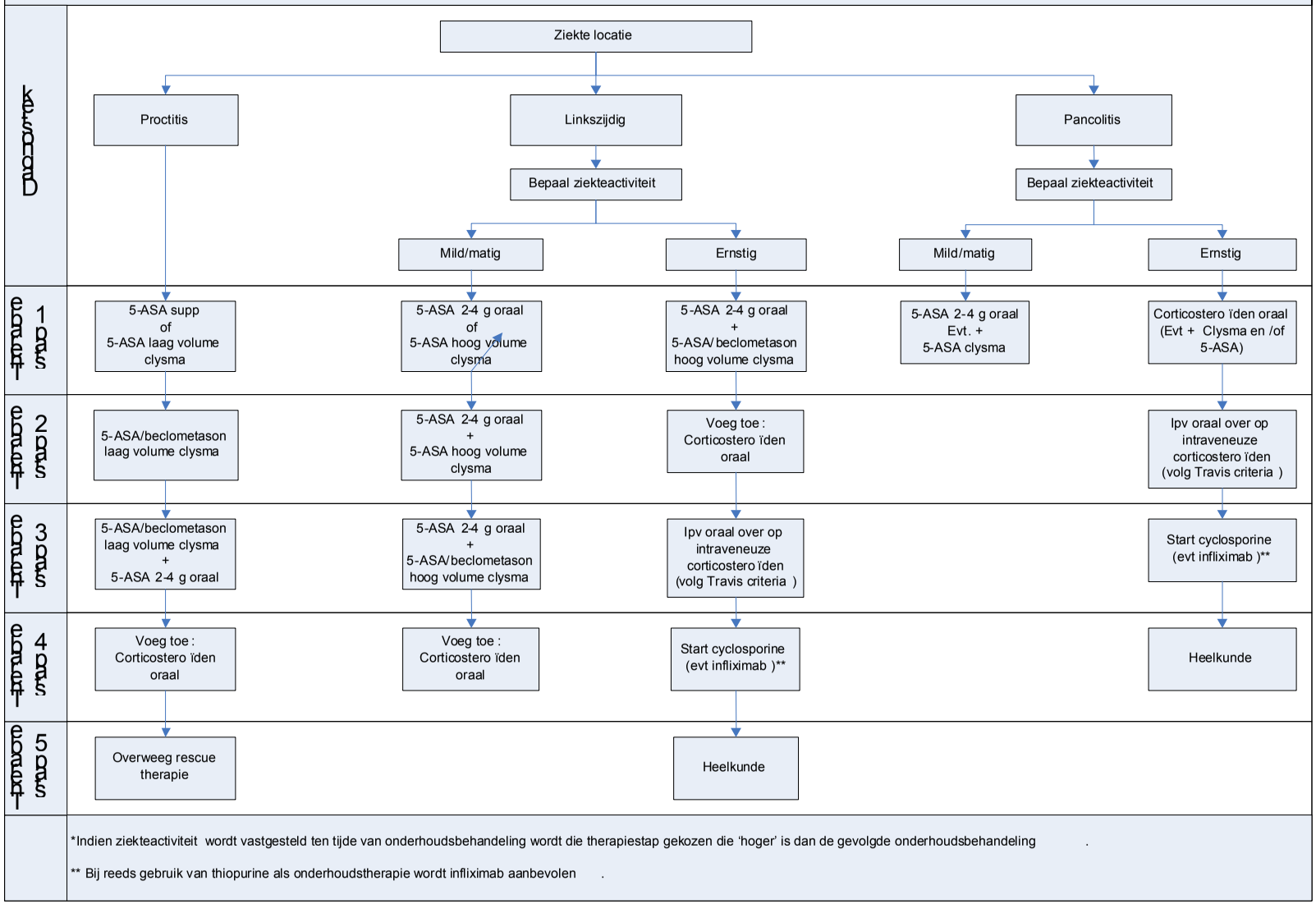
Classificerende factoren bij de ZvC	
Leeftijd bij diagnose • A1 • A2 • A3	 Jonger dan 16 Tussen 17 en 40 jaar Boven de 40 jaar
Ziekte localisatie • L1 • L2 • L3 • +L4 toevoegen • +P toevoegen	 Alleen ileum Alleen colon Ileum en colon Localisaties proximaal van het het ileum Bij aanwezigheid (fistelende) perianale ziekte
Ziekte gedrag • B1 • B2 • B3	 Niet stenoserend en niet penetrerend Stenoserend Penetrerend
Classificerende gegevens bij CU	
Uitbreiding van colitis • E1 • E2 • E3	 Beperkt tot het rectum Beperkt tot colon distaal van de flexura lienalis Uitbreidend tot proximaal van de flexura lienalis
Ernst van de colitis • S0 (Remissie) • S1 (Mild) • S2 (Matig) • S3 (Ernstig)	 Geen klachten Def < 5x/dag met of zonder bloed; BSE/ CRP normaal Def > 4x/dag, geringe aanwezigheid ziekteverschijnselen Def > 6x/dag én Pols > 90/min; temp > 37.5°C; Hb < 6.5 mmol/l; BSE > 30 mm

Voor onbegrepen buikklachten is videocapsule onderzoek niet geschikt. Rekening houdend met de cumulatief voor de patiënt niet te veronachtzamen (abdominale) stralingsbelasting genieten MRI en echografie evenwel de voorkeur. Fistelonderzoek wordt verricht op indicatie, waarbij MRI-onderzoek de meest volledige informatie verschaft. Laboratoriumonderzoek is ondersteunend. Biomarkers als pANCA en ASCA spelen geen rol in routinediagnostiek, CRP en fecale calprotectine kunnen dienen als ontstekingsparameter, zij het in aspecifieke zin. Voor de dagelijkse praktijk heeft het testen van genetische polymorfismes (o.a. van het NOD2-gen) geen meerwaarde. Aanvullend onderzoek als gastroscopie en andere modaliteiten is alleen op indicatie geïndiceerd.
Het sluitstuk van het diagnostisch traject is het vastleggen van de classificerende diagnose en het fenotype (volgens de Montreal classificatie die definitief kan worden vastgesteld als het ziektebeloop vijf jaar vervolgd is, (Satsangi, 2006)).

