



Use of the tumor necrosis factor-blockers for Crohn's disease

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Abstract

The use of anti-tumor necrosis factor- α therapy for inflammatory bowel disease represents the most important advance in the care of these patients since the publication of the National Co-operative Crohn's disease study thirty years ago. The recommendations of numerous consensus groups worldwide are now supported by a wealth of clinical trials and several meta-analyses. In general, it is suggested that tumor necrosis factor- α blockers (TNFBs) are indicated (1) for persons with moderately-severe Crohn's disease or ulcerative colitis (UC) who have failed two or more courses of glucocorticosteroids and an acceptably long course (8 wk to 12 wk) of an immune modulator such as azathioprine or methotrexate; (2) non-responsive perianal disease; and (3) severe UC not responding to a 3-d to 5-d course of steroids. Once TNFBs have been introduced and the patient is responsive, therapy given by the IV and SC route must be continued. It remains open to definitive evidence if concomitant immune

modulators are required with TNFB maintenance therapy, and when or if TNFB may be weaned and discontinued. The supportive evidence from a single study on the role of early versus later introduction of TNFB in the course of a patient's illness needs to be confirmed. The risk/benefit profile of TNFB appears to be acceptable as long as the patient is immunized and tested for tuberculosis and viral hepatitis before the initiation of TNFB, and as long as the long-term adverse effects on the development of lymphoma and other tumors do not prove to be problematic. Because the rates of benefits to TNFB are modest from a population perspective and the cost of therapy is very high, the ultimate application of use of TNFBs will likely be established by cost/benefit studies.

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INTRODUCTION

Crohn's disease (CD) affects about 500 000 persons in North America^[1], while the prevalence rates in northern Europe are 27-48 per 105^[2]. A selected group of these persons will benefit from the efficacy and safety of tumor necrosis factor- α blockers (TNFBs). This use of TNFB has been reviewed by way of meta-analysis of placebo-controlled trials^[3], as well as with recent consensus statements [e.g., Canadian Agency of Drugs and

Technologies in Health (CADTH, 2009)]. The overall view is that TNFBs are superior to placebo for the induction and maintenance of luminal CD or ulcerative colitis (UC). There are insufficient head-to-head studies comparing TNFB with mesalamine [5-aminosalicylic acid (5-ASA)], intermittent use of glucocorticosteroids (GCS), azathioprine (AZA), or methotrexate (MTX). In fistulizing CD, TNFBs other than infliximab (IFX) require further investigation. It remains to be established how early in the course of CD that TNFBs should be started, and what are the factors that predict which patient is most likely to require or to respond to this therapy.

MECHANISMS OF ACTION OF TNFB

There are numerous reviews on the molecule, cellular, physiological and pharmacological properties of TNFB^[4-9]. Tumor necrosis factor (TNF) (aka "cachectin") has been called the body's sentinel cytokine or "fire alarm"^[10], as it initiates the defence response to local injury. As a result of innate and adaptive immune responses, the level of tumor necrosis factor- α (TNF α) is increased in the serum and mucosa of patients with CD^[11-13], and is a trigger for and a mediator of positive and negative feedback loops which influence the chronicity of inflammation.

TNF in the membranes (tmTNF) is a protein which undergoes proteolysis by the protease TNF α converting enzyme, forming a soluble protein, sTNF. Reverse signalling by tmTNF α may alter cellular responses to stimuli such as bacterial lipopolysaccharide^[14-16]. The sTNF and the precursor tmTNF bind to the two TNF receptors, TNF receptor 1 (TNFR1) (aka p55 or DC120a), and TNFR2 (aka p75 or CD120b)^[1]. Binding the TNFR1R2 to the cleft in the TNF subunits causes activation, and initiates the expression of interleukin (IL)-1, IL-6, interferon-gamma (IFN- γ), cell adhesion molecules (e.g., intracellular adhesion molecule-1), as well as a number other inflammatory molecules^[17].

TNFR1 is expressed in all cells, and generates the proinflammatory properties of TNF. TNFR2 is present in immune as well as endothelial cells, and initiates the immunoregulatory properties of TNF^[7]. If the TNF/TNFR1 clusters in membrane lipid rafts, it becomes antiapoptotic, whereas if TNF/TNFR1 is internalized within the cell, it becomes proapoptotic. Whether TNFR1 activates apoptosis or not depends upon accessory cell proteins, such as TNF receptor-associated factor 2 (TRAF2). TNFB affects both sTNF-mediated mechanisms, as well as tmTNF-mediated mechanisms^[18]. TNFB neutralize sTNF with mean inhibitory concentrations in the nM range. TNFB alter tmTNF interactions with TNFR1 and 2, or as agonists that initiate differential induction of cytokine suppression through reverse signalling, involving signal-peptide-peptidase-like 2a (SPPL2a) and SPPL26. This leads to apoptosis, cell activation, cytokine suppression, induction of the adhesion membrane E-selectin, and resistance to endotoxin^[18,19].

Recruitment of Fas-associated death domain binds

and activates procaspase-8, which then activates caspase-3, and results in apoptosis. In this way, TRAF2 may lead to apoptosis. Alternatively, TRAF2 may recruit c1 activator-protein-1 (AP-1)-1 and c1AP-2. In turn, c1AP-1/-2 cause nuclear factor κ B (NF- κ B) and AP-1 to block apoptosis increase anti-inflammatory proteins, and enhance cell proliferation as well as differentiation. In addition, TNF increases IL-2 receptor, *HLA-DR* antigen gene expression, and I5-A costimulator of IL-2-dependent IFN- γ production.

TNF may be immunostimulatory or immunosuppressive, depending on the genetic background of the patient, the timing and concentration of TNF^[17,18], as well as depending on whether TRFR1 or TRFR2 are involved^[20]. In clinical situations, TNFB do not likely function as immunosuppressants: TNFB may in fact provide immune enhancements^[21], and TNFR may down-regulate some immune reactions that are activated in CD.

Reduced apoptosis in CD may cause inflammation^[22], and the death domains in TNFR may induce apoptosis^[23]. The tmTNF molecule has a cytoplasmic domain which can induce apoptosis by acting as a ligand for TNFRs, or as a receptor that transmits a reverse signal into the tmTNF-bearing cell^[14]. In this way, TNFB may block or induce tmTNFB-mediated apoptosis. TNF-expressing cells such as monocytes, macrophages and T-cells are acted upon either by pathogen-associated molecules which express toll-like receptors (TLRs), or by NF- κ B transportation factors which have been stimulated by inflammatory cytokines such as IL-1. The response to TNFB IFX in CD is determined by a single nucleotide polymorphism in the FCGR3A gene encoding for FC γ R IIIa receptors on NK cells and macrophages^[24]. TLR and NF- κ B act through p38 MAPK and NF- κ B to increase TNF mRNA (gene transcription) and TNF protein (translation).

Both IFX and adalimumab (ADA) induce apoptosis in peripheral blood monocytes as well as in lamina propria T-cells^[25,26]. Certolizumab (CER) does not produce apoptosis *via* tmTNF, possibly because it cannot form cross-linkages with tmTNF, or because of its different epitope specificity. The fact that CER does not induce apoptosis and yet is clinically effective in CD provides evidence for mechanisms of action in addition to apoptosis being important in the clinical benefit of TNFBs.

For IFX and ADA, the presence of antibodies to the TNF reduces the serum concentrations and effectiveness of the drugs^[27-29]. These antidrug antibodies form multivalent immune complexes with the TNFB, leading to their rapid clearance and therefore to reduced clinical response, as well as to the potential for the development of future infusion reactions.

It is not clear why IFX induces antinuclear, anti-dsDNA and anticardiolipid IgA or IgM antibodies. In reviewing this topic, Tracey *et al.*^[18] speculated that TNFB either dysregulated apoptosis and release autoimmunogenic plasma nucleosomes from the apoptotic cells, or inhibit some cytotoxic T-lymphocyte response that normally suppresses autoreactive B cells^[30].

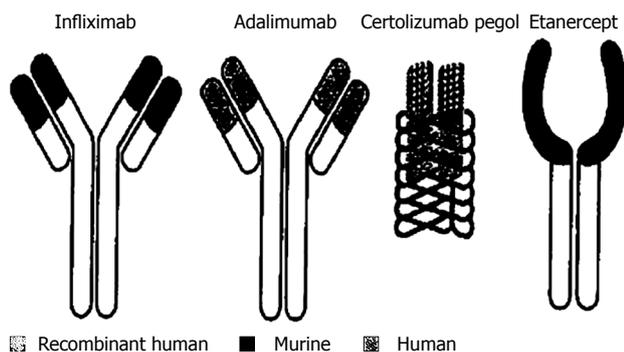


Figure 1 Comparative structures of the anti-tumor necrosis factor agents infiximab, adalimumab, certolizumab pergola and etanercept.

Control of intracellular infections such as *Mycobacterium* requires macrophages and T-cells in granulomas to come close to bacteria, and then wall them off. Etanercept (ETA) does not show efficacy against granulomatous diseases such as Wegener's granulomatosis and sarcoidosis^[18,31]. This is unlikely the main mechanism of clinical benefit of these TNFBs in CD, since ETA is not effective in this disease. Furthermore, ETA, IFX and ADA induce apoptosis, but again ETA is not clinically active in CD. Some other pathway(s) must represent the mechanism of action of IFX, ADA, and CER in CD. IFX, ADA and CER but not ETA almost completely inhibit lipopolysaccharide-stimulated IL-1 β release from monocytes, suggesting that inhibition of the production of cytokine may be important in the clinical efficacy of IFX, ADA and CER in CD^[32]. Because ETA has not been shown to be clinically effective in the treatment of CD, and will not be discussed further in this paper.

The general comparative structures and individual biological properties of the TNFBs which have been approved in various countries for use in persons with CD are shown in Figure 1, and in Tables 1-3. IFX, ADA and CER are discussed in the order in which they became generally available for clinical use in CD, and the order of presentation does not imply in any way the superiority of one TNFB over another.

Etanercept is a soluble TNF receptor fusion protein (humanized IgG1 Fc fragment fused with two identical humanized p75 TNF receptors) that binds and inactivates soluble, but not membrane-bound TNF α , and although effective for the treatment of rheumatoid arthritis and other forms of inflammatory joint diseases, etanercept failed to demonstrate efficacy at similar doses in a clinical trial for CD.

Biologics other than anti-TNF α agents

Recently, natalizumab, a humanized IgG4 monoclonal antibody that antagonizes integrin heterodimers containing α 4-integrin, was approved as a second-line biologic for therapy in the United States for CD patients who failed conventional therapies. Natalizumab inhibits leukocyte trafficking by preventing α 4-mediated adhesion of leukocytes to adhesion molecules and transmigration of leukocytes across endothelium into inflamed mu-

Table 1 The general biological properties of tumor necrosis factor blockers in clinical practice

Pro- or anti-apoptotic effects¹
↑ Adhesion molecules on endothelial cells
↑ Epithelial permeability
↑ Antigen-stimulated B-cell proliferation and differentiation
IL-2R production¹
↑ IL-2 dependent production of IFN- γ
↑ HLA-DR gene expression

¹Represent the data are increased. IFN- γ : Intracellular interferon- γ ; IL: Interleukin.

cosa^[33,34]. Natalizumab is well tolerated, but is associated with an increased risk for infections, acute hypersensitivity reactions, and hepatotoxicity. The primary concern regarding natalizumab therapy has been the reactivation of latent human JC polyomavirus that can lead to a fatal central nervous system infection, progressive multifocal leukoencephalopathy, which has an estimated risk of 1:1000^[35]. Therefore, natalizumab use has been restricted to monotherapy, without concomitant immune suppressants, and has a mandated special safety monitoring program and consent that has limited its patient acceptance. Nevertheless, natalizumab remains a viable option for patients who have lost a mechanistic response to anti-TNF α agents.

CLINICAL ASSESSMENTS REQUIRED BEFORE THE INITIATION OF TREATMENT WITH TNFBs

Absolute or relative contraindications for use of TNFBs

TNFBs are contraindicated if the CD patient has an abscess, intestinal stricture, a flare of colitis in association with an enteric infection with *Clostridium difficile* or cytomegalovirus, severe congestive cardiac failure (NYHA III or IV), uncontrolled HIV disease, endemic mycosis, multiple sclerosis, or evidence of tuberculosis (TB) (positive interferon-gamma assay and/or chest X-ray prior to a four weeks course of isoniazid). TNFBs should also be used with caution and balanced consideration in CD persons with neurological disease, chronic liver disease, a history of malignancy (especially lymphoma), and in the woman who is pregnant or plans to begin parenthood (see below).

TNFBs and pregnancy: Lactation and contraception

Because the peak prevalence of inflammatory bowel disease (IBD) is between approximately 20 years to 40 years of age, for the couple where one or both partners have CD or UC, the issues of pregnancy, lactation and contraception are important. These issues need to be discussed proactively and in detail with the patient and their sexual partner.

The American Food and Drug Administration (FDA) classifies IFX and ADA as pregnancy class B agents. So,

Table 2 Individual biological properties of tumor necrosis factor blockers

<p>IFX</p> <p>High sensitivity and specificity for binding to both sTNF and tmTNF</p> <p>2-3 IFX molecules bind to each TNF trimer, preventing TNF binding to cellular receptors, and reversing the actions of TNF</p> <p>The TNF trimer complexes are biologically inactive and are thought to be cleared by the hepatic reticuloendothelial system</p> <p>Most IFX is in the vascular compartment</p> <p>No systemic accumulation</p> <p>Clearance of IFN is slowed by MTX and is ATI</p> <p>The VOD at steady state is independent of dose</p> <p>VOD and clearance are not affected by patient age or weight. The effect of liver or kidney disease is unknown</p> <p>Does not produce a generalized suppression of the body's immune system</p> <p>Response to IFX is affected by CRP polymorphisms</p> <p>Linear relationship between dose and serum concentration of IFX</p> <p>Serum concentration is correlated with clinical response (in at least persons with rheumatoid arthritis)</p> <p>Reductions in IL-10 levels also correlate with improvement in clinical activity, and FGF and improvement in perianal disease</p> <p>For the 5 mg/kg dose, the median terminal half-life (<i>t</i>) is 10.9 d¹</p> <p>↓ Cells expressing TNF, IL-10, IFN-γ</p> <p>↓ Cells staining for CD4, CD5, CD6, MMP-9</p> <p>↓ TNF levels (that are ↑ in serum and diseased mucosa in CD)</p> <p>↓ ICAM-1</p> <p>↓ Lamina propria T-lymphocytes and peripheral blood monocytes</p> <p>↓ Growth hormone resistance</p> <p>↓ Markers of bone reabsorption, ↑ markers of bone formation</p> <p>ADA</p> <p>Forms high molecular weight complexes with human TNF (600-5000 kDa)</p> <p>Linear relation between dose and serum concentration</p> <p>Serum concentration is correlated with clinical response</p> <p>Mean serum <i>t</i> is 10-20 d</p> <p>Clearance is slowed by MTX, and is accelerated by ATA</p> <p>Certolizumab pegol</p> <p>Lacks IgG Fc domain, and thus does not fix lysed cells or complement</p> <p>The Fab' component of CER contains a free cysteine residue to the hinge region, which provides site-specific attachment of the PEG to the Fab' at a site well removed from the antigen binding site</p> <p>The retention time of protein conjugates in the blood is increased by pegylation, and immunogenicity is reduced. Pegylation increases in the half-life (<i>t</i>_{1/2}) of the antibody fragment, so dosing may be less frequent</p> <p>The half-life of CER in healthy volunteers is 313 h</p> <p>Site-specific pegylation of the Fab' fragment of CER is directed to a site well away from the antigen-binding region. In this way, the conjugate has the same high affinity of the TNF as the tmTNF and sTNF without the pegylation</p> <p>Does not cause apoptosis of lymphocytes and monocytes, and antibodies to IFX (ATI) do not cross-react with CER</p> <p>Accumulates preferentially in inflamed rather than in non-inflamed tissue</p> <p>Has a greater affinity for sTNFs than do IFX or ADA</p> <p>Has twice the neutralizing potency as IFX or ADA for sTNFα</p> <p>Has the same neutralizing potency as IFX and ADA for tmTNFα, and occurs through p55/p75 TNFR</p> <p>Anti-CER antibodies levels are low, and do not affect the efficacy of CER</p> <p>Does not cross-react with ATI (antibodies to IFX)</p> <p>Has a linear pharmacokinetic profile</p> <p>Bioavailability of subcutaneously administered CER is almost 100%</p> <p>Does not lyse cells, cause complement-dependant cytotoxicity, antibody-dependant cell-mediated cytotoxicity, apoptosis of activated monocytes or lymphocytes or necrosis of neutrophils</p>

¹Represent the counts or concentration is decreased. IFX: Infliximab; TNF: Tumor necrosis factor; MTX: Methotrexate; ATI: Accelerated by antibodies to IFX; VOD: Volume of distribution; CRP: C-reactive protein; FGF: Fibroblast growth factor; IFN- γ : Intracellular interferon- γ ; IL: Interleukin; MMP-9: Metalloproteinases; ADA: Adalimumab; ATA: Antibodies to ADA; ICAM-1: Intracellular adhesion molecule-1; PEG: Polyethylene glycol; CER: Certolizumab; CD: Crohn's disease; TNFR: TNF receptor.

IFX and ADA may be used during the first two trimesters of pregnancy if clinically indicated, and absolutely necessary^[36-38]. There is no detailed published data on the safety of CER in pregnancy. Because clinically significant levels of IFX have been described in the serum of a baby 6 wk after delivery^[39], it is recommended for the pregnant IBD mother to stop IFX in the third trimester of her pregnancy. There is no transfer of IFX to mother's breast milk, so the IFX may be restarted shortly after the child has been delivered.

Vaccination

Recommendations have been made for the regular scheduled monitoring of persons on TNFB^[40]. When the diagnosis of IBD is initially established, the patient's vaccination status should be reviewed. Unfortunately, the assessment of the IBD patient for vaccine-preventable diseases is not well considered by many healthcare providers^[41]. If the vaccination program is not current, then it must be updated before the use of TNFBs. Ideally, vaccinations should be updated before the use of immu-

Table 3 Comparison of *in vitro* properties of different tumor necrosis factor- α blockers in clinical practice for inflammatory bowel disease

Agent	Mediates			Increases proportion of apoptotic cells	Inhibits cytokine production	Effective in IBD patients
	Binds TNF	CDC	ADCC			
Infliximab	Yes	Yes	Yes	Yes	Yes	Yes
Etanercept	Yes	Yes	Yes	Yes	No	No
Adalimumab	Yes	Yes	Yes	Yes	Yes	Yes
Certolizumab pegol	Yes	No	No	No	Yes	Yes

TNF: Tumor necrosis factor; ADCC: Antibody-dependent cell-mediated cytotoxicity; CDC: Complement-dependent cytotoxicity; IBD: Inflammatory bowel disease.

Table 4 Management of hepatitis B virus infection in inflammatory bowel disease patient being considered for tumor necrosis factor- α blockers therapy

Serology	Management
HBsAg+, LE \uparrow	Treat HBV
HBsAg+, normal LE	Vaccinate for HBV; monitor LE and HBV-DNA
HBsAg-	Vaccinate for HBV
Consider giving a combined vaccination for HAV-HBV	Measure anti-HBs-Ab titer 1 mo after third injection to determine adequacy of response; additional doses may be necessary

LE: Liver enzymes; HBV: Hepatitis B virus; HAV: Hepatitis A virus; HBsAg: Hepatitis B surface antigen.

nosuppressants such as AZA or MTX, or GCS.

Under no circumstance should the patient on TNFB be given live vaccines. To stress, these include vaccines for measles-mumps-rubella, varicella (oral), yellow fever vaccine, or oral polio vaccine. The injectable (non-oral) vaccines for polio and for typhoid are considered to be safe. Live vaccines may be given safely three weeks before or three months after stopping AZA or metronidazole (MTZ), or given at any time to persons on GCS, as long as the dose is below prednisone 20 mg/d. There are no guidelines for the ideal time to vaccinate before or after the use of higher doses of GCS.

In the IBD patient who is hepatitis B virus (HBV) positive (regardless of negative hepatitis B surface antigen, and regardless of elevated or normal liver enzyme test), the HBV must be treated before starting TNFB (Table 4).

The regular travel precautions are taken for malaria. As with all travellers, ciprofloxacin and/or metronidazole should be available to the traveler, in the event that they develop symptoms suggestive of traveller's diarrhea. It is useful if the traveler has a typed copy of their medical records, a copy of their consultant physicians' most recent letter, documentation for custom officials of their prescribed medications, purchase of traveller's insurance without exclusion for pre-existing conditions (i.e., IBD), contact names and numbers of physicians in foreign countries with IBD experience, and contact numbers for care-givers at home. IBD patients with an ileostomy should be aware of the importance of their not becoming dehydrated.

APPROVED INDICATIONS FOR TNFBS IN CD

The approved indications for the use of TNFB vary from country to country. According to the Canadian Association of Gastroenterology, as well as the Canadian Expert Drug Advisory Committee^[42,43], IFX is recommended: (1) For patients with moderately to severely active CD who have continuing symptoms despite the use of conventional therapies (5-ASA, antibiotics, GCS, AZA, MTX); (2) For patients with CD who cannot tolerate conventional therapy; (3) For fistulizing CD; and (4) For pediatric CD with inadequate response to conventional therapy.

When to avoid TNFB

There are several situations when TNFB should not be used, or used after full consideration of the consequences and patient awareness and patient awareness and consent.

Narrowing of bowel and TNFB use

Narrowing of bowel and TNFB use: (1) Inflammatory-no pre-stenotic dilation); and (2) Fibrostenotic-no.

Latent infection

Latent infection: (1) TB; (2) HBV; (3) HIV; and (4) Live vaccines within last 3 mo.

Active infection

Active infection: Perianal or intra-abdominal abscess must be drained.

Present malignancy or disorder

Present malignancy or disorder: Present/previous malignancy (other than non-melanoma skin cancer) or lymphoproliferative disorder.

Cautious use in children

Cautious use in children: Because of 48 cases of malignancy, 88% (almost 9 out of 10) of which were while the patient was on both TNFB plus immunomodulators, and half developed lymphoma.

Efficacy of TNFBs

General considerations: There are several goals of therapy in CD (Table 5). It is important to consider a

Table 5 Goals of therapy in Crohn's disease

Induce and maintain remission off steroids
Improve patient's quality of life
Reduced risk of need for surgery or hospitalization
Reduce risk of development of adenocarcinoma/lymphoma
Maintain mucosal healing as a possible predictor or surrogate marker of better future disease outcome
Acceptable efficacy/safety balance

number of factors pertaining to the clinical trials which have been used in meta-analyses to provide therapeutic recommendations for the use of TNFBs for induction and maintenance of CD. What proportion of CD patients will have an initial non-response to IFX (primary non-response), a continued response or remission, and a secondary non-response? The definition of response and remission may vary between studies, the time of assessment of these outcomes may vary, and most studies exclude the primary non-responders at 2 wk. Also, the placebo response rates vary widely, and therefore so too does the therapeutic gain [therapeutic gain (TG); therapeutic minus placebo response]. Some patients may have a short or a long duration of CD before IFX for example was initiated used, and some trial participants were previously or concurrently on GCS, AZA, or MTX, and the dose and duration of use of GCS, AZA and MTX may have varied widely.

About a quarter of persons treated with TNFB will be primary non-responders, i.e., will not respond to an initial dose of TNFB. Because primary non-responders are often excluded from analysis, the response and remission rates in the intention-to-treat group are much lower than the per-protocol group^[44]. Patients and physicians must be made aware that some of the published rates of TNFB response (about 2/3 of TNFB users) and remission (about 1/3) are in those persons who responded initially, and do not include the percentages based on all users (i.e., intention-to-treat). The overall desired outcome of TNFB therapy is prolonged steroid-free remission, mucosal healing, good quality of life, and normalization of laboratory markers of inflammation [e.g., C-reactive protein (CRP), erythrocyte sedimentation rate], an acceptably low risk/benefit ratio, and acceptable cost to ensure widespread availability.

There are different ways in which a response to therapy may be defined, and these definitions vary from study to study. In clinical trials of CD, the CD activity index (CDAI) is often used as one of the outcome measures. The CDAI is based on the patient's symptoms, the presence of an abdominal mass, anemia (reduced hematocrit), weight loss, and use of an anti-diarrheal agent. CD is arbitrarily said to be "active" if the CDAI is above 150 points. Clinical response in CD may be a decrease in CDAI of ≥ 70 points, or a decrease in CDAI of 70 to 100 points plus a 25% improvement from baseline^[45]. Clinical remission might be variably defined as a CDAI of < 150 , or CDAI < 150 plus a decrease by 50 to 100 points from baseline. Because of these variations in

Table 6 Predictors of good response to tumor necrosis factor- α blockers

Luminal
Short history of CD
Less severe disease
Isolated colonic disease
Inflammatory CD ^[46-49]
No previous abdominal surgery
Use shortly after ileocolonic resection
CRP > 5 mg/L (76% vs 46% response to TNFB), or \uparrow CRP returning to normal detectable through serum TNFB (IFX) levels. CRP concentrations are inversely correlated with the rates of placebo response ^[50]
Non-smoking
Fistulizing
Perhaps for response with rectovaginal fistula

TNFB: Tumor necrosis factor- α blocker; CD: Crohn's disease; CRP: C-reactive protein; IFX: Infliximab.

definition, the results from one study cannot be directly compared with another study. Comparing the placebo responses gives only a very rough approximation of the comparison of the population of patients examined in two studies, because of the very large heterogeneity of CD sufferers. The only totally valid method of comparison of one TNFB to another is a head-to-head randomized controlled trial (RCT). Note that there are no head-to-head comparisons of IFX, ADA, CER. Taking the largest trials into account, and considering all of these previously mentioned cautionary points, it is suggested that there are numerically similar post-induction success rates of clinical remission and fistula closure for IFX, ADA and CER.

Specific considerations: Induction of remission, and primary non-response: Patient selection characteristics and the time in the course of the patients' disease will influence outcomes with TNFB therapy, so there may be large variations in the placebo response in one study vs another, and therefore gain achieved with TNFB (Table 6)^[46-50]. Careful consideration must be given as when to start TNFB therapy: When to start TNFB depends upon consideration of (1) clinical characteristics (steroid-refractory and steroid-dependent); (2) previous response to treatment; (3) complications and comorbidity; (4) cost/availability; and (5) patient preference and IFX. The 2 wk induction response rates for IFX ranges from 52% to 73% (Table 7). However, the therapeutic gain for single dose IFX for induction of response and remission in CD varies with the time of assessment and dose, and is quite modest, for example, only a 10% to 22% remission rate at week 12. Quoting from the CADTH review^[51], "a total of 47 citations reporting 20 RCTs and 17 observational and uncontrolled studies were included. All the RCTs had a parallel group design. Four studies were open-label, single-arm trials. Of the remaining 13 cohort studies, seven studies used a prospective design, and the remaining six studies used a retrospective design. Five cohort studies and one RCT were published as abstracts only. The remaining studies had at least one full peer-

Table 7 Therapeutic gain for single dose infliximab for induction Crohn's disease: Response and remission (%)

Assessment week	IFX (mg/kg)			PL	Therapeutic gain
	5	10	20		
Response					
2	73	52	53	17	56-35-36
4	81	50	65	17	64-33-48
12	48	29	46	12	36-17-34
Remission					
2	40	22	22	4	36-18-18
4	50	26	26	4	46-22-22
12	30	18	25	8	22-10-17

PL: Placebo; IFX: Infliximab.

reviewed publication. IFX was used as the treatment for patients with CD in eight RCTs (total number of participants 1091; range: 36-335) and 10 observational and uncontrolled studies (total number of participants 1402; range: 12-614), and for patients with UC in six RCTs (total number of participants 1477; range: 299-499) and five observational and uncontrolled studies (total number of participants 157; range: 15-36). One cohort study (10 participants) reported the use of ADA in UC. One RCT of 43 participants evaluated the effects of ENT in patients with CD. Of six which included placebo-controlled trials assessing the effectiveness of IFX in the treatment of CD, three studies used short-term regimens of IFX to induce disease remission, and three RCTs evaluated the effectiveness of long-term IFX in maintenance of remission^[51].

For the treatment of fistulizing CD, reporting on 776 patients in 10 studies, after open-label induction, maintenance trials showed a mean difference of 16% (95%CI: 8%-25%, $P < 0.001$)^[3]. Thus, only 11% had induction of remission as compared to placebo, and only 8% maintained their remission for about half a year.

The TG is the treatment response minus placebo response. The TG for significant response at weeks 4, 12, 24, and 30 and 54, a response will be seen in 50% and 37%, 30, 52, and 54 is 48%, 29%, 28%, 23%, 18%, and 22% with TG for remission of 16% and 13%.

In IFX primary non-responders, there is no proven benefit in using ADA. Of those who do respond initially at 2 wk, then after 4 wk of IFX about two-thirds respond (CDAI > 70 point reduction), and about one-third are in remission (CDAI < 150 points)^[52]. At 24 wk, 57% will still show a response, but will not be in remission [IFX = placebo (PL), $P = 0.31$]^[52,53]. At 30 wk and 54 wk, 39% and 28% were in remission^[54].

Adalimumab

The two major studies evaluating ADA in CD need to be evaluated separately due to heterogeneity in terms of whether the CD patients were naive to TNFB^[51]. Similar to IFX, about 30% of persons with CD given ADA will be primary non-responders. Of those who do respond initially at week 1, about 52% will have responded at 4

Table 8 Comparison of tumor necrosis factor- α blockers for Crohn's disease remission and fistula closure

	IFX (mg/kg)	ADA (mg)	CER (mg)
Remission (26-30 wk)	42	43	48
Fistula closure	36 ^[78]	32	54

CER: Certolizumab; IFX: Infliximab; ADA: Adalimumab.

wk and 21% will be in remission. The secondary non-response rate to ADA is 23%-48% at 24-26 wk and 23%-59% at 56 wk. The TG (active agent-placebo response) at weeks 4, 26, and 56 was 14%, 23%-25% and 23%-24% (Table 8)^[54-56].

The Community Economic Development Assistance Corporation recommends ADA for patients with moderate to severely active CD who are "refractory to or who experience contraindication to an adequate course of 5-ASA and corticosteroids and other immunosuppressive therapy"^[42]. It is not defined how long the patient must have been on conventional therapies before declaring that they have continuing symptoms, or how minor these continuing symptoms may be before considering adding TNFB therapy. It is not clear whether patient preference represents a "contraindication" to an adequate course of conventional therapy.

The mean percentage of loss of response to ADA among primary responders was 18.2% and the annual risk was 20.3% per patient-year. The mean percentage of patients who required dose intensification among primary responders to ADA was 37% and the annual risk was 24.8% per patient-year. When considering initial responders and patients with primary non-response, the mean percentage of patients who needed an ADA dose escalation was 21.4% and the annual risk was 24.4% per patient-year. Pooled analysis showed that dose escalation permitted response to be regained in 71.4% and remission in 39.9% of patients. Predictors for loss of response or dose escalation were male gender, current/former smoker status, family history of inflammatory bowel disease, isolated colonic disease, extra-intestinal manifestations, 80/40 mg induction therapy, longer disease duration, greater baseline Crohn's Disease Activity Index (Table 9), concomitant corticosteroid use, no deep remission at week 12, low serum trough concentrations of ADA, previous IFX non-response and being previously treated with an anti-tumor necrosis factor agent.

Certolizumab pegol

The Precise 2 trial with CER in CD over 26 wk showed clear superiority to placebo in terms of clinical response and remission^[57].

Meta-analysis

There have been five systematic reviews and meta-analyses published on the efficacy of TNFB in inducing remission of active luminal CD^[3,58-61], as well as Cochrane review of the efficacy of natalizumab in the same clinical

Table 9 Therapeutic gain for adalimumab induction of response and remission (%)

Study	Assessment week	ADA ¹	ADA ²	ADA ³	PL	Therapeutic gain	
Gain	Response (CDAI ↓ ≥ 100 pts)						
	1	-	-	20	12	8	
	2	-	-	37	18	19	
	4	-	-	38	25	13	
	Remission						
	1	-	-	6	4	2	
	2	-	-	21	6	15	
	4	-	-	21	7	14	
	(Classic 1)	Response (CDAI ↓ ≥ 100 pts)					
		1	23	25	21	16	7-9-5
		2	31	37	31	15	16-22-16
		4	34	40	50	25	9-15-25
Remission							
1		16	13	16	7	9-6-9	
2		14	20	24	14	0-6-10	
4		18	24	36	12	6-12-24	
(Classic 1)		Response (CDAI ↓ ≥ 70 pts)					
		1	-	-	6	4	2
		2	-	-	21	6	15
		4	-	-	21	7	14
	Response						
	1	37	40	32	24	13-16-8	
	2	44	55	45	30	14-25-15	
	4	54	59	59	37	17-22-22	

¹40 mg at week 0, 20 mg at week 2; ²80 mg at week 0, 40 mg at week 2; ³160 mg at week 0, 80 mg at week 2. PL: Placebo; CDAI: Crohn's disease activity index; ADA: Adalimumab.

cal setting^[62]. The most recent meta-analyses on the therapeutic management of IBD have appeared in the "Red Journal" (Table 10)^[61]. Funnel plot asymmetry was considered regarding evidence of publication bias and small study effects, and Cochran *Q* values for heterogeneity. The criteria for inclusion of studies was stringent, using rigorous and conservative methodologies and these data should be used to better guide and care for patients suffering from CD and UC.