Opvlamming van IBD
Bij verdenking op een opvlamming van IBD is gericht onderzoek (laboratorium -, microbieel-, en endoscopisch onderzoek) vaak aangewezen voordat de juiste therapie kan worden gekozen. Bij studies bijde ZvC is het gebruikelijk een CDAI-score > 220 te nemen als maat voor actieve ziekte (zeker in studieverband). Deze score wordt in belangrijke mate bepaald door algemene ziekteverschijnselen en buikpijnklachten en heeft daarom grote overlap met klachten van een prikkelbaar darmsyndroom. Hogere scores (geassocieerd met actievere ziekte) zijn meer specifiek voor de ZvC. Met deze CDAI kan echter milde (endoscopisch waarneembare of zogeheten mucosale) ziekteactiviteit vaak niet goed worden bepaald.

2. Therapie
De therapeutische benadering van een patiënt met IBD start met een inventarisatie van type, lokalisatie en mate van activiteit van de ziekte. In eerste instantie richt de behandeling zich op de darmontsteking. Verdere therapie is gericht op voedingstoestand, extra-intestinale verschijnselen en eventuele psychosociale problematiek.
Na vaststellen van type en lokalisatie van de IBD wordt eerst actieve ziekte tot rust gebracht (inductietherapie). Vervolgens wordt een onderhoudsbehandeling ingesteld. Gebruikelijk is de zogeheten step-up strategie te kiezen, waarbij initieel middelen met een betrekkelijk mild bijwerkingprofiel worden ingezet. Deels afhankelijk van de algehele klinische inschatting wordt na 1 tot 2 weken beoordeeld of de gekozen therapeutische strategie voldoende effectief is, of dat een ander, veelal sterker werkend, inductiemiddel moet worden gestart. Het onlangs geïntroduceerde concept van de top-down benadering bij de ZvC (waarbij de krachtigste middelen zo snel mogelijk na vaststellen van 1^{e} ziekteactiviteit worden ingezet, gevolgd door immuunsuppressieve onderhoudsbehandeling) is vooralsnog onvoldoende onderbouwd voor standaardtherapie.
De step-up strategie wordt gehanteerd voor inductie- en onderhoudsbehandeling van zowel CU als de ZvC. Niet-classificeerbare colitis wordt hierbij benaderd als een CU. Bij falen van medicamenteuze inductie- of onderhoudsbehandeling is chirurgische interventie aangewezen (zie verder).
Voor de verscheidene fases en lokalisatie van ziekte zijn de volgende flowcharts aanbevolen:

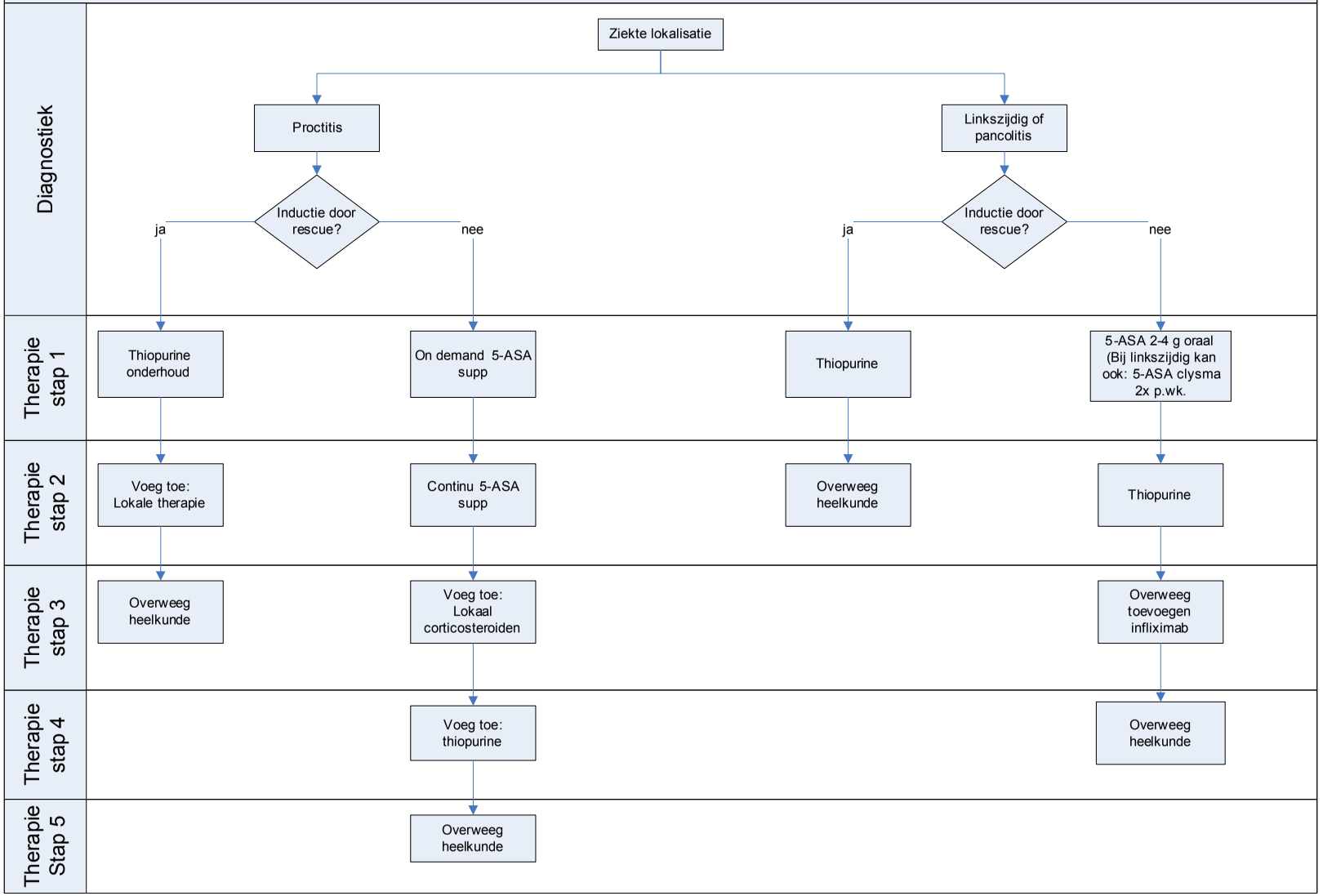
Actieve* Colitis Ulcerosa

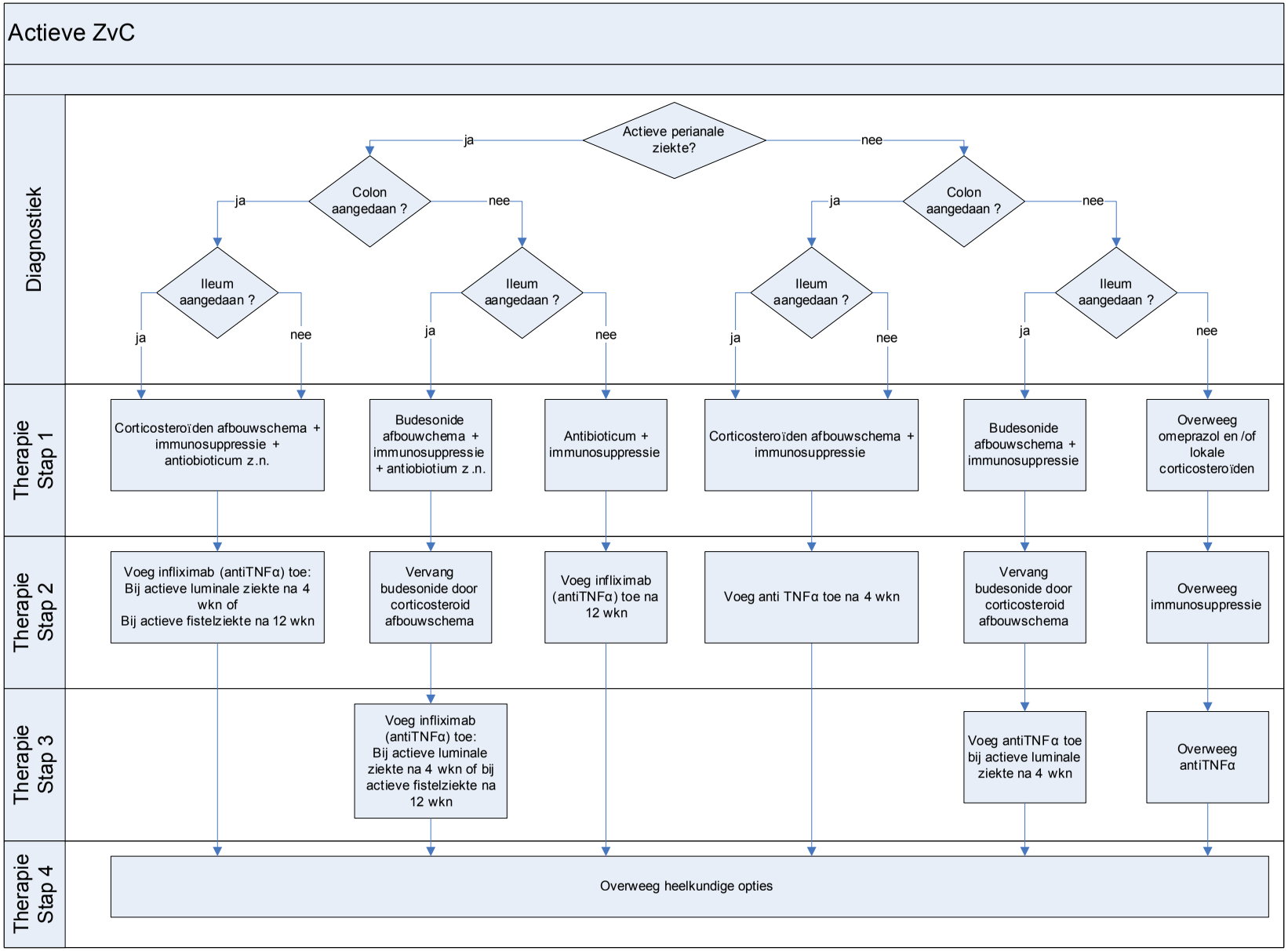


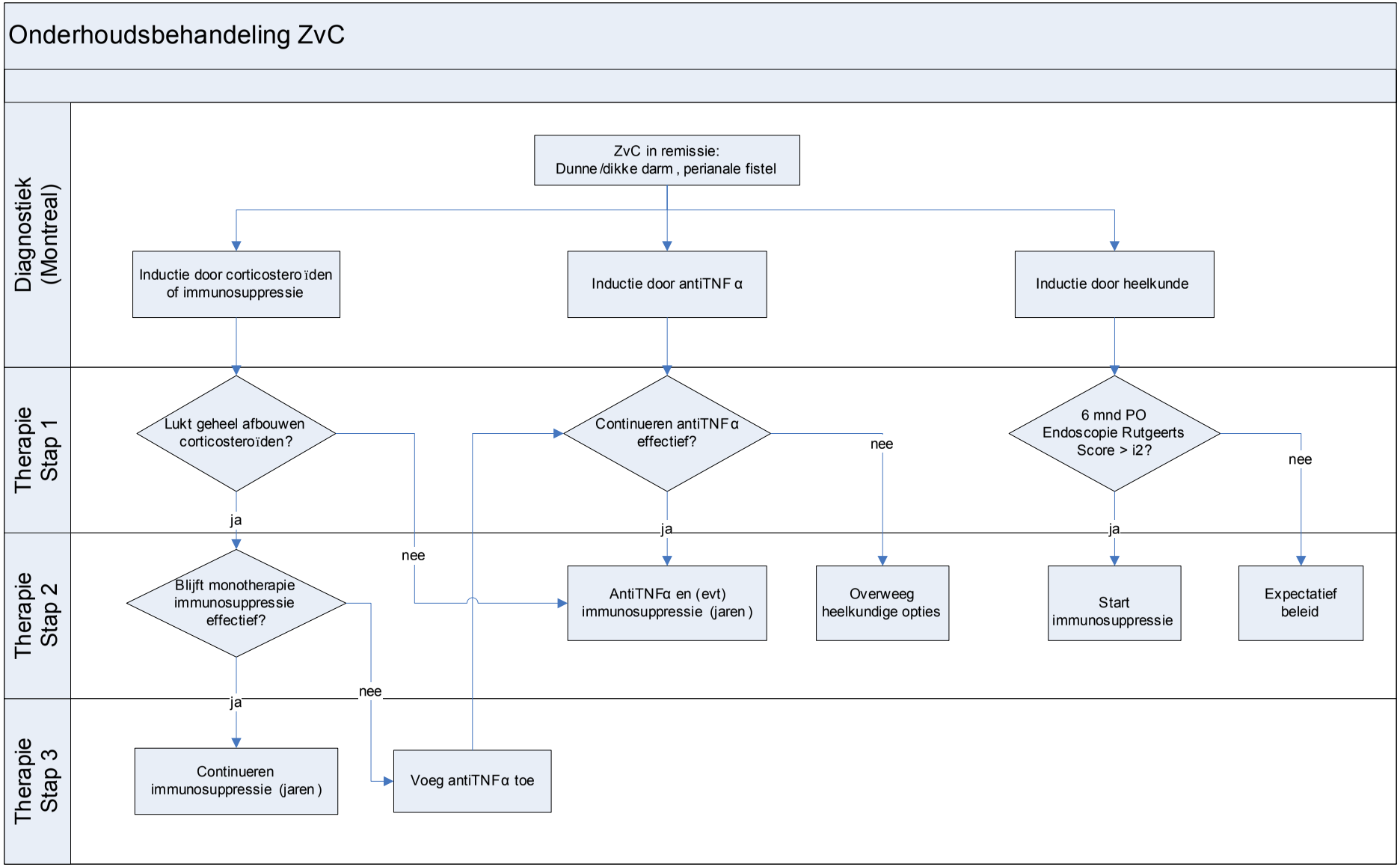
*Indien ziekteactiviteit wordt vastgesteld ten tijde van onderhoudsbehandeling wordt die therapiestap gekozen die 'hoger' is dan de gevolgde onderhoudsbehandeling .

** Bij reeds gebruik van thiopurine als onderhoudstherapie wordt infliximab aanbevolen .

Colitis Ulcerosa onderhoud




Actieve ZvC
Diagnostiek
Actieve perianale ziekte?
ja
nee
Colon aangedaan ?
ja
nee
Colon aangedaan ?
ja
nee
Ileum aangedaan ?
ja
nee
Ileum aangedaan ?
ja
nee
Ileum aangedaan ?
ja
nee
Ileum aangedaan ?
ja
nee
Therapie Stap 1
Corticosteroïden afbouwschema + immunosuppressie + antiobioticum z.n.
Budesonide afbouwchema + immunosuppressie + antiobiotium z.n.
Antibioticum + immunosuppressie
Corticosteroïden afbouwschema + immunosuppressie
Budesonide afbouwschema + immunosuppressie
Overweeg omeprazol en /of lokale corticosteroïden
Therapie Stap 2
Voeg infliximab (antiTNFα) toe: Bij actieve luminale ziekte na 4 wkn of Bij actieve fistelziekte na 12 wkn
Vervang budesonide door corticosteroid afbouwschema
Voeg infliximab (antiTNFα) toe na 12 wkn
Voeg anti TNFα toe na 4 wkn
Vervang budesonide door corticosteroid afbouwschema
Overweeg immunosuppressie
Therapie Stap 3
Voeg infliximab (antiTNFα) toe: Bij actieve luminale ziekte na 4 wkn of bij actieve fistelziekte na 12 wkn
Voeg antiTNFα toe bij actieve luminale ziekte na 4 wkn
Overweeg antiTNFα
Therapie Stap 4
Overweeg heelkundige opties