In summary, in persons with active luminal CD who have failed treatment with first and second-line agents or who are corticosteroid dependent, for induction of remission of active luminal CD, "IFX, natalizumab, and ADA appear to have the most evidence for their use, although the latter two therapies performed only moderately in this setting"^[61].

Primary non-response

The clinical definition of primary non-response is lack of improvement of clinical signs and symptoms with induction therapy. Definitions and time-frames for the assessment of response and non-response have varied amongst clinical trials for different biological agents; in the original "Targan" study of IFX in refractory CD, response was defined as a 70-point reduction in the CDAI after 4 wk^[52].

To a shift in the dominant mechanism of inflammation (loss of the pharmacodynamic effect), increasing

Table 10 Meta-analysis of efficacy and safety of anti-tumor necrosis factor α antibodies vs placebo (4 wk to 12 wk) in inducing remission in active luminal Crohn's disease

Treatment	Outcome (RR of remission not achieving)
All biological vs PL	RR = 0.87; 95%CI: 0.80-0.94; NNT = 8 (95%CI: 6-17)
IFX vs PL ¹	RR = 0.68; 95%CI: 0.52-0.90, <i>I</i> ² = 78%, <i>P</i> = 0.01; NNT = 4 (95%CI: 3-7)
ADA vs PL	RR = 0.85; 95%CI: 0.79-0.91, <i>I</i> ² = 0%, <i>P</i> = 0.99; NNT = 7 (95%CI: 5-12.5)
CER vs PL	RR = 0.95; 95%CI: 0.90-1.01, <i>I</i> ² = 0%, <i>P</i> = 0.62
Natalizumab vs PL	RR = 0.88; 95%CI: 0.83-0.94, <i>I</i> ² = 0%, <i>P</i> = 0.72
Adverse effects	No statistically significant difference in the incidence of adverse events was detected with TNFB vs placebo (RR of experiencing any adverse event, including infusion or injection site reactions = 0.99; 95%CI: 0.90-1.08)
	With anti-α4-integrin antibodies (natalizumab) vs PL, significantly more patients reported headache (compared with placebo: RR = 1.23; 95%CI: 1.03 to 1.47, <i>I</i> ² = 0%)
	With NAT there were trends towards more infusion reactions (RR = 1.41; 95%CI: 0.94 to 2.10, <i>I</i> ² = 0%) and infections (RR = 1.12; 95%CI: 0.97 to 1.30, <i>I</i> ² = 0%)
	Number needed to harm with NAT = 17 (95%CI: 9-71)

Independent data extraction was undertaken by two reviewers, and discrepancies checked and resolved intention-to-treat. Analysis and pooled data with a random effects model was used, including the reporting of the search strategy, inclusion criteria, and data extraction processes. ¹Note that when the Sonic trail was excluded from analysis, there was no statistically significant difference between IFX vs placebo. RR: Risk ratio; IFX: Infliximab; ADA: Adalimumab; CER: Certolizumab; PL: Placebo; CI: Confidence interval; TNFB: Tumor necrosis factor-α blockers; NAT: Natalizumab; NNT: Needed to treat.

symptoms or signs not related to IBD activity (for example, irritable bowel syndrome, concomitant infection, bacterial overgrowth, and so on), or failure to wean off corticosteroids. Loss of response can also imply.

A "relative" term for patients who have shorter durations of response (for example, less than 4 wk for IFX, 1 wk for ADA, or 2 wk for certolizumab) or require dose escalation, which may become economically impractical.

In the Accent I study of IFX, which assessed the maintenance benefits of IFX, the initial response was defined as a 70-point reduction in the CDAI at 2 wk^[54]. Most clinicians will consider lack of response after two consecutive infusions of IFX of at least 5 mg/kg body weight and will assess treatment failure at 4 wk^[50].

Recent data suggest that patients who initially respond may, more gradually, accrue remissions over time^[55].

All three currently approved anti-TNFα biological agents are administered differently and have different pharmacokinetics and dosing intervals, and a reasonable assessment of lack of response to IFX would be after 2 wk, and to ADA and certolizumab pegol would be made after completion of induction therapy at 4 wk and 6 wk.

In approximate terms, 70% of IFX-treated CD patients show a response after 2 wk of treatment. In these primary responders, the secondary non-response rate (i.e.,

Table 11 Mechanisms which are speculated to be the cause of primary non-response

Lack of response may be due to different immunoinflammatory mechanism(s) ^[63]
A differential role of TNF α in certain stages of disease
Individual differences in drug metabolism and elimination, drug binding in serum or tissues based on disease activity level ^[27,148]
The presence of innate anti-TNF α antibodies that may exhibit greater neutralizing activity in non-responders ^[175]
Absence of inflammation accounting for clinical symptoms
Unidentified, genetic or pharmacogenetic or serological backgrounds of individual patients ^[24,176-179]
Individual differences in bioavailability and pharmacokinetics, leading to inadequate concentrations of a biologic secondary to immunogenicity (neutralizing or non-neutralizing antibodies, or unmeasured or unknown antibody) or other factors that increase drug clearance (decreased circulation half-life and possible high consumption in severe disease) ^[27,128]

TNF α : Tumor necrosis factor- α .

Table 12 Secondary failure rates

Maintenance of response month (%)	Loss of response (%)	Loss of response per month (%)
13 (64)	36	2.8
55 (63)	37	0.7
28 (78)	22	0.8

In another long-term maintenance study, the percentage of Crohn's disease patients who maintained response declined over time: 30 wk, 83%; 54 wk, 64%; 108 wk, 45%.

those who initially respond, but then lose their response) is 40%-50% at 24-30 wk, and 60%-63% at 52-54 wk. At one year, about 30% of the initial responders will still be responding, and about 20% will be in remission.

About 30% of persons given TNFB therapy do not initially respond (primary non-response). The explanation of this is unknown, but it may be speculated that this may be done to the use of too low a dose of IFX (the serum through concentration of TNFB generally correlates with CD response), or the inflammatory process may be independent of TNF α . Of the initial primary non-response responders, about 70% respond and 35% go into remission. Including all persons with active CD, and taking into consideration the initial non-responders, out of 100 CD patients with active disease treated with TNFBs, approximately ($100 \times 70\% = 70$, $70 \times 70\% = 49$) will respond and ($70 \times 30\% = 21$) will go into remission. These figures are lower than historically reported clinical response and remission rate with conventional (i.e., standard-of-care) management with GCS or, AZA/MTX, however it must be stressed again that because of large differences in study populations and study designs, the clinician must be very caution about accepting comparisons in anything other than direct head-to-head studies.

There are numerous possible reasons for lack of response (Table 11)^[63].

MAINTENANCE OF REMISSION AND SECONDARY FAILURES

Once the CD patient has gone into remission, we wish to prevent relapse. In CD, we lack benefit from 5-ASA/Sulfasalazine (SASP). Antibiotic maintenance has been shown to be significantly better than placebo, but there

Table 13 Therapeutic options for tumor necrosis factor- α blockers secondary non-response

Continue the same TNFB, but use a higher dose at the same time interval
Continue the same TNFB and the same starting dose, but use a shorter interval between doses
Re-induction therapy with another TNFB
Use another therapeutic option (e.g., tacrolimus or cyclophosphamide)
Surgery

TNFBs: Tumor necrosis factor- α blockers.

are insufficient studies for most clinicians to use long-term antibiotics as suppressive therapy. Few clinicians are sufficiently adapt at complex statistical methodology to understand the subtle aspects of whether to believe results reported as risk ratios (RRs) or odds ratio (ORs); immunosuppressives will likely continue to be used for maintenance therapy in CD, at least in the foreseeable future.

About 43% of patients with CD require GCS again within one year of starting GCS. The lifetime need to use GCS is 44%^[64]. At 14 wk of use of full therapeutic doses of GCS for moderately active CD, 84% respond and 58% are in remission. At one year 32% are in remission, 28% are still on GCS (steroid-dependent), and 40% have required surgery. It may be speculated that the use of GCS may identify a group of patients who have more aggressive disease, and in whom immunosuppression or TNFB might need to be started early in the course of the disease^[65]. AZA/MTX reduce steroid-dependence and maintain disease remission, but do not reduce the need for surgery^[66].

Using meta-analysis, Akobeng^[67,68] demonstrated that MTX, IFX, ADA, and CER were more effective than placebo for maintaining remission in CD, with number needed to treat (NNT) of 4-6. GCS, 5-ASA, budesonide, cyclosporine, antimicrobials and probiotics did not differ from placebo for maintaining remission at 6-24 mo. Enteral nutrition (EN) was more effective than no EN. Over 50% of CD patients become steroid-dependent or have a surgical resection within one year of starting GCS^[64]. The monthly rate of loss of response to TNFB is higher in the shorter than in the longer durations of follow-up, ranging from 2.8% loss of response per month in a 13-mo study, to 0.7%-0.8% loss of response per month for 28- to 55-mo long study (Table 12).

Table 14 Therapeutic gain of infliximab for Crohn's disease maintenance of response and remission (%)

Assessment week	Treatment	IFX (mg/kg)			PL	Therapeutic gain
		5	10	20		
Remission	0, 2, 6 wk					
12		75 ¹	-	-	38	37 ¹
24		57 ¹	-	-	29	28 ¹
52		40 ¹	-	-	22	18 ¹
Response	2, 6, 8 wk					
30		50 ¹	58 ¹	-	27	23-31 ¹
54		37 ¹	47 ¹	-	15	22-32 ¹
Remission	2, 6, 8 wk					
30		39 ¹	39	-	21	18 ¹ -18
54		28 ¹	38	-	14	14 ¹ -24
Response	q8 wk					
54	until week 54	36 ¹	-	-	6	30 ¹
Response	q8 wk (4 infusions)					
36		-	72 ¹	-	44	28 ¹
44		-	62 ¹	-	37	25 ¹
Remission	q8 wk (4 infusions)					
12		-	14 ¹		44	-30 ¹
36		-	60 ¹		35	25 ¹
44		-	53 ¹		20	33 ¹

¹Significant difference. PL: Placebo; IFX: Infliximab.

Those who have initially responded, but then subsequently relapse, are said to be secondary non-responders. In those persons who initially respond to TNFB, and then lose the benefit (CDAI increases, representing active disease; secondary non-response), there are several therapeutic options (Table 13).

IFX

Secondary failures to IFX may be as common as 48% in the first year of anti-TNF therapy, and 66% in the second year^[69]. In secondary IFX non-responders, switching to ADA results in a response in 59%-83%, and remission in 29%-50%^[70-72].

Secondary non-responders may respond to an increase in IFX dose, or a decrease in dosing interval, or both^[73]. In secondary non-responders to IFX, 80%-90% responded to treatment intensification with IFX^[54,74]. After two and a half years after an initial response to IFX, about half (54%) of patients require dose intensification^[51,75]. Other studies have confirmed the use of dose escalation^[76,77]. Dose acceleration helps maintain response: for luminal disease, 90%^[74], for fistulising disease, 60%^[78]. At 40 wk, 65% were still responding after the last dose intensification over 52 wk^[72,73]. The therapeutic gain for IFX maintenance of remission was low, ranging from 14% to 33% at one year (Table 14).

In the Accent I Study^[54], dose escalation was needed for persons who initially responded but then worsened at some time during the 54 wk study in 49% of persons on episodic treatment, 30% on 5 mg/kg IFX scheduled treatment, and 26% on 10 mg/kg scheduled treatments (secondary, non-response). Response was re-established with higher doses in 90% of the 5 mg/kg and 80% of the 10 mg/kg scheduled treatment groups treated with higher doses. Most of the cross-overs to higher doses

occurred at week 14. In a 40 wk study, 83% of secondary IFX non-responders did respond after the first intensification of IFX, and 65% of patients were still responding after the last intensification dose.

Patients who lost their response to IFX were switched to ADA, and then continued with it for 52 wk. Secondary non-response to ADA was seen in 25%, and therefore, patients required a dose escalation^[72]. These response rates are even higher in persons treated with ADA for the first time (i.e., IFX- and ADA-naive CD patients). Two RCTs and four observational and uncontrolled studies assessed the clinical effects of ADA after a loss of response or intolerance to IFX^[51]. Re-induction therapy with ADA has a 60% clinical response^[79]. Similarly, the Precise II study^[57] showed a benefit of reinduction in clinical response and remission of CD with CER in those patients who had received IFX in the past.

Long-term maintenance with IFX 3 mg/kg maintains mucosal integrity and avoids CD recurrence one year after surgery^[80]. Another study evaluated endoscopic recurrence of CD post-operatively and found the rates to be lower with IFX at one year *vs* placebo (9.1% *vs* 85%)^[81]. However, clinical remission was not significant (80% IFX *vs* 53.8% placebo, *P* = 0.38). A recent review of the literature also shows that there is statistical benefit with IFX use within 4 wk of surgery on mucosal healing. But this effect was not statistically significant in reduction of CDAI.

Adalimumab

There are two RCTs^[55,56] and four observational and uncontrolled studies^[70-72,82,83] assessing the clinical effects of ADA after a loss of response or intolerance to IFX. Blinded clinical trials show that ADA is effective first-line therapy for TNFB-naive CD patients, and is an option for IFX-refractory or-intolerant persons^[84]. In the Gain study^[55], secondary non-responders to IFX responded better when switched to ADA than when switched to placebo (IFX→ADA *vs* IFX→PL). In an uncontrolled open-label study, the switch from IFX to ADA (IFX→ADA) was associated at week 12 with a 59% clinical response and 29% remission rate^[70]. A 50% or greater decrease in the number of draining fistulas was seen in 56%, while 33% had complete absence of fistula. In a second study^[82], switching from IFX to ADA (IFX→ADA) gave a partial response in 31% and a complete response in 54%. In a single-arm study^[72], 50% of IFX→ADA had a clinical remission at week 52. Four weeks after switching to ADA, 83% had a clinical response and 42% were in remission^[72].

In the Crohn's trial of the fully human antibody adalimumab for remission maintenance (CHARM) study^[56], there was no statistically significant response to ADA in IFX non-responders (IFX→ADA) or in those who were IFX-naive. When switching from IFX to ADA^[56], the response at 26 and 56 wk in the TNFB-naive patients was 47% and 42%, compared to 32% and 31% in the non-responder group. Overall the ADA

Table 15 Therapeutic gain of adalimumab maintenance of response and remission (%)

Study	Assessment week	ADA ²	ADA ³	PL	Therapeutic gain
Maintenance					
CHARM	Response (CDAI ↓ ≥ 100 pts)				
	26	52 ¹	52 ¹	27	25 ¹ -25 ¹
	56	41 ¹	48 ¹	17	24 ¹ -31 ¹
	Response (CDAI ↓ ≥ 70 pts)				
	26	54 ¹	56 ¹	28	26 ¹ -28 ¹
	52	43 ¹	49 ¹	18	25 ¹ -31 ¹
(Classic II)	Response (CDAI ↓ ≥ 100 pts)				
	24	84	94 ¹	61	23-33 ¹
	56	79	89 ¹	56	23-33 ¹
	Remission (CDAI ↓ ≥ 100 pts)				
	26	40 ¹	46 ¹	17	23 ¹ -29 ¹
	56	36 ¹	41 ¹	12	24 ¹ -19 ¹
	Remission (CDAI ↓ ≥ 70 pts)				
	24	95	94	83	12-11
	56	79	89	72	7-17
	Remission				
	4	95	100 ¹	89	6-11 ¹
	12	90 ¹	89 ¹	56	44 ¹ -33 ¹
24	84 ¹	94 ¹	50	34 ¹ -44 ¹	
32	84 ¹	100 ¹	39	45 ¹ -61 ¹	
48	74	94	44	30-50	
56	79	83	44	35-39	

¹Significant difference; ²40 mg at week 0, 20 mg at week 1; ³80 mg at week 0, 40 mg at week 2. CDAI: Crohn's disease activity index; PL: Placebo; pts: Points; ADA: Adalimumab; CHARM: Crohn's trial of the fully human antibody adalimumab for remission maintenance.

treated group did better than the placebo group. The ADA group had a higher rate of staying free of steroids for > 90 d and achieved clinical remission at week 26 (19% for 40 mg every other weeks *vs* 15% for 40 mg every week *vs* 3% for placebo, $P < 0.001$). The therapeutic gain of ADA for maintenance of remission ranged from only 25% to 39% (Table 15).