Onderhoudsbehandeling ZvC
Diagnostiek (Montreal)
Therapie Stap 1
Therapie Stap 2
Therapie Stap 3
ZvC in remissie:
Dunne/dikke darm , perianale fistel
Inductie door corticosteroïden of immunosuppressie
Inductie door antiTNF α
Inductie door heelkunde
Lukt geheel afbouwen corticosteroïden?
Continueren antiTNF α effectief?
6 mnd PO Endoscopie Rutgeerts Score > i2?
ja
nee
Blijft monotherapie immunosuppressie effectief?
AntiTNFα en (evt) immunosuppressie (jaren)
Overweeg heelkundige opties
Start immunosuppressie
Expectatief beleid
Continueren immunosuppressie (jaren)
Voeg antiTNFα toe

Chirurgie en IBD

De werkgroep is van mening dat bij CU indicaties voor operatie zijn:

- Acuut: therapieresistente toxische colitis of toxisch megacolon, perforatie, bloeding die niet op niet-chirurgische wijze te stelpen is.
- Electief: geen of onvolledige respons op optimale therapie, complicaties van medicatie, dysplasie of maligniteit, reconstructie na acute colectomie.

Proctocolectomie met ileoanale pouch wordt de standaardbehandeling geacht voor CU-patiënten met therapieresistentie of premaligne dysplasie of maligniteiten in het colon. Het aanleggen van een tijdelijk ontlastend stoma proximaal van een aangelegde pouch-anale reconstructie is te overwegen om de kans op complicatieloze wondgenezing te vergroten. Dit kan eventueel laparoscopisch(-geassisteerd) worden uitgevoerd met gebruikmaking van staplers. Er zijn aanwijzingen dat het preserveren van de “transitional zone” bij proctocolectomie en pouchprocedure veilig is.

Een (semi)acute totale colectomie met eindstandig ileostoma wordt de standaardbehandeling geacht bij therapieresistente toxische colitis of megacolon bij CU. Na lichamelijk en geestelijk herstel van een (semi)acute colectomie kan 3-6 maanden na de colectomie een restproctocolectomie plaatsvinden met aanleggen van een ileoanale pouch indien de patiënt dat wenst (na afbouwen van corticosteroïden).

Bij de ZvC zijn indicaties voor operatie:

- Acuut: persisterende ileus, bloeding die niet op een niet-chirurgische wijze te stelpen is, abces drainage niet toegankelijk voor percutane drainage, perianale abcessen.
- Electief: therapieresistente passageklachten, maligniteit en perianale fistels, eventueel refractaire ziekteactiviteit.

Bij patiënten met de ZvC is het aangetoond dat bij aanwezigheid van chirurgische expertise een laparoscopische ileocecaal resectie de voorkeur heeft boven open ileocecaal resectie. In geval van laparotomie is een mediane laparotomie sterk aanbevolen. Resecties bij de ZvC worden zo sparend mogelijk verricht ter voorkomen van intestinaal falen. Er zijn aanwijzingen dat geen plaats is voor een ruimere resectie dan van macroscopisch afwijkende darm gekenmerkt door wandverdikking, overkruipend mesenteriaal vet (fatty overgrowth) en versterkte vaattekening. Dit geldt zowel voor de ZvC van de dunne - als van de dikke darm. Indien het doelorgaan bij een inwendige fistel niet door de ZvC is aangedaan, kan het defect na excisie zonder resectie veilig gesloten worden.

Verder lijkt percutane drainage in geval van intra-abdominale abcessen bij de ZvC te verkiezen boven chirurgische drainage. Bij stenoses over een beperkte lengte kunnen plastieken (tot 10 cm) of endoscopische ballondilataties (tot 5 cm lengte) worden overwogen na uitsluiting van maligne processen. Gebruik van corticosteroïden >20 mg dagelijks verhoogd het risico op postoperatieve, vooral infectieuze, complicaties in tegenstelling tot monotherapie met immunosuppressiva of antiTNF therapie.

Enkelvoudige lage (submuceuze, intersfincterische) perianale fistels bij patiënten met de ZvC kunnen met behulp van een fistulotomie behandeld worden, resulterend in een succespercentage van rond de 80%. Hoge perianale fistels bij patiënten met de ZvC kunnen met behulp van setondrainage of soms met advancement plastieken behandeld worden in geval van recidiverende, hinderlijke, lokale abcesvorming. Vanwege de complexe oorzaak en het moeizame beloop van fistelziekte bij de ZvC wordt behandeling in een multidisciplinair team sterk aanbevolen.

Expertise van chirurg en centrum is geassocieerd met minder complicaties en een betere functie van een pouch, een gunstiger prognose na colectomie bij CU en minder

naadproblematiek bij de ZvC. Chirurgie bij patiënten met IBD wordt daarom bij voorkeur uitgevoerd in een expertisecentrum door ervaren gastrointestinale chirurgen.

Voeding en probiotica
Voeding noch dieet spelen een primaire therapeutische rol bij de behandeling van volwassen IBD patienten. Het specifieke karakter van de ziekte brengt echter met zich mee dat er verhoogd risico op ondervoeding en puntdeficiënties bestaat zowel in actieve als rustige fase van IBD. Dit dient tijdig onderkend en, indien aanwezig, behandeld te worden. Probiotica hebben een aangetoond effect bij voorkomen van pouchitis, zo niet bij de behandeling van IBD, een veld waar overigens veel onderzoek gaande is.