The proportion of ADA-treated patients who required dose escalation and the results of treatment were reported in two RCTs and one small before-after study^[51]. In secondary non-responders to ADA, 76% responded to dose escalation and 45% went into remission^[55,72,85].

There is no data available to assess the effectiveness of using IFX for secondary non-responders of ADA. In the CHARM study^[55], 46% of the persons randomized to receive ADA were secondary non-responders. Of those who received dose escalation of ADA, 76% had a no-point response rate and 45% went into clinical remission. In the Classic II study^[55] (following from the Classic I study), only 5% of patients who completed the 56 wk of treatment needed dose escalation.

Certolizumab pegol

In CD patients who responded to CER induction therapy (Precise 2), and then relapsed during continuous or interrupted maintenance therapy, recapture therapy with CER was provided. The response rates at week 4 were 63%-65%, and 55%-59% at 1 year (Precise 4)^[86]. Using Certolizumab pegol maintenance therapy for persons

Table 16 Therapeutic gain of certolizumab Induction of response and remission (%)

Week	Response		TG (CER-PL)
	CER	PL	
CRP < 10 mg/L			
6	37 ¹	26	11 ¹
26	22	12	10
Overall population			
6	35 ²	27	8 ¹
26	23 ²	16	7 ¹
Remission			
6	17	22	-
6 + 26	10	14	-
Maintenance with CER			
Week 26 clinical response	62 ¹	34	28 ¹
Overall	63 ¹	36	27 ¹
Group			

¹Significant difference; ²The secondary failure rates for CRP were 72% at 26 wk (approximately 10% per month). Precise I study (Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy I). PL: Placebo; CRP: C-reactive protein; CER: Certolizumab; TG: Therapeutic gain.

with CD, there was clinically meaningful improvement with the Inflammatory Bowel Disease Questionnaire score (60% *vs* 40%, $P < 0.001$), Short Form 36-Item Health Survey (SF-36) physical (51% *vs* 34%, $P < 0.001$) and mental component summary responses (44% *vs* 32%, $P = 0.016$), and the proportion of persons living a normal life (21.4% *vs* 12.4%, $P = 0.019$), (57% *vs* 35%, $P = 0.001$). The therapeutic gain of CER for maintenance of remission was at 28% at week 26 (Table 16), similar to the 24 wk and 30 wk result for IFX and ADA. The therapeutic gain of CER varied little between weeks 2 and 12, and with doses of CER 100 mg, 200 mg and 400 mg (Table 17).

In the Precise 2 trial, the 26 wk therapeutic gain in response rates of therapeutic gain with CER were lower in those who had first failed IFX, than in those starting CER and never previously having been on IFX (19% *vs* 29%)^[87]. This was also the case with IFX in the Precise 2 study: the response in the IFX-naive group was 69%, compared with 44% ($P < 0.001$) in the non-naive group. Thus, there may be benefit switching from IFX to ADA in the IFX-failure patient. In patients who were treated with IFX and experienced secondary failure, and then were treated with open-label CER, 62% enjoyed a response and 39% remission rate at week 6^[88]. When extended to 26 wk, the response and remission rates were 40% and 37%, respectively. CER also improved work productivity during the induction and maintenance components of the Precise study^[89].

Also from the Precise 2 study, 58 CD patients with draining fistulas (mostly perianal fistula) who responded initially to CER were continued on CER or placebo^[90]. At week 26, 36% on CER had fistula obscure compared with 17% receiving placebo (TG, 19%). Using the definition of ≥ 50% closure at two consecutive post-baseline visits ≥ 3 wk apart, there was only a trend for achieving this end point (54% *vs* 43%, $P = 0.069$).

Table 17 Therapeutic gain of varying doses of certolizumab

Week	Response			Therapeutic gain			
	PL	CER (mg)		CER (mg)			
		100	200	400	100	200	400
2	18	33	19	28	15	1	10
4	19	37 ¹	26	33	18 ¹	7	11
6	18	36 ¹	31	39 ¹	18 ¹	13	21 ¹
8	22	36	29	39 ¹	14	7	17 ¹
10	27	44	36	44 ¹	17	9	17 ¹
12	23	38	24	39 ¹	15	1	16 ¹

¹Significant difference. PL: Placebo; CER: Certolizumab.

Table 18 Meta-analysis of efficacy and safety of biological therapies (26 wk to 60 wk) vs placebo in preventing relapse of disease activity in quiescent luminal Crohn's disease

Treatment	Outcome (RR in preventing relapse)
IFX, ADA, CER	RR = 0.71 (95%CI: 0.65-0.76, I ² = 5%, P = 0.38); NNT = 4 (95%CI: 3-5)
IFX, CER	Superior to PL
ADA	No statistically significant difference between ADA vs PL in preventing relapse
NAT (only one trial)	RR = 0.71; 95%CI: 0.61-0.84
Adverse events	
Any event	RR = 0.93; 95%CI: 0.84-1.03
Infusion or injection site reactions	RR = 0.64; 95%CI: 0.06-6.66; (note that these reactions were actually fewer in those on anti-TNFα therapy, but the difference was not statistically significant)

PL: Placebo; CER: Certolizumab; IFX: Infliximab; ADA: Adalimumab; TNF: Tumor necrosis factor; RR: Risk ratio; CI: Confidence interval; NAT: Natalizumab.

The maintenance response rate was inversely related to the duration of the patient's history of CD: maintenance of response to CER was present in 90% of patients with a CD diagnosis less than one year, compared with 57% continued response in those with a CD diagnosis ≥ 5 years^[91]. Corresponding remission rates were 68% vs 44%. This suggests that there may be improved efficacy of TNFB maintenance therapy when initiated "early" as compared "late" in the history of the patient's disease^[92].

Meta-analysis

The results of the most recent vigorous meta-analysis of biological therapies in preventing relapse of disease activity in quiescent luminal CD is shown in Table 18. These authors suggest that the most marked effect of biological therapies was in preventing relapse of luminal CD once remission had been achieved, with a NNT of only 4. This benefit was observed for both IFX and certolizumab, but not for adalimumab^[61].

Secondary non-response

About a third of patients treated with anti-TNFα therapy, who meet the criteria for an initial clinical response, eventually lose response, with the magnitude depending

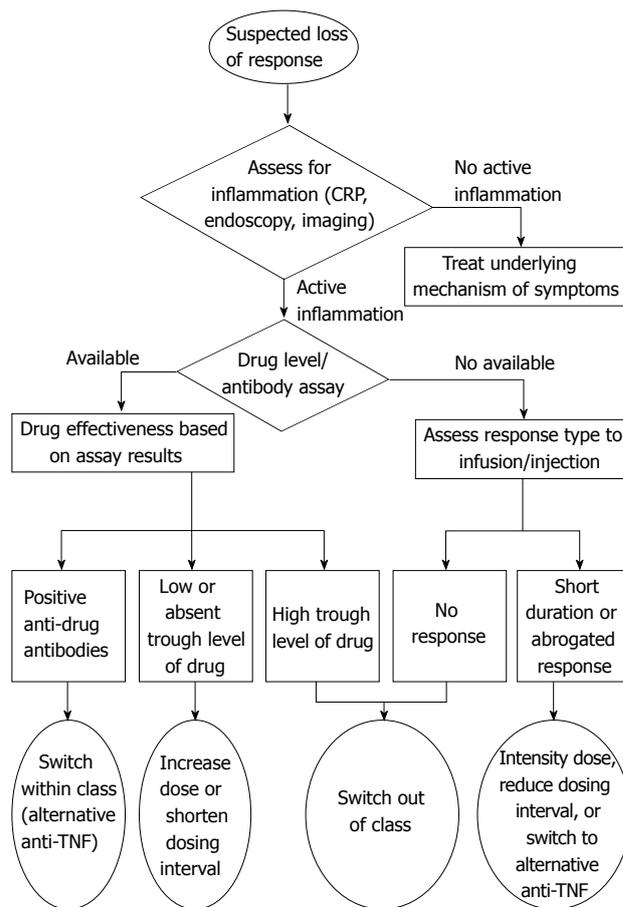


Figure 2 Suggested clinical approach to loss of response to anti-tumor necrosis factor-α therapy. CRP: C-reactive protein; TNF: Tumor necrosis factor.

on the duration of follow-up on maintenance therapy. Loss of response, also referred to as secondary non-response, is defined as recurrence of disease activity during maintenance therapy after achieving an appropriate induction response. In maintenance trials with IFX and ADA, significant percentages of patients required increased doses (IFX) and or decreased treatment intervals (adalimumab) in order to restore response after interval symptoms developed between dosing^[54,56,78,93]. Even after scheduled maintenance therapy and dose adjustments, substantial numbers of patients will still have a poor response^[44]. Of the initial responders, 65% need dose escalation, which appears to be successful in approximately 70%, and the probability for dose escalation throughout time is approximately 80% at 120 wk^[94].

From the Figure 1, it is apparent that approximately 10% (56%/5 years.) of patients treated with TNFB lose their response each year. If patients who are doing well on IFX + AZA, and the IFX is stopped, 39% relapse within one year^[95]. Persons who are likely to relapse when IFX is stopped are those with objective signs of continued inflammatory activity (↑CRP, Crohn's disease endoscopic index of severity ≥ 2) or low IFX trough level. Fortunately, almost all (> 95%) of those who recurred when IFX was stopped respond to IFX retreatment. Presumably a greater proportion relapse as this

interval is followed out beyond one year; it is unknown if those longer term relapsers will continue to have such a favorable response to retreatment with the originally successful TNFB.

How is this loss of response to TNFB managed? A useful suggested clinical approach to loss of response to TNFB therapy has been published (Figure 2). First determine if the patients symptoms might be due to something other than active CA. For example, exclude enteric infection (including *Clostridium difficile*) or small intestinal bacterial overgrowth, bile salt wastage, or adverse reaction to other drugs. What are the options if the CD is active^[96]? The initially chosen TNFB is increased in dose, decreased in dosing interval, or both! If there is no response, switch to another TNFB^[96].

Suggested clinical approach to loss of response to TNFB (Figure 2), to quote the approach suggested by Yanai *et al.*^[63]: (1) Confirm that intestinal inflammation is the cause of the “loss of response”; (2) Measure IFX levels at 4 wk after an infusion (therapeutic $\geq 12 \mu\text{g}/\text{mL}$); (3) Measure antibodies to IFX (ATI) measurements not available for ADA or CER. The Mayo Clinic group has demonstrated the utility of combining IFX levels and determination of ATI in the clinical management of patients who lose response to IFX^[97]; (4) “Patients who lose response to a first agent are more likely to lose response to a second and, similarly, those with toxicity to a first agent are more likely to develop toxicity from a second anti-TNF α agent. This diminishing outcome may, in part, be due to a class effect”; (5) “Patients who lose response to IFX associated with anti-IFX antibodies respond well to switching to adalimumab or certolizumab pegol”; (6) “In the majority of patients, response can be restored by dose and interval adjustments”^[44,94]; (7) “Switching between biologics is an important strategy for patients who lose response because of immunogenicity followed by rapid drug clearance or when a significant alternative pathogenic role is suspected. Switching can be within class or with an alternative class”; and (8) “Efficacy of successive agents is decreased compared with the primary agent”.

In this situation where there has developed secondary failure, 75% to 78% regain a durable response after dose intensification^[73,98,99]. It is recognized that over time after a surgical resection “cure”, most CD patients recur endoscopically, and fewer recur symptomatically. In the study by Regueiro *et al.*^[81], the endoscopic recurrence rate of 85% was reduced to 9% with continued IFX treatment.

TERTIARY FAILURES

If two TNFBs fail, there may be value in switching to a third TNFB^[100], with 6 wk response seen in 58%. This, however, needs to be supported by further data^[101]. In a European prospective cohort study of 67 adult CD patients who either lost response or developed intolerance to two TNFBs (usually IFX and ADA), treatment with

Table 19 Comparative efficacy of infliximab, adalimumab and certolizumab (%)

Induction	Response ¹	Remission ²		Therapeutic gain
		TNFBs	PL	
Accent I	58	39	21	18
CHARM	58	46	17	29
Precise 2	64	48	29	19

¹Weeks 2 to 6; ²Weeks 26 to 30. Remission is often defined by the Crohn's disease activity index, but may also be defined using the Inflammatory Bowel Disease Questionnaire. PL: Placebo; TNFBs: Tumor necrosis factor- α blockers; CHARM: Crohn's trial of the fully human antibody adalimumab for remission maintenance.

a third TNFB resulted in a 6-wk response and remission rate of 61% and 22%, respectively^[100]. “Concomitant therapy with corticosteroids or immunosuppressants order of anti-TNF administration, and prior history of response (i.e., primary non-response, secondary loss response or intolerance) to anti-TNFs did not affect patient's response to the third anti-TNF”.

The NNT for induction of remission was 9. In maintenance studies, when initial non-responders were excluded, NNT was 4 among responders, but NNT was 9 when including both responders and non-responders^[3]. Peyrin-Biroulet *et al.*^[3] performed a meta-analysis of 14 placebo-controlled trials enrolling 3995 CD patients, of TNFB efficacy and safety in CD. The TNFBs included IFX, ADA, CER, ETA. Quoting directly from their report, “In overall analysis, anti-TNF therapy was effective for induction of remission at week 4 (mean difference, 11%; 95%CI: 6%-16%, $P < 0.001$) and maintenance of remission at weeks 20-30 in patients who responded to induction therapy and in patients randomized before induction (mean difference, 23%; 95%CI: 18%-28% and mean difference, 8%; 95%CI: 3%-12%, respectively; $P < 0.001$, for all comparisons)”.

In adult CD patients who either lost response or became intolerant of two TNFBs given at optimal doses, when switched to a third TNFB, 22% achieved full remission and 51% continuing a clinical response to week 20^[100].

How long to use TNFB

How long to treat with TNFB? Five observational studies have shown the response to IFX or ADA ranges from 73% to 100% at year one, 65% to 90% at year two, 61% to 68% at year three, and 52% to 58% at year five^[102-105]. RCT data is not available yet for more than one year. Clear evidence based guidelines have not been developed as to when to stop TNF therapy, but reasonable empirical suggestions would be with loss of response or severe adverse effects to TNFB. Perhaps after one year TNFB treatment, when the patient is in clinical remission, there are no signs of active inflammation, and perhaps when mucosal healing is achieved, stopping TNFB therapy may be considered and discussed with the patient.

Comparative efficacy of IFX, ADA and CER

There are no head-to-head trials of one TNFB against another. There is heterogeneity in the CD patients recruited for the clinical studies, but interestingly the therapeutic gain for remission at weeks 26 to 30 were close to 18% to 23% (Table 19). It is unfortunate that these rates are so low.

Patient-reported outcome (PRO) instruments are used to provide information about health-related quality of life. The minimal clinically important difference (MCID) and minimal important difference (MID). PRO score changes have been determined from two TNFB clinical trials^[106]. The MCID is the smallest difference in a PRO score that is associated with a clinically relevant difference or change^[1,107]. The MID is the smallest difference in a PRO score that a patient can perceive as beneficial and would require a change in their treatment. The MCID and MID units are meaningful measures to assess alterations in PRO scores, rather than changes which albeit are statistically significant, are not necessarily useful in a practical sense.

When considering possible advantages of different TNFB, for example, ADA *vs* IFX, ADA has greater ease of administration (subcutaneous, self-administered *vs* infusion facility), no infusion reactions, higher remission rates among secondary non-responders to IFX^[72,108], possibly reduced need for dose escalation over time [fewer secondary failures^[109]], higher later rates of response and remission (maintenance), lower cost [\$ incremental cost-utility ratios (ICUR) per quality-adjusted life-year (QALY)]^[51], and lower risk of developing neutralizing antibodies. Again it must be stressed that there is no head-to-head direct data to allow for a definitive statement to be made about any comparison, including cost and patient preference. These conclusions are based on observations.

In contrast, the possible advantages of IFX *vs* ADA include no injection site reactions or infections, fewer numbers of individual adverse effects, higher early rates (induction) of response and remission, and high rate of fistula improvement or remission with both short- and long-term therapy. IFX also gave higher initial response and remission rates as compared to ADA. Comparatively, the use of ADA led to lower relapse rates, indicating that patients retained longer benefit from ADA *vs* IFX^[51].

Continuation of immunosuppression with TNFB therapy

Most guidelines suggest that TNFB therapy be started when immunosuppression alone has failed. The use of TNFB plus immunosuppression is known as concomitant immunosuppression (CI). To understand the subtle aspects of the question about CI use with TNFBs in CD, we need to reflect upon several important studies.

Scheduled maintenance IFX treatment is more effective than episodic treatment (Accent I)^[74]; Scheduled maintenance therapy is superior to episodic treatment in terms of the use of steroids or the use of hospitalization and

Table 20 Concurrent immunosuppression with azathioprine plus infliximab *vs* azathioprine alone in Crohn's disease^[53] (%)

	Week		
	12	24	52
AZA	38	29	22
AZA + IFX x3	75 ¹	57 ¹	40
Therapeutic gain	37 ¹	28 ¹	18

¹Significant difference. AZA: Azathioprine; IFX: Infliximab.

surgery^[44]. IFX induction plus azathioprine/6-mercaptopurine (6-MP) is more effective than azathioprine/6-MP alone in AZA-naive patients who are steroid-dependent (GETAID)^[53]. Early treatment with IFX in combination with an antimetabolite is more effective than conventional therapy (step-up top-down)^[110]. IFX plus azathioprine is significantly better for inducing steroid-free remission and mucosal healing than azathioprine alone in azathioprine-naive patients [study of biologic and immunomodulator naive patients in Crohn's disease (SONIC)]^[102]. In initial IFX responders, the maintenance of response falls from 83% at 30 wk, to 64% at 54 wk, and to 45% at 108 wk^[111].

Scheduled maintenance IFX is more effective than episodic treatment^[74]. The standard of care is to use TNFB on a regular and scheduled basis. The benefit of scheduled *vs* episodic use of IFX is related to there being lower levels of antibodies to IFX (ATI), fewer infusion reactions, and fewer hospitalizations and major surgery^[54,112,113]. IFX induction plus AZA/6-MP is more effective than AZA/6-MP alone in AZA-naive patients who are steroid-dependent^[53]. Early treatment with IFX in combination with an immunosuppressant is more effective than conventional therapy^[110]. IFX plus AZA is significantly better for inducing steroid-free remission and mucosal healing, than is AZA alone in AZA-naive patients^[114].

There is no additional benefit of adding MTX in the steroid-treated CD patient who is also on IFX^[115]. It remains unknown if the continuation of MTX might be useful if the person were just on MTX + TNFB, rather than just being on GCS.

Most current guidelines recommend that AZA/MTX must have been used and be considered to have failed before TNFBs are introduced what should be. The duration of previous use of this immunosuppression and should AZA be continued TNFB once has been started is not known. Some data suggested that continuation of AZA after the introduction of IFX offers no additional benefit beyond 6 mo of combined therapy, as long as the TNFB is used on the basis of a regular schedule, rather than being given episodically. The authors of one trial suggested that "continuation of immunosuppression for more than 6 mo offers no clear benefit over scheduled IFX monotherapy"^[116]. IFX monotherapy is superior to IFX plus immunosuppressive therapy after CD induction with IFX. In one study, four times more relapses occur with AZA maintenance after IFX induc-

tion, as compared with IFX induction and placebo maintenance^[53]. In a second study, maintenance of remission of CD was no different when AZA plus IFX were given for maintenance, *vs* IFX alone^[117].

In the study by Van Assche *et al*^[116], at 6 mo in person on IFX in whom AZA had been withdrawn (IFX plus AZA D/C *vs* IFX + AZA), the CRP levels were higher, and IFX levels were significantly lower. Perhaps if the patients had been followed for longer than 6 mo, the AZA discontinuation group might have begun to experience more recurrences. The RAND appropriateness methodology, through a modified Delphi panel approach based on expert interpretation of the available literature, has been used with a “globally diverse panel of 13 gastroenterologists clinically experienced in inflammatory bowel disease”^[118]. Using a total of 134 clinical scenarios, concomitant use of immunomodulatory was generally rated inappropriate for young males, and in some scenarios involving uncomplicated disease. However, CI were appropriate for those with extensive disease, shorter duration of disease, perianal involvement, prior surgery, females, and older patients (> 26 years)”. In the GETAID study, the IFX + AZA (CI) gave a significant therapeutic gain of clinical remission off steroids, as compared with AZA alone, of 37% and 28% at weeks 12 and 24 respectively. But the benefit was lost at week 18 (Table 20).

Several important aspects to consider when attempting to answer the question of the benefit of using CI with IFX are the duration of follow up, whether the patient is naive to the immunosuppressants or the TNFB, whether the activity of the disease is high as suggested by an elevated surrogate marker such as CRP or mucosal lesions, what is using an endpoint of immunogenicity (such as antibody to TNFB or a disease activity index or QoL score), and whether the question is focused on the CD patient in whom you are trying to achieve induction or maintenance of remission. CI is clearly beneficial when added to IFX regimens which are episodic^[112,119], but the controversy about CI comes from studies using regularly scheduled TNFB, the method which is new to the standard of care.

In the SONIC study, CD patients who were naive to both immunosuppression and to TNFB, the rate of clinical remission at week 26 was higher in those given IFX + AZA as compared with IFX alone or AZA alone (57%, 44%, and 31%, respectively)^[120]. In a subgroup of patients who initially had both an elevated CRP and mucosal lesions at baseline, the IFX plus AZA + IFX alone values were even higher (69% and 57%, respectively). Since the difference between IFX + AZA was statistically greater than IFX alone, the data may be interpreted to indicate that CI is advisable, at least in the relatively short period of 26 wk, for steroid-free remission. However, the benefit of CI appears to fade after 6 mo to 12 mo^[116,121].

In the infliximab maintenance immunosuppression discontinuation study (Van Assche), in CD patients who had been on AZA/MTX before starting IFX, stopping

the immunosuppression at 6 mo did not have an adverse effect at 2 years to shorten the interval between IFX infusions, or the time to stopping IFX dosing. The prevalence of antibodies to IFX were similarly low in each group, and CI with IFX + AZA had no different effect in terms of mucosal healing.

The same message comes from the 2-year long COMMIT trial of steroid-requiring CD patients on IFX or IFX + MTX (Feagan 2010): CI does not provide a medium term (2-year) advantage. On the other hand, CI may increase the risk of adverse effects such as non-Hodgkin's lymphoma in adults^[122], hepatosplenic lymphomas in children^[123], as well as other concerns in children^[124]. As well, CI did not benefit the medium term risk of surgery^[125]. These individual studies suggest that in many CD patients, CI is “bridge” therapy for 6 mo while the full effect of TNFB is being achieved.

In an observational serial observation of 88 CD patients in remission and on IFX, half had their CI with AZA stopped. The IFX failure free status was 85% at 12 mo, and 41% at 24 mo and 32 mo^[126]. This failure rate of IFX maintenance may have been due to the withdrawal of CI with AZA. Failure of CI on AZA-withdrawal was more likely to occur if the initial duration of IFX-AZA therapy was less than 27 mo, if the CRP was greater than 5 mg/L or the platelet count higher than 298 109/L. Until further data becomes available, we can be encouraged by “expert opinion” from the BRIDGE group analysis^[118], suggesting that bridging CI may not be necessary such as in young males especially with limited disease, or some case scenarios including uncomplicated CD.

CI^[127] treatment also reduces antibody to IFX (ATI) formation [24% *vs* 63%, on CI *vs* not on CI, $P = 0.007$; 43% *vs* 75%, $P < 0.01$]. Former researchers have proposed a time-structural treatment algorithm for moderate CD. This may of course need to be altered in future if “top down” (IFX→AZA→GCS) approaches to CD are shown to be beneficial.

The major role of CI may be in the patient who is on episodic IFX: in these persons, the incidence of ATI was 0% on CI *vs* 60%, not on CI, $P = 0.018$ ^[128]. Comparatively, CI had no relationship on ATIs with scheduled IFX infusions. Combined immunomodulator with TNFB provides small therapeutic gain for 24 wk. Then, it is likely that CI can be abandoned without any detrimental effect of clinical response, and possibly a lower risk of adverse events. In fair balance for the issue of AZA discontinuation in the TNFB-treated patient, the “jury is still out”, or as the Scots would say, the case is “not prove”. Clearly, more data is needed.

In summary of Combination therapy: (1) In AZA and TNFB naive persons, with ↑ CRP or mucosal lesions on colonoscopy, remission and one year mucosal healing response to combination therapy (SONIC) A AZA = TNFB; (2) Unknown what to do after one year: for IFX alone after successful induction, maintenance for 54 wk gave a therapeutic gain of (28%-14%) 14% and 24% (38%-14%) for 5 mg/kg and 10 mg/kg IFX (Ac-

Table 21 Infliximab for fistulizing Crohn's disease: Induction and maintenance (%)

Study	Week of assessment	Outcome	IFX (mg/kg)		PL	TG
			5	10		
Present <i>et al</i> ^[75] (ACCENT II)	18	Response	68 ¹	56 ¹	26	42-30
		Closure	55 ¹	38 ¹	13	42-25
	54	Response	46 ¹		23	23
		Closure	36 ¹		19	17

¹Complete closure of draining fistulas; *P* value for each IFX group *vs* placebo group. For IFX 5 mg/kg, the TG for fistula closure ranged from 42% at 18 wk to 23% to 54 wk. Adapted from CADTH ('09). These differences are statistically significant. See Tables 3 and 4 of the CADTH report for *P*-values, number of participants and events. IFX: Infliximab; PL: Placebo; TG: Therapeutic gain.

Table 22 Adalimumab for fistulizing Crohn's disease induction, response and closure (%)

Study	Assessment week	ADA ¹	ADA ²	ADA ³	PL	TG
GAIN	Response					
	4	-	-	15	20	(-5)
	Closure					
	4	-	-	5	8	(-3)
Classic I	Response					
	4	75	20	8	33	(42, -13, -25)
	Closure					
	4	75	0	0	17	(58, -17, -17)

¹40 mg at week 0, 20 mg at week 2; ²80 mg at week 0, 40 mg at week 2; ³160 mg at week 0, 80 mg at week 2. ADA: Adalimumab; PL: Placebo; TG: Therapeutic gain.

cent I). It is unknown what is best to do after one year treatment with IFX; (3) In post hoc analysis of combination therapy of immunomodulators plus IFX/ADA/certolizumab pegol (CZP) *vs* monotherapy with TNFB, there is no benefit in terms of induction synergy; (4) Because of study design, it is not possible to comment whether MTX plus TNFB is superior to TNFB alone; and (5) Not possible yet to predict which patient can be induced with TNFB and maintained on AZA (TNFB as a "bridge").

FISTULIZING DISEASE

Because between 20% to 40% of CD patients will develop fistulas^[75,129], and because of the seriousness of perianal fistulas^[78,129,130], the improved healing of fistulizing CD with TNFB would be anticipated to reduce the patient's lifetime need for major surgery. The presence of fistulas increases the risk of the need for colectomy^[69,82]. Anti-TNF therapy is indicated for use in fistulizing CD. What is the evidence for IFX or ADA in this clinical setting? In the IFX infusion study by Present *et al*^[75], IFX was given at 0 wk, 2 wk and 6 wk, and fistula response and complete closure of draining fistulas were assessed at 18 wk. As compared with placebo, IFX 5 mg/kg and 10 mg/kg gave 18-wk fistula response rates of 68% (*P* = 0.002) and 56% (*P* = 0.02) *vs* 26%, respectively. The corresponding closure rates were 55% (*P* = 0.001), 38%

Table 23 Adalimumab for fistulizing Crohn's disease maintenance (%)

Study	Assessment week	Combined ADA group ¹	PL	TG
CHARM	Closure			
	26	30	13	17
	56	33	13	20

¹Statistically significant. Note that the two higher dose regimes of ADA do poorly for induction of fistulizing CD. The TG for IFX and ADA for fistula closure at 54-56 wk is a similar low value of 17%. PL: Placebo; TG: Therapeutic gain; ADA: Adalimumab; CHARM: Crohn's trial of the fully human antibody adalimumab for remission maintenance; IFX: Infliximab; CD: Crohn's disease. 140 mg q0w and 40 mg qw.

Table 24 Meta-analysis of efficacy and safety of biological therapies *vs* placebo (4 wk to 26 wk) in healing of fistulizing Crohn's disease

Treatment	Outcome (RR of fistulas remaining unhealed)
IFX, ADA, CER <i>vs</i> PL (4 wk to 26 wk)	RR = 0.88; 95%CI: 0.73-1.05; <i>I</i> ² = 67%, <i>P</i> = 0.01 (considerable heterogeneity between studies, with no statistically significant difference in fistula healing at 4 wk to 26 wk, compared to placebo, when considering the 3 TNFB)
IFX <i>vs</i> PL (one trial)	RR = 0.62; 95%CI: 0.48-0.81
IFX, ADA, CER <i>vs</i> PL (excluding 2 trials reporting fistula healing up to only 4 wk)	RR = 0.80; 95%CI: 0.65-0.98; <i>I</i> ² = 56%, <i>P</i> = 0.08 (heterogeneity between studies remained)
IFX (only 1 trial) <i>vs</i> > PL (followed until 54 wk)	RR = 0.81; 95%CI: 0.68-0.96

Adverse events could not be determined from data. CER: Certolizumab; IFX: Infliximab; ADA: Adalimumab; PL: Placebo; RR: Risk ratio; TNFB: TNF- α blockers; CI: Confidence interval.

(*P* = 0.040), and 13% at 18 wk. For the 5 mg/kg dose of IFX for fistulizing CD, this gave a therapeutic gain of 42% for both fistula response and closure.

In the IFX maintenance study by Sands *et al*^[130] (Accent II), IFX was infused every 8 wk until week 54. As compared with placebo, IFX 5 mg/kg gave 54 wk response rates of 46% *vs* 23% (*P* = 0.001); and the complete closure rates were 36% *vs* 19% (*P* = 0.009). This gave a 54 wk therapeutic gain of 23% and 17% for response and closure, respectively. Note the need to caution your CD patient with fistulizing CD: while early TG for response and closure was an encouraging 42%, at one year half this benefit was lost (falling to 23% and 17% at 54 wk)^[75,78,129].

The TG in fistula response and closure for IFX (5 mg/kg) at 19 wk was 42% and 42%, respectively, with curiously lower rates of response for the 10 mg/kg IFX dose. At 54 wk, the TG for fistula response and closure was 23% and 17%, respectively. These are low values, but clearly IFX is of considerable benefit to individual patients who may have failed conventional therapy.

The 4-wk fistula response and closure rates for ADA (160 mg at week 0 and 80 mg at week 2) was not statistically different from placebo, but at weeks 26 and 56, the TGs were 17% and 20%, respectively. In the CHARM study, complete healing of fistulas was achieved in 30%

of those receiving ADA either weekly or every other week by week 26. This compared to 13% in the placebo group ($P = 0.043$). Recall that with fistulizing CD, the early response and closure with IFX was statistically significant, but was not so with ADA. At one year, the fistula response and closure rates were numerically similar for IFX and ADA, but the TGs were small for both TNFBs (Tables 21-23). Therefore, at this time, it is best to use IFX as 1st line to treat fistulising disease. There is insufficient data to recommend the same for CER. Meta-analyses have been performed for biological therapies in healing fistulising CD (Table 24). These authors suggested that "In preventing recrudescence of fistula, there was only one RCT reporting on this end point, which demonstrated that IFX was superior to placebo (Table 24). Although concerns about adverse events arising from the long-term use of these drugs are understandable, the data from the RCTs included in this meta-analysis did not demonstrate any increase in overall adverse events, or serious adverse events, with use for up to 1 year^[61]."

In summary of the use of TNFB in fistulising CD "... there is less evidence for the use of biological therapies, though there was a clear beneficial effect when only IFX was studied, although in one trial, and when only RCTs with follow-up in excess of 4 wk were considered in the analysis. There was also a benefit in favour of biological therapies over placebo when only studies that reported fistula healing in the longer term were included in the analysis."