Alternatieve geneeswijzen
Alternatieve geneeswijzen hebben geen enkele therapeutische rol bij de behandeling van IBD.

Surveillance strategieën
Het risico op het krijgen van een colorectaal carcinoom is verhoogd voor patiënten met CU of de ZvC. In geval van CU is het risico onafhankelijk geassocieerd met de duur, ernst en de anatomische uitbreiding van de ziekte. Een begeleidende PSC, familiair voorkomen van coloncarcinoom, het debuut van de ziekte op jeugdige leeftijd en de aanwezigheid van pseudopoliepen worden alle in wisselende mate in verband gebracht met een cumulatief verhoogd risico. Er zijn aanwijzingen dat surveillance door middel van coloscopie van waarde is om mogelijke maligniteit tijdig te ontdekken bij IBD-patiënten. Of een surveillance strategie de levensverwachting beïnvloedt, is niet bekend.
Het gebruik van chemoprotectieve geneesmiddelen, zoals mesalazine, ursodeoxycholzuur en foliumzuur, is onvoldoende onderbouwd voor algemene aanbeveling. Het gebruik van mesalazine (minimaal 1,2 g dagelijks, oraal) bij groepen met verhoogde risico op colorectaal carcinoom is, alles afwegende, echter wel te rechtvaardigen.

Bij alle IBD patienten met in ieder geval betrokkenheid van het rectosigmoïd is het daarom aan te bevelen surveillance te starten, 8 jaar na het ontstaan van de ziekte-geassocieerde klachten. Hierbij zou in de eerste surveillance-decade eenmaal per 3 jaar gescreend moeten worden, in de tweede decade eenmaal per 2 jaar, en hierna jaarlijks. Dit schema is nog aan wetenschappelijke discussie onderhevig. Patiënten met PSC dienen meteen, volgend op de diagnose, in een surveillance programma te worden opgenomen, waarbij jaarlijkse coloscopieën aanbevolen worden. Detectie van dysplasie is belangrijk bij surveillance van IBD-patiënten. De kans om aanwezige dysplasie op te sporen met het nemen van 33 of meer “at random’ biopten” wordt geschat op ruim 90%. Daarom wordt aangeraden bij de coloscopie om de 10 cm at random 4 biopten te nemen op minimaal 9 plaatsen vanaf het coecum tot en met het rectum. Daarbij wordt nauwkeurig gekeken naar locale afwijkingen en poliepen, die apart worden gebiopteerd. Het verhogen van de opbrengst met chromoendoscopie verdient aanbeveling. Een proctocolectomie is aangewezen bij IBD-patiënten in geval van een bij coloscopie vastgesteld carcinoom, een bewezen DALM of een hooggradige dysplasie. In geval van een polipeuze afwijking met het aspect van een sporadisch adenoom kan deze verwijderd worden waarna initieel frequente nacontroles dienen plaats te vinden. Hierbij mag geen dysplasie in de omgevende normaal uitziende mucosa aanwezig zijn: dan is er waarschijnlijk toch sprake van een DALM. In geval van door 2 pathologen bevestigde laaggradige dysplasie in de vlakke mucosa is er eveneens een indicatie voor een

proctocolectomie, zeker als er sprake is van multifocaliteit. Bij (chronisch actieve of diffuse) ZvC van het colon wordt surveillance op gelijke wijze aanbevolen als bij patiënten met pancolitis ulcerosa.

3. Extraintestinale (EI) manifestaties

De extra-intestinale verschijnselen zijn in te delen in drie groepen: 1. reactieve (inflammatoire) condities, zoals inflammatoire huidracties, perifere artropathie en oogontsteking, 2. geassocieerde condities die meer voorkomen bij IBD maar hier niet direct aan gerelateerd zijn, zoals ankyloserende spondylitis (ziekte van Bechterew) en chronische leverziekte, en 3. condities die ontstaan als gevolg van een langer bestaande darmziekte. Dit betreft bijvoorbeeld metabole consequenties, malabsorptie, galstenen, nierstenen en amyloidose.
Daarnaast is er klinisch een overlap tussen IBS en IBD, veel patiënten krijgen de diagnose IBS voordat de diagnose IBD gesteld wordt en 42-57% van patiënten met IBD in remissie hebben IBS-achtige klachten.
Voor therapeutische interventies is het daarom van belang mucosale ontsteking (IBD-activiteit) vast te stellen. De step-up benadering van behandeling van EI manifestaties is eerst ziekteactiviteit van IBD behandelen en daarna, bij ernstige klachten eventueel tegelijkertijd, te starten met gerichte therapie van EI verschijnselen. Bij complexe casuïstiek (uveitis, axiale artritis, PSC) is multidisciplinaire diagnostiek en behandeling aangewezen.