THERAPEUTIC GAINS

Induction and maintenance, response and remission

At 2 wk and 4 wk after a single dose of IFX (5 mg/kg), the therapeutic gain (TG; IFX response minus the PL response) for clinical response was 56% and 64%, respectively (Table 7), and then fell to 36% at 12 wk^[52]. The TG for remission was 36% and 46%, respectively, for weeks 2 and 4. When IFX (5 mg/kg) is given 2, 6 and every 8 wk until week 48^[54] or 54^[69,82], the week 54 TG for response ranged from 22%^[54] to 30%^[69,82], and for remission, the TG was 14% for IFX 5 mg/kg and 24% for 10 mg/kg. IFX doses of 10 mg/kg or 20 mg/kg did not give higher therapeutic gains in terms of response.

Thus, after excluding the approximately 30% initial IFX primary non-responders, about the two-thirds will respond and about one-third will go into remission at 4 wk (therapeutic gain). With continued 8-weekly IFX infusion for approximately one year, the TG for response is about one in four, and for remission one in eight. These represent relatively small gains which are not necessarily higher than reported historical figures for conventional therapy induction or maintenance therapy in CD. In children with CD, Kaplan-Meier analysis has shown that the cumulative probability of losing response to IFX after 1 year, 3 years and 5 years is 13%, 40% and 50%^[131]. In adults with CD who chose to stop their IFX

after achieving remission, 50% relapsed within 477 d after IFX discontinuation^[132].

For the currently recommended dose of ADA of 160 mg at weeks 0 and 80 mg at week 2, TGs for response range from 15% to 19% at week 2, and 13% to 25% at week 4 (Sandborn *et al.*^[93]). The corresponding TGs for remission at 2 wk and 4 wk range from 10% and 14%-24%. The TGs for response at 56 wk range from 7%-25% when ADA is given as 40 mg q every other week, to 15%-33% when ADA is given as 40 mg q weekly^[55,56,85,127,133]. The corresponding values for TG for remission at 56 wk range from a low of 4% to a high of 39%^[55,56,85,127,133]. The values for the initial TGs in response and remission for induction therapy are numerically slightly lower for ADA; it is slightly higher for ADA for maintenance of response and remission. After two years of maintenance therapy with ADA every other week, 42% were in remission compared to 38% on placebo^[134], and 50% with weekly ADA. This study also showed an improvement in IBD QoL questionnaires, suggesting clinical response. There is insufficient evidence at this time to recommend one type of ADA therapy over another.

In addition to therapeutic gains in terms of response and remission rates, other important clinical outcomes include improvements in quality of life, hospitalization and surgery. In patients with RA, combinations of TNFB with low-dose MTX are generally more efficacious than either drug used alone^[135], the mechanism of anti-inflammatory properties of this combination is not totally clarified and it is not known if TNFB plus MTX have a synergistic mechanism^[136], especially in CD.

Health utilization

Hospitalization: In Canada, about 20% of persons with CD have IBD-associated hospitalizations per year^[2]. The proportion of patients who needed hospitalization for IBD were reported in three IFX trials and one ADA trial. Two IFX trials and one ADA trial reported the patients who needed surgery^[51]. Overall, CD patients who received IFX maintenance therapy had an approximately 50% reduction in the rate and duration of hospitalization^[74,129]. Lower hospitalization rates were also seen with ADA^[93]. Infusing IFX on a scheduled *vs* an episodic basis reduces the rate of all-cause hospitalization, as well as IBD-related hospitalization. For example, in Accent I^[74,137], the rate of IBD-related hospitalization was 28% in the episodic treatment group *vs* 23% in the IFX 5 mg/kg group ($P = 0.047$) and 24% in the 10 mg/kg group ($P = 0.023$). Furthermore, the number and duration of hospitalizations were lower in the scheduled *vs* episodic group ($P = 0.018$). In Accent II^[129], the hospitalization rates were lower with IFX than placebo (14% *vs* 31%, $P < 0.01$), and 11% *vs* 33% in the initial IFX responders *vs* placebo ($P < 0.05$). Also, the mean duration of days in hospital was less with IFX *vs* placebo (0.5 d *vs* 2.5 d, $P < 0.05$).

In a population based study from the University of Manitoba of health care resource use among IFX us-

Table 25 Reduction (%) of health service utilization in Crohn's disease patients treated with Infliximab

	All CD patients ^[180]	CD fistula patients	
		(Rubenstein <i>et al.</i> ^[180])	(Harrison <i>et al.</i> ^[181])
ER visits	66	64	372
All surgery	38	66	
GI surgery	18	59	
Hospitalizations		59	37
Endoscopies	43		52
Radiographs	12	40	58-147
Outpatient visits	16	27	22-33

CD: Crohn's disease; ER: Emergency Room; GI: Gastrointestinal.

Table 26 Natural history of Crohn's disease and ulcerative colitis %

Natural history			
UC		CD ¹	
Remission at any point in time	50	Relapse	10-30
Overall intermittent course	90	Low activity	15-20
Remission: 3-7 yr after diagnosis	25	Remission	55-65
Yearly relapse	18	Chronic active	13-20
Intermittent relapse	51	Chronic intermittent	67-73
		Remission for 10 yr	13
10 yr colectomy rate	10	Surgery by 20 yr	> 75
Change in site of UC over 25 yr		Change in behavior	
LC → C	50	NSNF → S	27
C → LC	75	NSNF → F	29

¹Course 1 year after diagnosis. C: Entire colon; LC: Left colon; S: Structuring; F: Fistulising; NSNF: Non-structuring, non-fistulizing; UC: Ulcerative colitis; CD: Crohn's disease.

ers, hospitalizations were higher in the IFX cohort until 18-24 mo after the first IFX prescription, at which point the rate of hospitalization in the IFX group fell to the level of the CD patients treated with AZA or GCS^[138]. The likelihood of surgery was similar in IFX and GCS, which was higher than in AZA; even at 3 years post-closing. Overall physician visits were similar between IFX, GCS and AZA. Interestingly, ADA reduced hospitalization rates at 12 mo from 14% with placebo *vs* 10% and 3% with maintenance ADA given every other week and every week ($P = 0.12$ and $P < 0.01$, respectively)^[115]. Hospitalizations account for more than 50% of the direct costs of CD^[115]. Thus, in responders, TNFB reduced the rate of hospitalization, and this reduction in hospital days carries a major economic impact, which has to be countered against the high cost of maintenance TNFB requiring long-term use of drug, and the cost of management of adverse effects.

Surgery

CD-related surgery was more likely in the episodic *vs* the scheduled treatment groups (9% *vs* 3%, $P = 0.01$)^[74], and the mean number of surgeries was higher (118 *vs* 60, $P < 0.01$). As compared with the placebo group, the mean number of surgeries in the IFX group was 13 *vs* 2 per

Table 27 Meta-analysis of efficacy and safety of biological therapies *vs* placebo in inducing remission in moderately to severely active ulcerative colitis^[61]

Treatment	Outcome (RR of remission not being achieved)
IFX <i>vs</i> PL	RR = 0.72; 95%CI: 0.57-0.91 NNT = 4 (95%CI: 3-8)
Adverse event	
Any adverse event was no higher in IFX <i>vs</i> PL, and risk of serious adverse events was lower	RR of serious adverse event = 0.64; 95%CI: 0.41-1.00, $P = 0.05$ NNH = 13 (95%CI: 8-50)

IFX: Infliximab; PL: Placebo; RR: Risk ratio; CI: Confidence interval; UC: Ulcerative colitis; NNT: Needed to treat.

100 in all patients, and from 11 to 11 per 100 in the IFX initial responders^[78]. With ADA maintenance, the 12-mo risk of major surgeries was 0.6% *vs* 3.8% in the placebo group ($P = 0.0005$)^[115]. Data to date shows that TNFB reduce serious health utilization in persons with IBD.

TNFBs AND THE NATURAL HISTORY OF CD

It is not yet certain whether TNFB will achieve disease modification, or sustained mucosal healing^[139]. CD is very heterogenic, and we need much more data on the possibility of patient risk-stratification based on environmental factors, disease phenotype, genotype and disease-initiating and-perpetuating factors (Table 25)^[140].

A brief consideration of the use of TNFB in ulcerative colitis

There are many differences between CD and UC (Table 26). Only for purposes of comparison, a very brief overview is provided on IFX use in persons with UC, bearing in mind that these are separate and distinct conditions. About 20% of UC patients on 5-ASA maintenance therapy will have an acute attack each year, and about 10% of those with more severe symptoms will require hospitalization, usually for intravenous (IV) steroid therapy, cyclosporine or TNFB therapy; or surgery. About a third of these will not respond to IV steroids, and may be candidates for colectomy, cyclosporine or IFX.

In the Accent I and 2 studies, approximately half as many of those in the combined IFX group than placebo-treated UC patients required surgery (74% *vs* 8%), and the number of hospitalizations were also lower (18/102 patients *vs* 9/102 patients, $P < 0.01$)^[74,115,129]. The colectomy rate in the placebo group is also approximately twice as high as in the IFX group: at 90 d, 67% *vs* 29% ($P = 0.017$)^[141], and at 2 years, 76% *vs* 46% ($P < 0.05$)^[142]. When IV GCS fail in patients with severe UC admitted to hospital for IFX^[143], colectomy rates were as follows: in hospital colectomy, 24%; later colectomy, 14%; no colectomy, 62%. It is not clear how many will eventually require colectomy, whether they will need to

Table 28 Associations of mucosal healing in Crohn's disease

Fewer symptoms	
No previous surgery	
Previous surgery	
Less inflammation at 5 yr requiring steroid use	
Less use of steroids	
Steroid-free remission and no flare at years 3 and 4	Yes (TG, 44%)
Steroid-free remission, no flare and no TNFB at years 3 and 4	Yes (TG, 44%)
No new or persistently active fistulas	No

How do these associations with mucosal healing (MH) in CD compare with UC? About 90% of patients remain asymptomatic after achieving MH on once-a-day 5-aminosalicylic acid (Mezavant[®]), and after MH, 40% of UC patients remain asymptomatic (TG, 22%). TG: Therapeutic gain; CD: Crohn's disease; UC: Ulcerative colitis; TNFB: Tumor necrosis factor- α blockers (response in active treatment group minus response in placebo group; differences statistically significant).

Table 29 Rates of therapy-associated mucosal healing

Drug	CD		UC	
	Week ¹	MH, %	Week ¹	MH, %
5-ASA			4-8	25-71
Prednisone	4-9	0-27		
AZA	16-96	40-73	26	53-69
MTX	12-60	36-38		
IFX	4-104	29-100	8-52	62-71
ADA	12	27	8	30
CER	10	5-55		

¹Time for endoscopic assessment of mucosal healing. CD: Crohn's disease; UC: Ulcerative colitis; MH: Mucosal healing; 5-ASA: 5-Aminosalicylic acid; AZA: Azathioprine; MTX: Methotrexate; IFX: Infliximab; ADA: Adalimumab; CER: Certolizumab.

be maintained long-term on IFX, or if they should simply be maintained on AZA or 5-ASA.

Primary non-response has been noted in 22% of UC patients treated with IFX^[126]. IFX dose optimization was required in 45%, and colectomy was required in 19%. In a single-centre, prospective out-patient cohort of UC patients, response to induction therapy with IFX was 96% and 80% for ADA^[144]. For maintenance therapy response to IFX and ADA, the rates were 78% and 70%. None of these differences was statistically significant.

Recent meta-analysis has considered the efficacy and safety of biological therapies in inducing remission in moderately to severely active UC (Table 27)^[61].

The summary points are as follows: (1) No data on the efficacy and safety of biological therapies *vs* placebo in preventing relapse of disease activity in quiescent UC; (2) "IFX was highly effective in inducing remission in patients with moderate to severely active UC who had failed therapy with first and second-line agents, and who had also failed to respond to a course of high-dose corticosteroids, with a NNT of only 4^[61]"; (3) IFX for rescue therapy in severe UC, with a therapeutic gain of (71%-33%) 38% (NNT, 3); (4) IFX will induce and maintain clinical remission and mucosal healing in treatment-refractory, moderate/severe UC; (5) Unknown if

Table 30 Complete mucosal healing¹

	ADA	PL [ADA induction only (3 doses)]	TG (%)
ITT		PL	
week 12	27%	13% ($P = 0.056$)	14
week 52	24%	0% ($P < 0.001$)	24
PP			
week 12	28%	13% ($P = 0.046$)	15

¹Extend: Open-label adalimumab^[182]. Of patients with CMH at week 12, 46% of ADA every other weeks had CMH at week 52 *vs* 0% CMH in those receiving only ADA induction. ITT: Intention-to-treat; PP: Per protocol; TG: Therapeutic gain; PL: Placebo; ADA: Adalimumab.

IFX plus AZA is superior to monotherapy with AZA or IFX; (6) Before starting IFX in UC, discuss options of AZA, cyclosporine A (Cy A), and pan proctocolectomy with ileoanal pouch procedure; (7) Unknown comparison of Cy A *vs* TNFB for rescue therapy; (8) Short term: young age, absent pANCA (in CD, presence of pANCA, ASCA, or pANCA + ASCA had no predictive value); and (9) Long-term (predictors for no colectomy): short term clinical response to CRP < 5 mg/L, no previous treatment with IV steroids or Cy A.

Importance of mucosal healing

There are a number of potential advantages in achieving mucosal healing in CD (Table 28). In both CD and UC, the rates of mucosal healing range widely depending upon the therapeutic agent and the duration of treatment (Table 29).

In clinical trials, there has been no uniform standard for defining mucosal healing (MH), no agreed-upon optimal time for assessing MH. It is not surprising then that the ranges of MH are very wide.

The clinical trials of agents used to treat IBD have used a variety of clinical scores heavily based on symptoms (CDAI), measures of QoL, appearance of the mucosa on diagnostic imaging, endoscopic appearance, or histopathology. Some patients with CD treated with TNFB achieved MH and the question was raised whether MH by itself, independent of patient's symptoms or QoL, was an important outcome variable. MH would be an important outcome if it were to be shown that it was associated with reduced risk of recurrence (i.e., greater likelihood of maintenance of remission), reduced risk of extraintestinal complications, reduced risk of medical treatment-associated complications, long-term risk of hospitalization, surgery or development of colorectal cancer. The risk of development of stricture or fistula in CD increases over time^[46,145], so maintaining mucosal healing may decrease these problems. However, there is no evidence to answer the above asked questions.

It seems self-evident that MH should become an outcome objective of therapy in IBD. However, this needs to be proven. Because the prevalence of MH may decline over time, and the number of the week of study repeating MH varied widely, it is not possible to assert which class of drug has the highest rate of MH (Table 29), nor is it plau-

Table 31 Meta-analysis efficacy of 5-aminosalicylic acid/sulfasalazine to induce remission or to prevent relapse in Crohn's disease

	Induce remission (RR of not being in remission) on active therapy	Prevent relapse (RR of relapse) (RR of relapse)
CD	SASP (only 2 RCTs) 0.83 (95%CI: 0.69-1.00; trend)	SASP/5-ASA, ITT analysis, no benefit
	5-ASA 0.91 (95%CI: 0.77-1.06; not significant)	5-ASA, PP analysis: RR = 0.79 (95%CI: 0.66-0.95; NNT = 13 to prevent relapse)
UC	0.79 (95%CI: 0.73-0.85; NNT = 6)	0.65 (95%CI: 0.55-0.76; NNT = 4 to prevent relapse)

CD: Crohn's disease; ITT: Intention-to-treat; PP: Per protocol; SASP: Sulfasalazine; 5-ASA: 5-Aminosalicylic acid; CI: Confidence interval; UC: Ulcerative colitis; NNT: Needed to treat; RR: Relative risk; RCT: Randomized controlled trial.

sible to compare IFX with ADA or CER. In an open-label study of ADA in which there was a “placebo” (3 doses of ADA for induction), the therapeutic gain in the 12 wk complete mucosal healing (CMH) was 14% in the intention-to-treat analysis (ITT) and 15% in the per-protocol analysis, with 52 wk ITT CMH of 24% (Table 30).

When and how to start TNFB therapy: Start early, vs follow the current guidelines

This question may also be considered as “step-up” *vs* “start high”. When considering a comparison in outcomes from a management approach starting early with biological therapy in the patients’ lifelong CD course, *vs* the standard of care of step-up therapy, we must reflect the strength of the evidence supporting each of the components of the traditional approach in CD of using 5-ASA products, antibodies, GCS, and the immune suppressants AZA and MTX. The excellent systematic reviews and meta-analyses in the “Red Journal”^[61] are very helpful in this regard, and will be reviewed briefly here to demonstrate the potential limitations of the currently accepted standard of care.

5-aminosalicylates therapy: In contrast to the supportive data in UC for the use of 5-ASA to induce remission and to prevent relapse, the data for CD is poor (Table 31)^[61]. Thus, for the usually accepted ITT analyses, neither SASP nor 5-ASA can any longer be recommended in persons with CD to induce or maintain remission.

Antibiotic therapy: There is diversity in the design of antibiotic studies in IBD, including which antibiotic, as well as dose and duration of therapy. The antibiotics often used in clinical practice for this indication were metronidazole, cipro[®], and rifaximin (not yet available in Canada). While taking into account these events, it may surprise some readers that antibiotics are superior to placebo for the induction and maintenance of remission in CD, as well as induction of remission UC (Table 32)^[146].

Glucocorticosteroid therapy: Standard GCS remains

Table 32 Efficacy of various antibiotics to induce remission or to prevent relapse in Crohn's disease

	Induce remission (RR of not remission) on active therapy	Prevent relapse (RR of relapse)
CD	Inflammatory disease 0.85 (95%CI: 0.73-0.99, P = 0.03)	0.62 (95%CI: 0.46-0.84)
	Perianal fistula 0.80 (95%CI: 0.66-0.98)	
UC	0.64 (95%CI: 0.43-0.96)	

UC: Ulcerative colitis; CD: Crohn's disease; CI: Confidence interval; RR: Risk ratio.

the standard for inducing remission in moderate-to-severe UC, but must never be used for maintenance of disease because of its lack of efficacy and its high adverse effects risk profile. While the trials of GCS in active CD individually showed efficacy because of heterogeneity between studies ($I^2 = 88\%$, $P = 0.004$) and the small size of the studies. When the risk difference was used as the summary statistic, the treatment effect became significant, with NNT = 3 (95%CI: 2-11)^[61]. Furthermore, systematic review and meta-analysis showed that standard GCS were superior to the locally acting budesonide in achieving remission in active CD (RR = 0.82; 95%CI: 0.68-0.98); oral budesonide itself was superior to placebo for CD remission (RR = 0.73; 95%CI: 0.63-0.84). Oral budesonide used for up to one year delays the time to recurrence of active CD.

Adverse effects of GCS therapy in the setting of treating active CD could not be determined in the studies of Ghosh *et al*^[34] and Summers *et al*. Standard GCS-related adverse effects were more frequent than with budesonide (RR = 1.64; 95%CI: 1.34-2.00). Thus, GCS and budesonide will continue to be used for short term treatment of active CD, and the choice between standard GCS *vs* budesonide must be made on the trade-off of efficacy, adverse effects and cost.

Immunosuppressive therapy: The meta-analysis of the use of Immunosuppressants in CD was disappointing; example (Table 33), the relative risk of not being in remission for active CD was not different from placebo. However, if OR was used rather than RRs as the summary statistic, then the result was significant, using a random effects model (OR = 0.42; 95%CI: 0.2-0.89). While some clinicians would accept significant ORs of AZA/6-MP/MTX *vs* placebo as reason to use immunosuppression to induce remission of active disease, the onset of biological benefit takes 2-3 mo. While many gastroenterologists use AZA/6-MP/MTX to prevent relapse in CD, this is likely based on the evidence of individual trials or previous meta-analysis. Surprising to some, while immunosuppressant therapy in UC was not significantly superior to placebo to induce remission, azathioprine was efficacious to prevent relapse (Table 33).

In summary then of the standard step-up approach to the care of patients with CD, in the treatment of active disease to achieve remission, the step using 5-ASA/

Table 33 Meta-analysis of efficacy of immunosuppressive therapy to induce remission or to prevent relapse in Crohn's disease and ulcerative colitis

	Induce remission (RR of not being in remission on active therapy)	Prevent relapse (RR of relapse)
CD AZA/6-MP vs placebo/no therapy	0.87 (95%CI: 0.71-1.06) If OR was used rather than RRs as the summary statistic, then the result was significant, using a random effects model (OR = 0.42; 95%CI: 0.2-0.89)	0.64 (95%CI: 0.34-1.23) There was no statistically significant benefit for continuing AZA to prevent CD relapse (RR = 0.39; 95%CI: 0.21-0.74)
MTX vs placebo	0.82 (95%CI: 0.65-1.03), no statistically significant benefit If or used, then the result was statistically significant: OR = 0.47; 95%CI: 0.23-0.99	IM MTX: 0.57 (95%CI: 0.35-0.94); NNT = 4 (95%CI: 2-25) to prevent one relapse PO MTX to facilitate steroid withdrawal: 0.82 (95%CI: 0.58-1.17)
Cyclosporine vs placebo (only one trial)	0.84 (95%CI: 0.62-1.07; tacrolimus, one study, no improvement: RR = 0.64; 95%CI: 0.44-0.92)	0.96 (95%CI: 0.77-1.20)
UC AZA vs placebo	0.85 (95%CI: 0.71-1.01, <i>P</i> = 0.07)	0.60 (95%CI: 0.37-0.95, <i>P</i> = 0.03); NNT = 4, 95%CI: 2-10
MTX vs placebo	0.59 (95%CI: 0.04-7.90)	

UC: Ulcerative colitis; AZA: Azathioprine; MTX: Methotrexate; RR: Risk ratio; OR: Odds ratio; NNT: Needed to treat; CI: Confidence interval; IM: Intra-muscular; PO: Oral; CD: Crohn's disease; 6-MP: 6-mercaptopurine.

Table 34 Benefits of mucosal healing in Crohn's disease^[183]

Positive: IBSEN, Step-up/top-down, SONIC IBSEN (Frosli): 5-yr longitudinal study of IBD patients not on TNFB and enjoying mucosal healing CD: ↓ Inflammation, ↓ Future use of steroids UC: ↓ Risk of future colectomy Negative: Music

IBSEN: The inflammatory bowel south-eastern Norway (study group of gastroenterologists); SONIC: Study of biologic and immunomodulator naive patients in Crohn's disease; TNFB: Tumor necrosis factor- α blockers; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

SASP should be removed; the antibiotic and GCS/budesonide steps remain, and the AZA/6-MP/MTX step is rather shaky and quite slow.

In the end, we may believe that early use of biologics is too aggressive a step, which needs to be shored up by more data, but we need to acknowledge that the standard step-up approach is not as good as we used to accept.

The presence of two mutant nucleotide-binding oligomerization domain-containing protein 2 (NOD2) alleles may be quite specific for future complicated disease. Although the sensitivity is poor and the area under the sROC curve is poor, the high degree of specificity may be sufficient to recommend testing for double mutations if we can identify therapies that can truly change the outcomes for this high-risk stratum of patients. Testing for double mutations would likely miss many patients with aggressive disease. However, the presence of double mutations, particularly mutations in P.Leu1007fsX1008, does identify a high risk stratum of reagent-grade patients that should be identified and analyzed as a distinct subgroup in clinical trials. If prospective trials can show a change in outcomes in these patients, this would be a strong justification for targeted top-down therapy in this group of high-risk patients to prevent stricturing or fistulising complications.

The other major finding of this meta-analysis is the

Table 35 SONIC (Crohn's disease diagnosed within 4 years) %

Conventional step-up (steroids→AZA→IFX)	Step-down (IFX x3, with AZA)	
2 yr	30	73 (43)
3-4 yr		
No flare, no steroids, on demand IFX	about 65	about 20 (about 45)
No flare, no steroids, no TNFB	about 60	about 15 (about 45)
New or persistent fistulas	about 2	about 22 (about 20)

IFX: Infliximab; AZA: Azathioprine; TNFB: Tumor necrosis factor- α blockers.

lack of prognostic value of the presence of one mutant allele for predicting CD behaviour. Although we specifically studied NOD2 mutations, recent genome-wide association studies have identified numerous other genes that contribute to the susceptibility of developing CD. It is likely that the level at which genetics contributes to phenotypic disease expression is complex and multiple risk alleles contribute to complex interactions. Further studies addressing disease behaviour will likely require large-scale, multicenter trials to obtain sufficient clinical data to accurately ascertain the cumulative risk from clinical, genetic, and environmental factors. Once additional predictive factors are identified and validated, we will be better able to study targeted therapies in high-risk patients.

In a prospective extension of a patient cohort study of 133 newly-diagnosed CD patients recruited from 18 European Centres, half of the patients were initially treated with as "top-down", and the other half as step up^[147]. In the 46 persons who had endoscopically proven mucosal healing at two years, ileocolonoscopies were continued at year three and four. The results can be interpreted as being either for or against mucosal healing as an important therapeutic outcome: complete mucosal healing at year two was associated with a greater proportion of steroid-free clinical remissions (71% vs 27%, respectively; *P* = 0.036). While MH may be associated with

Table 36 Sonic naïve (no azathioprine, no tumor necrosis factor- α blockers) %

	Clinical remission, off steroids		
	AZA	IFX	AZA + IFX
26 wk	30	44	57
50 wk	24	35	46
	17	30	44 ¹

¹AZA + IFX *vs* IFX ($P = 0.55$) or *vs* AZA ($P \leq 0.001$). IFX: Infliximab; AZA: Azathioprine.

later steroid-free remission, it is not clear if this correlates with fewer adverse effects, or better outcomes such as QoL, hospitalizations or surgery. There are studies in which the support for the benefit of MH is positive, or negative (Table 34). The case remains “unproven” about the long-term importance of mucosal healing rather than symptom relief as the major end point of treatment of CD.

In accordance with recommendations from current guidelines, the TNFBs are usually initiated in the CD patient who has failed the “step up” approach of sequential use of GCS, ASA/MTX. Initial clinical trials of TNFB were designed to take this conventional sequence into account, and to use TNFB as “add-on” therapy. The terms “step-up, step-down” “top-down” and “fast forward” all related to the concept of whether CD patients will do better in the long-term if using TNFBs earlier *vs* relatively later after the diagnosis of CD, in an attempt to possibly alter the course of the disease and to thereby improve patient outcomes.

Is the response to TNFBs greater when used early in the history of the person's CD? Is there benefit of starting recently diagnosed CD patients on IFX or IFX+AZA immediately, i.e., “top down” *vs* the “step-up” of GCS→AZA/MTX→TNFB? In the open label trial of D'Haens *et al.*¹¹⁰, newly diagnosed CD patients were treated either with AZA + IFX, or conventional therapy with GCS, followed by AZA, and then followed by IFX (GCS→AZA→IFX). With the early use of AZA + IFX with GCS (top-down), at week 26 and 52 the proportion who were steroid-free and who had not undergone IBD-related surgery was 60% and 62%, respectively. In the step up group, the corresponding figures were lower at 36% ($P = 0.006$) and 42%, respectively. Although the top down group achieved remission faster than did the GCS-AZA-IFX group ($P = 0.018$), at 53 wk a similar percent of patients in each group were in remission (Table 35).

What then is the influence of confounders such as CD duration, or being TNFB- or AZA/MTX naïves? In a post-hoc analysis of the use of ADA in the Charm study¹⁵⁷, after adjustment for potential confounders, disease duration had an effect on clinical remission (RR: 0.96, 95%CI: 0.94, $P = 0.002$). In the Sonic study (REMICADE), patients with CD who had not previously received treatment with anti-TNFBs or immunomodulators (anti-TNF naïve as well as anti-AZA/MTX naïve) were randomized to IFX, AZA, or IFX + AZA.

At 26 wk, the steroid-free remission rate was higher with IFX monotherapy ($P = 0.022$) or AZA monotherapy ($P = 0.009$) groups (Table 36).

When IFX was used within one year of the diagnosis of CD, 78% of the early treatment group responded and 76% were in remission, as compared to 47% and 37% ($P < 0.001$ and $P = 0.002$, respectively)⁵¹. This suggests that earlier use of TNFB may be better when looked from the perspective of this relatively short term follow-up. But of course, those persons started earlier on TNFBs might possibly have more total adverse events (AEs), because of their potentially longer duration of total exposure to drug.

Clearly, current guidelines must be respected. More data is necessary, but it looks promising that the early use of TNFBs (or AZA) may provide outcome advantages. If this possibility becomes evidence based, then guidelines and clinical practice will need to change appropriately.

ADVERSE EFFECTS

Anti-IFX antibodies

In some CD patients who develop secondary non-response to TNFB, this may be due to the development of neutralizing antibodies, what proportion of patients on IFX or ADA develop antibodies to IFX (ATIs), or antibodies to ADA [antibodies to adalimumab (ATAs)]? In patients given scheduled IFX 5 mg/kg, 10%-16% develop ATI, whereas ATA occur in 0.04%-2.60%. Infusion reactions with IFX are more common if there are ATI (36%-50% with, and 21%-24% without ATI). Concurrent immunosuppressant (CI) therapy reduces ATI (63%-75% with concurrent AZA/MTX, *vs* 24%-43% with no concurrent AZA/MTX). This beneficial effect of concurrent immunosuppressant on the rate of development of ATI or ATA is most pronounced with episodic rather than with the scheduled use of IFN. This is because the development of ATIs is greater with episodic than with scheduled infusion of 5 mg/kg or 10 mg/kg IFX: 30%, 10%, and 7%, respectively ($P < 0.001$)¹¹³; 39% episodic *vs* 16% scheduled ($P = 0.036$)¹²⁸.

The presence of ATI/ATA is of clinical importance. In fact, there is a negative correlation between the concentration of ATIs and the duration of response to IFX ($P < 0.001$)¹¹². Furthermore, the median ATI concentration was 15-fold higher in those with loss of response to IFX than in those who maintained response ($P < 0.0001$)¹⁴⁸.

The development of ATAs is uncommon: in Classic I, the rate of ATA formation at week 4 was 0.04%¹⁴⁹. In Classic II, 2.6% showed ATA¹⁵¹. The presence of ATA is also clinically important: there is a significant relationship between the presence of ATAs and non-response to ADA (OR = 12.7, 95%CI: 1.7-92.6, $P = 0.05$)⁸³.

Protection against the development of ATIs may be achieved with intravenous hydrocortisone premedication given immediately before each IFX infusion, with lower

Table 37 Adverse effects for infliximab and adalimumab¹

	IFX	ADA
All AEs	-	-
Serious AEs	-6.6	-4.7 ²
Nausea	+7.9 ³	+2.4
Pharyngitis	+16.1	+3.7 ²
Injection site infection	-	+3.8 ²
Injection site reaction	-	+10.5 ²
Arthralgias	-	+4.3 ²
Urinary tract infections	-	+3.5 ²

¹The rates are shown as the percentage differences in the rates of AEs in tumor necrosis factor- α blocker minus placebo groups. AEs are shown, with the increased (+) or decreased (-) difference from placebo. Note that the duration of follow-up observation varied between study, and has not been standardized here (e.g., per 100 treatment years); ²The statistically significant or trends: (1) Note that the rates of all AEs as well as serious AEs were lower than in the placebo groups; and (2) Serious AEs include lymphoma and other cancers; ³Significant difference. IFX: Infliximab; ADA: Adalimumab; AEs: Adverse effects.

median levels of ATI^[150]. However, in this study, even though ATIs were lower, the use of hydrocortisone did not affect the rate of infusion reactions or increase clinical response. As noted previously, the major role of concurrent immunosuppression with maintenance TNFB may be when TNFB is not given in the recommended scheduled manner. Therefore, due to higher rate of ATI with episodic treatment, it is not a recommended route of therapy.

Other adverse effects

When considering the safety of TNFB, it is important to consider whether the TNFB was given with immunosuppressants or steroids, and for how long therapy was undertaken. In one study, steroid use in persons on IFX were the only independent risk factor for infections [OR 2.69 (95%CI: 1.18-6.12, $P = 0.018$)]^[151]. The overall rate of AEs in IFX-treated patients is about 13%^[77,111,151,152], which is not statistically significantly different from the 19% AE rate quoted for non-IFX treated patients [OR = 1.33 (95%CI: 0.56-3.00, $P = 0.45$)]^[151].

In a case-controlled family practice, population-based retrospective study of 15 471 IBD patients followed for an average of 6.4 years, AZA did not increase the risk for solid organ cancer development (OR = 1.04, 95%CI: 0.89-1.21), but the risk of lymphoma was enhanced 3.22-fold^[153]. If myelosuppression occurs with AZA in naive CD patients, it does so in the first 6 wk of AZA therapy^[154].