Tabel 2 Extra-intestinale verschijnselen, associatie met IBD-activiteit, therapie

Aangedane orgaan	Associatie met IBD-activiteit *	Therapie
Huid / Mondholte		
1. Aften	+	1. Locale anesthesie, respectievelijk locaal budesonide, eventueel thalidomide
2. Cheilitis granulomatosa	-	2. Clofazimine, hydroxychloroquine, sulfasalazine, eventueel infliximab
3. Erythema Nodosum	+	3. corticosteroiden, eventueel + thiopurine, eventueel + infliximab
4. Pyoderma gangrenosum	+/-	4. corticosteroiden/tacrolimus locaal, eventueel 1 van beide per os/i.v., eventueel infliximab
Lever		
1. PSC	-	1. UDCA (12-15mg/kg), bij dominante strictuur lokale therapie (ERCP), eventueel levertransplantatie
Gewrichten / skelet		
1. Perifere arthritis		
a) Type 1 (<5 gewrichten)	+	1a. symptomatisch, zo nodig COX2 remmers (NSAID?), eventueel intra-articulaire corticosteroiden
b) Type 2 (kleine	-	

gewrichten) 2. Axiale arthritis 3. Osteoporose	- -	1b. symptomatisch, zo nodig NSAID/COX2 remmers 2. symptomatisch en fysiotherapie, eventueel (continu) NSAID/COX2 remmers, eventueel antiTNF therapie 3. Calcium, vitamine D en lichaamsbeweging indien insufficiënt, zo nodig bisfosfonaat

* = bij associatie met IBD-activiteit dit eerst adequaat behandelen

IBD en zwangerschap

Relevant onderzoek over de invloed van IBD op gynaecologische problemen ontbreekt. De fertiliteit bij vrouwen met CU of de ZvC die nooit geopereerd zijn, is vergelijkbaar met vrouwen zonder deze aandoening. Met uitzondering van methotrexaat bij beide geslachten en van sulfasalazine bij mannen is van geen der gebruikelijke medicamenten voor IBD een ongunstige invloed op de fertiliteit bekend.

Na buikoperaties neemt de fertiliteit af. In de literatuur wordt melding gemaakt van toename van frequentie van seksuele dysfunctie van 8% preoperatief naar 25% postoperatief. Gezien de conflicterende en beperkte onderzoeksgegevens kunnen geen conclusies getrokken worden met betrekking tot de seksualiteit en IBD. Gebruik van OAC door vrouwen met IBD heeft geen invloed op de activiteit van de ziekte. De betrouwbaarheid van OAC is onvoldoende onderzocht, maar lijkt ongewijzigd.

In geval van zwangerschapswens gelden de volgende vuistregels; preconceptioneel bespreken van de tijdens de graviditeit noodzakelijke medicatie en van het geadviseerde beleid tijdens zwangerschap, bevalling en kraambed wordt aanbevolen. Foliumzuursuppletie voorafgaand aan en tijdens het eerste trimester van de zwangerschap wordt aanbevolen. IBD-patiënten wordt geadviseerd om alleen in een rustige fase van de aandoening zwanger te worden, bij voorkeur minimaal één jaar na diagnose of na laatste opvlamming van ziekte. De kans op zwangerschapscomplicaties (vroeggeboorte of foetale groeirestrictie) is waarschijnlijk niet verhoogd indien de IBD in een remissie is. Van vrijwel alle medicatie wordt geen directe associatie tussen medicatiegebruik en een ongunstig beloop van de zwangerschap of vruchtontwikkeling gemeld, waarbij methotrexaat een belangrijke uitzondering vormt. Verder wordt aanbevolen de (onderhouds)medicatie voor IBD die noodzakelijk is gebleken voortgaand te gebruiken tot en ten tijde van en na de zwangerschap.

De kans op aangeboren afwijkingen bij kinderen van wie de moeder aan IBD lijdt, lijkt niet verhoogd te zijn. De kans dat een kind van een ouder met de ZvC een IBD ontwikkelt, wordt geschat op 13% bij meisjes en 8% bij jongens. Bij kinderen van ouders met de ZvC wordt de ziekte veelal op jongere leeftijd vastgesteld dan bij de ouders.

De bevalling bij vrouwen met IBD is in essentie niet anders dan bij vrouwen zonder IBD. In geval van bijzondere situaties is nauw overleg tussen de behandelende gynaecoloog en MDL-arts noodzakelijk. Vaginale kunstverlossing, een grote perineumruptuur of een episiotomie vergroten de kans op fecale incontinentieklachten op langere termijn bij vrouwen met een ileo-anale pouch. Bij nullipara met een ileo-anale pouch (of de verwachting dat deze op termijn aangelegd moet worden) is moeilijker in te schatten of een baring vlot zal vorderen hetwelk mogelijk eerder kan leiden tot advisering om een geplande sectio te verrichten. In het geval van perianale actieve ziekte of gecompliceerde fistelproblematiek wordt een sectio

geadviseerd. In overige gevallen kan de besluitvorming omtrent het beleid bij de baring afhangen van obstetrische argumenten. Een klinisch kraambed wordt alleen geadviseerd bij vrouwen met een actieve IBD in de zwangerschap.
Borstvoeding wordt in het algemeen geadviseerd. Borstvoeding kan door IBD-moeders worden gegeven waarbij wel overwogen dient te worden dat metabolieten van medicamenten, zoals thiopurines, in de moedermelk (kunnen) komen. Er zijn geen nadelige effecten beschreven, echter de beschikbare documentatie is beperkt. Het wordt ontraden onderhoudsmedicatie te staken vanwege de wens tot borstvoeding.

Psychische begeleiding
Psychologische stress door opvlamming van IBD en psychische nood (i.e. angst of depressie) naast IBD symptomen moeten onderscheiden worden in het beloop van IBD. Het leren accepteren van het chronisch karakter van een ziekte als IBD met de daarbij eventueel optredende beperkingen is een belangrijke opgave in de opeenvolgende fasen van de ziekte. De (psychische) kwaliteit van leven wordt bepaald door factoren als ziekteactiviteit, kwaliteit van zorg (waaronder begrepen communicatie en informatie van de kant van hulpverleners), (de kwaliteit van de) sociale steun, stress ('life events' maar ook 'daily hassles'), psychische toestand (met name angst en depressie) en het hanteren van dit alles en van IBD als chronische ziekte. De diversiteit aan klachten maakt het zeer wenselijk aan patiënten mondelinge en schriftelijke informatie te verschaffen over wat voor soort hulp, steun of begeleiding aan te raden is. Dit geldt in verhoogde mate voor patiënten in de periode kort na diagnose, vaak jonge mensen dus.
Psychologische hulp is met name dan aangewezen wanneer sprake is van geringe ziekteacceptatie en bij gevoelens van hulpeloosheid. Vooralsnog wordt niet-ziektespecifieke psychotherapeutische behandeling, indien geïndiceerd, uitgevoerd. Specifiek voor IBD wordt vervolgonderzoek naar de veelbelovende initiatieven tot verbetering van zelfzorg (self-empowerment) gewenst.
Zoals bij alle chronische patiënten, en dus ook bij de IBD-patiënt is het sterk aan te bevelen steeds alert blijven op mogelijke therapieontrouw. Adherentie (therapietrouw) is van groot belang voor het effectueren van medisch beleid en het verbeteren van de kwaliteit van leven van de IBD-patiënt. Een goede hulpverlener-patiënt relatie is een eerste vereiste en verdient daarom veel aandacht te krijgen.

Sociale begeleiding
Arbeidsparticipatie. De mate van door IBD veroorzaakte beperkingen is afhankelijk van de mate van ziekte-activiteit. IBD leidt tot een lagere arbeidsparticipatie en een hogere kans op arbeidsongeschiktheid, in geval van de ZvC meer dan bij CU. Dat laat onverlet dat werkgever en werknemer gehouden zijn om los van welke medische diagnose dan ook, te bezien wat qua arbeidsinzet wel mogelijk is en wat er voor nodig is die mogelijkheden verder uit te breiden zonder dat dit leidt tot gezondheidsschade. Er wordt verschillend gedacht over de belemmeringen die het hebben van IBD in het werk oplevert. Hier is slechts weinig literatuur beschikbaar. Er zal volgens de werkgroep rekening gehouden moeten worden met de individuele belasting en belastbaarheid. Dat betekent dat een adequate informatie van partijen, een goede communicatie tussen partijen en wederzijds begrip, essentieel zijn voor de mogelijkheid van een goede arbeidsrelatie en -prestatie maar ook voor een potentiële duurzame inzetbaarheid.

Levensverwachting. De levensverwachting voor de totale groep patiënten met CU is normaal. De levensverwachting voor de totale groep patiënten met de ZvC is licht verlaagd. De oversterfte bij patiënten met de ZvC blijkt vooral te worden veroorzaakt door infecties en gastro-intestinale aandoeningen, anders dan IBD zelf. De sterfte ten gevolge van colorectaal carcinoom is bij patiënten met CU en de ZvC hoger en treedt op jongere leeftijd op maar de totale sterfte aan carcinomen is niet verhoogd. Aanvullend constateert de werkgroep dat patiënten met IBD door hun ziekte problemen ondervinden bij het aanvragen en aangaan van een levens- of arbeidsongeschiktheidsverzekering die niet in overeenstemming zijn met de huidige inzichten omtrent levensverwachting en risico's. Levensverzekeringsmaatschappen kunnen de premie voor levensverzekering voor IBD-patiënten gelijk houden aan die van referentiepopulaties.

4. Zorgorganisatie

De veelvormige en door veel professionals te verlenen zorg voor een IBD-patiënt stelt hoge eisen aan de organisatie van de zorg door ziekenhuizen en behandelaars. In IBD geschoolde en ervaren zorgverleners, veelal in multidisciplinaire vorm, zijn noodzakelijk op het gebied van MDL, gastrointestinale chirurgie, gynaecologie, diëtetiek en ondersteunende specialisaties als reumatologie, dermatologie, interne geneeskunde en oogheelkunde.

In geval van kinderen met IBD is overdracht van behandeling van kinderarts naar MDL-arts van groot belang. Dit transitieproces kan met ouders en kinderen vanaf de leeftijd van 12 jaar starten. Door het ontwikkelen en volgen van een lokaal (of nationaal) transitieprotocol verbetert de klinische zorg voor deze patiënten. Optimale continuïteit wordt gewaarborgd door middel van een transitiepolikliniek, waarbij de kinderartsgastro-enteroloog en de MDL-arts gezamenlijk spreekuur doen.

Voor deze groep maar zeker ook voor volwassen IBD-patiënten kan een gespecialiseerde verpleegkundige voor IBD-patiënten een verbetering van zorg betekenen. Door een laagdrempelige karakter en snelle toegang voor advies is de IBD-verpleegkundige eerder in staat om knelpunten in de behandeling te inventariseren. De IBD-verpleegkundige kan aanvullend voorzien in de (toenemende) behoefte aan informatie over ziekte en behandeling en kan meer tijd plannen voor begeleiding van patiënt en familie.

Goed geïnformeerde patiënten lijken een betere kwaliteit van leven te hebben en gaan bewuster om met medicatie. De werkgroep is van mening dat niet alleen artsen, maar ook de Crohn en Colitis Ulcerosa Vereniging Nederland en de IBD-verpleegkundigen een belangrijke taak hebben in de voorlichting van patiënten en hun omgeving. De informatie dient goed en eenduidig te zijn.