AE data has been collected from 10 TNFB randomized controlled trials in IBD [(five IFX^[45,52-54,69], four ADA^[55,56,85,93] and one with etanercept^[31]). More AEs (serious AEs, pharyngitis, urinary tract infection, injection site reaction or infection) were reported with ADA *vs* placebo than IFX *vs* placebo (Table 37). From four ADA placebo-controlled trials^[54-56,93], there was no difference between ADA and placebo in the percentage of persons with overall AEs (77% *vs* 80%, $P = 0.145$). AEs that were more common in the ADA than the placebo group

were pharyngitis (10% *vs* 6%, $P = 0.047$), injection site infection (4.9% *vs* 1.1%, $P = 0.005$), injection site reaction (22% *vs* 12%, $P = 0.003$), arthralgia (10.4% *vs* 6.1%, $P = 0.014$) and urinary tract infection (5.0% *vs* 1.5%, $P = 0.017$) (Table 37). Curiously, ADA had significantly fewer serious AEs than did placebo (6% *vs* 10%, $P < 0.001$), and the placebo group from one study had numerically more AEs than another placebo group (11% *vs* 18%, $P = 0.065$).

The medium-term safety of TNFB has been reviewed: In 21 studies enrolling 5356 CD patients, TNFBs did not increase the risk of serious infection malignancy or death^[5]. However, as cautioned by these authors, "definitive conclusions cannot be drawn because of methodological limitations (safety analyses satisfied by concomitant therapy were not performed in the individual studies". Fortunately, not all trials reported death as an outcome. In AC-CENT I^[54], with IFX 5 mg/kg, two patients unfortunately died from sepsis and one from a myocardial infection.

The most common AEs with CER were upper respiratory tract infection (20%), urinary tract infection (7%) and arthralgia (6%)^[155]. From five IFX placebo-controlled trials^[52-54,78,156], there was no difference between IFX and placebo in the percentage of persons with overall AEs (93% *vs* 95%, $P = 0.355$). The absolute serious AE was 7% higher in IFX *vs* the placebo groups (24% *vs* 17%, $P = 0.019$), and only sinusitis was reported more frequently in UC given IFX *vs* placebo (9% *vs* 5%, $P = 0.04$). Concomitant immunosuppression with maintenance IFX does not significantly extend the duration of clinical response^[111]. Nausea was the only AE which was more frequent in IFX than placebo (15% *vs* 7%, $P < 0.031$), with a higher trend for pharyngitis (18.9% *vs* 2.8%, $P = 0.056$). Importantly, the increased role of infections in CD or in CD patients on IFX may be from their concomitant use of GCS^[129,151].

Life-threatening side effects occur in 2%-5% of persons on IFX, with twice the rate of sepsis, myelotoxicity or risk of lymphoma as those on thiopurines^[157]. However, IFX has been used by approximately one million persons worldwide. As a class, the main complications of TNFBs are infections, lymphoproliferative disorders and malignancy^[158]. As well, neurological, dermatological, autoimmune and cardiac complications commonly occur with these agents (Table 37). Deaths have been reported in persons using TNFB. The risk of sepsis, malignancies and myelosuppression is higher if AZA/MTX is given with TNFB. For example^[159], the risk of opportunistic infections is increased with TNFB (OR = 4.4), and is increased much more if two or more immunosuppressants and used (OR = 12.9).

It is recommended that the complete blood count (CBC) be performed at 1 wk, 2 wk, 3 wk, 4 wk, 6 wk and 8 wk after starting AZA therapy, and then to continue a monthly CBC thereafter. During the first 8 wk of AZA therapy, the risk of leucopenia (white blood cell, $< 1.0 \times 10^9/L$), neutropenia (platelet-neutrophil complexes, $< 1.0 \times 10^9/L$), and thrombocytopenia (platelet count, $< 20 \times 10^9/L$) were 0.3%, 1.0% and 0.2%, respectively^[154]. For

treatment intervals of greater than 26 wk, these hematological risks were 0.2%, 1.1% and 0.1%.

IBD patients, including those on GCS and AZA/MTX, have an increased risk of TB (RR = 2.36, 95%CI: 1.17-4.74). TB reactivation is an accepted risk of TNFBs, with the RR for reactivation 2-20 times that of the general population^[160,161]. In high-risk areas, IBD patients who are scheduled to be placed on TNFBs must be screened for histoplasmosis and coccidiomycosis^[162].

Some authors suggest that CD itself, in the absence of the use of AZA/MTX/TNFB, does not have an increased risk for the development of lymphoma^[163]. Others would argue that CD itself does carry a small increased risk. However, these drugs used to treat CD certainly are associated with as much as a 4-fold increased risk of the development of lymphoma^[157]. And yet, in the Treat registry of IBD patients, the incidence of malignancies was 0.53 per 100 patient years in the IFX group and 0.49 in the non-IFX group^[164]. A small number of adolescents with CD on IFX and thiopurines have been reported as developing hepatosplenic T-cell lymphoma^[165]. This consensus is that the concurrent use of both AZA/MTX plus TNFB should not be used in non-adults.

ECONOMIC EVALUATION

Within the context of an economic evaluation, there are several special considerations: (1) Safety (immunizations complete, no TB, no personal/ or family history or demyelination disorders); (2) Perhaps early after the diagnosis of IBD has been made; (3) Perhaps in those with predictors of likely response to TNFB; (4) About 1/3 of persons treated with IFX, ADA and CZP will have a primary failure; (5) Use same TNFB in higher dose or same dose more frequently or, switch to another TNFB; (6) With a secondary failure, the initial response to another TNFB is lower; and (7) Exclude concurrent infection/abscess as a reason for "failed" effect on luminal inflammation.

Anti-TNF therapy is expensive. While there are reductions in all areas of disease-related resource use following IFX therapy, in the United Kingdom, this was not sufficient to cover the cost of TNFB therapy^[166]. Future studies of these pharmacoeconomic issues will also need to include considerations on indirect cost-savings and changes in the quality of life^[167]. A cost-utility analysis was determined as a part of the CADTH report, giving cost per QALY. The cost of usual standard of care (SOC) was \$17 107, that for ADA was \$45 480, and for IFX \$54 084. The QALY for SOC was 2.555, and the value for ADA and IFX were only slightly higher at 2.701 and 2.721, respectively. This resulted in ICUR of \$193 305 and \$222 955 for ADA and IFX, respectively. When comparing IFX with ADA for the ICUR efficiency using a five-year time horizon, the values were \$193 305 *vs* \$451 165. These cost efficiencies of IFX *vs* ADA were not so much due to variations in the values of their QALY, but rather to higher initial remission and response rates with IFX including with fistulizing CD,

lower relapse rates with ADA, and higher remission rates amongst the patients who stopped responding to initial IFX and were switched to ADA^[72,108]. It is important to stress that this comment is based on very preliminary data. From an economic perspective, it is preferential to switch an IFX non-responder to ADA, rather to increase the dose from 5 mg/kg to 10 mg/kg. There is insufficient evidence of the use of treating an IFX non-responder to a reduced dose interval. Also, the lower rates of hospitalization and need for IBD-related surgery in the TNFB groups was partly offset by the higher drug costs. The true economic impacts of SOC *vs* TNFBs will depend upon longer term data.

For interest, the cost of usual care for UC patients was \$24 268 and the QALY was 2.015. For a strategy of IFX 5 mg/kg every 8 wk for maintenance, and for those who do not respond to IFX or lose the initial benefit, the patient is switched to ADA. This escalated the cost to \$82 756 and is associated with a very small increase in QALY from 2.015 to 2.178. For an incremental QALY of 0.163, the ICUR was an astounding \$308 088. In contrast, an economic evaluation in the United Kingdom gave a more favourable ICUR for IFX of about \$70 000 (using the 2008 currency exchange rate). While there are other economic evaluations of TNFB^[168-170], the CADTH study is the first to compare the initiation and maintenance therapy costs of IFX and ADA. The authors of the CADTH review suggested, with regards to the economics of the use of TNFBs, that "...the incremental cost-effectiveness in managing this IBD patient population may not be perceived as favourable for anti-TNF α drugs compared with usual care without these drugs. This finding was supported by deterministic sensitivity analysis and probabilistic sensitivity analysis".

Over the past four years (2006 to 2010), and based on acceptable incidence and prevalence estimates of CD and UC^[2], the number of IBD patients has risen by about 5% (1% per year), yet between 2006 to 2008, the annualized increases in public spending on IFX and ADA in IBD have risen 25% and 18%, respectively. There is no evidence that over the past five years there has been a marked increase in the number of IBD sufferers who have suddenly developed severe or non-responsive disease. This 5-fold greater use in TNFBs as compared with the increase in the number of sufferers may reflect the wider dissemination and acceptance of TNFB guidelines, or may be the result of inappropriate over usage.

The economic analysis of the health services impact suggest that "...Adalimumab and IFX for the treatment of IBD may not be perceived to be a cost-effective use of health care resources"^[51]. There are no head-to-head trials comparing standard-of-care *vs* anti-TNF therapy. What do TNFBs add to the annual cost of care of every IBD patient in Canada? "Based on trends in expenditures over the past three years, total public expenditures on anti-TNFs for IBD are projected to be \$94 832 652 in fiscal year 2010-2011. The estimated annual drug costs for IBD patients who are on maintenance therapy with

Table 38 Some of the important anti-tumor necrosis factor studies still to be reported

Direct head-to-head comparisons of various anti-TNFs Further evidence that treating with anti-TNFs earlier after the diagnosis of CD is better Further clarification of the role of using scheduled anti-TNF therapy without concomitant AZA/MTX Head-to-head trials comparing the effectiveness of IFX, ADA, and CER peg with conventional therapy in refractory CD (other than newly diagnosed and treatment naive patients) Long-term safety Evidence for efficacy of switch from ADA → IFX for ADA secondary loss of response Optimal therapy for anti-TNF therapy primary non-responders The comparison of standard-of-care <i>vs</i> anti-TNF therapy for maintenance therapy in UC Are physicians correctly distinguishing mild from moderate or severe CD? What is the profile of the patient who is most likely to respond? Are they genotypic or phenotypic characteristics? When is the optimal time in the course of the patient's illness to begin anti-TNF therapy?

TNF: Tumor necrosis factor; CD: Crohn's disease; AZA: Azathioprine; MTX: Methotrexate; IFX: Infliximab; ADA: Adalimumab; CER: Certolizumab; UC: Ulcerative colitis.

anti-TNF drugs vary from \$23 000 to \$38 000^[159]. Similar benefits of IFX on rate of hospitalization, surgery and procedures were described in the Accent I and II trials^[54,164].

This reduction in health serious utilization could be partially offset by the high cost of biologics, so that cost effectiveness and cost-utility analysis are necessary. A UK cost utility analysis reported that maintenance treatment with IFX every 8 wk was cost-effective for patients with luminal and fistula CD^[171]. For example, for luminal CD, an incremental cost per QALY gained for IFX was £26 128 (using the exchange rate at the time of publication of this paper, this equates to approximately \$70 000 Cdn). However, the use of QALY for the measurement of cost-effectiveness is of questionable value for diseases such as IBD, which have a young patient base and low mortality rate but high morbidity^[167]. Also, indirect costs are high in persons with IBD: In Sweden or Scotland, about two thirds of the costs are indirect^[172,173], and in the Accent I trial of IFX, about half the patients at baseline were not employed^[54]. Because of this the result of studies of cost-effectiveness and cost-utility need to be challenged, since direct costs are often not taken into consideration^[174].

To quote from the report of Canadian Agency of Drugs and Technologies in Health^[51], "Using cost-utility analysis cost per QALY allows for the incorporation of quality-of-life impact of clinical effects of CD treatment strategies..." and "allow for comparison with evaluation of disease area that use this outcome." The incremental cost-utility ratio for ADA and IFX, compared with usual care, was \$193 305 and \$451 165, respectively^[51]. "...IFX and ADA have proven clinical benefit when compared to placebo, the primary and secondary non-response rates are high, the therapeutic gain is small, and..."^[51] the costs associated with these treatments could be perceived as high. Furthermore, based on incremental cost utility findings from our primary economic evaluations. Adalimumab and IFX for the treatment of IBD may not be perceived to be a cost effective use of health care resources^[51] (Table 38).

CONCLUSION

The results of these and the recent meta-analyses may differ because of "... a less contemporaneous search data, the inclusion of non-FDA-approved therapies in the analysis, and different time points for data extraction, which were not the primary end points of the included trials"^[61].

In persons with luminal CD who have failed treatment with first and second-line agents or who are corticosteroid dependent, for induction of remission of active luminal CD, "IFX, natalizumab, and adalimumab appear to have the most evidence for their use, although the latter two therapies performed only moderately in this setting"^[61].

"The most marked effect of biological therapies was in preventing relapse of luminal CD once remission had been achieved, with a NNT of only 4. This benefit was observed for both IFX and certolizumab, but not for adalimumab"^[61].

"In terms of fistulizing CD, there is less evidence for the use of biological therapies, though there was a clear beneficial effect when only IFX was studied, although in one trial, and when only RCTs with follow-up in excess of 4 wk were considered in the analysis. There was also a benefit in favour of biological therapies over placebo when only studies that reported fistula healing in the longer term were included in the analysis."

"In preventing recrudescence of fistula, there was only one RCT reporting on this end point, which demonstrated that IFX was superior to placebo. Although concerns about adverse events, arising from the long-term use of these drugs is understandable, the data from the RCTs included in this meta-analysis did not demonstrate any increase in overall adverse events, or serious adverse events, with use for up to 1 year."

"Clinical trials for the three anti-TNF α agents approved for CD or UC have used different end point criteria and response time, in addition to the different modes of administration. Interpretations of these differences and their overall clinical relevance remain contro-

versial.”

“The efficacy of anti-TNF α is limited. A total of 20%-30% of patients with refractory CD and roughly 40% of patients with refractory UC do not respond to anti-TNF α treatment and are defined as primary failures.”

“Long-term therapy with biologics is associated with significant loss of response (up to 40%).”

“TNFBs represent a major advancement in the management of carefully selected patients with IBD, such as those with active fistulizing CD and active CD not responding to adequate doses of steroids and/or immunosuppressants. It is important to give these agents for an adequate duration before declaring failure of treatment. The specific time period of use is unknown, but it includes side effects to any medications or failure to achieve remission of disease.”

It must be appreciated that in most TNFB studies, there is a run-in interval, and the initially approximately 30% non-responsive patients may be excluded from the final reporting of response rates; the methodology for the statistical analysis of each study must be carefully considered.

There is insufficient current evidence to support “top-down” TNFB therapy (starting early in the course of the patient's disease with TNFBs rather than the SOC progression to steroids and immunosuppressants.

The use of mucosal healing as an endpoint of successful therapy, rather than clinical response, has not been proven.

The initial response rate of fistulizing CD for induction may be higher with IFX than ADA, but longer term maintenance with ADA may be superior to IFX.

There are wide ranges in the reported rates of minor or severe adverse effects in short-term users of TNFBs. The increased risk of serious infection, lymphoma and cervical dysplasia may be as much related to the concurrent use of immunosuppressants (AZA/MTX) with TNFBs, as the TNFBs themselves. The longer term risk of TNFBs remains to be established.

It remains controversial whether immunosuppressants (AZA/MTX) should be used concurrently with TNFBs when starting TNFBs for induction therapy or continuing TNFBs for maintenance of remission. For now the international guidelines recommended using both immunomodulators and TNFB for induction of remission and mucosal healing. As well, combination therapy is preferred in moderate to severe CD as data shows reduced efficacy with single agent therapy (immunomodulators or TNFB).

It is unknown if TNFBs change the natural history of IBD.

In the UC patient who is experiencing frequent clinical recurrences while on 5-ASA, AZA or MTZ maintenance therapy, or who is hospitalized for an acute episode of their disease and fail to respond to IV steroids, it remains unclear whether IV cyclosporine followed by colectomy, AZA or IFX maintenance represent optimal therapy.

In persons with chronic continually or intermittently active UC or Crohn's colitis, it is unknown if colonoscopic surveillance protocols need to be changed to offset any potential TNFB-associated alteration in the risk of dysplasia.

When standard methods are used for economic evaluation, it is difficult to justify the use of TNFBs, based on available clinical data.

Given that some persons with IBD require TNFBs because of non-response to conventional therapies SOC, future research must solve the dilemma of predicting who will need TNFBs in the future who will be a TNFB primary or secondary non-responder, and who would benefit from early use of TNFBs. Above all, the pathogenesis of IBD needs to be identified in order that modifiable risk factors may be treated, and the diseases eventually may be prevented and cured.

The estimated 2010 expenditure on TNFBs is over \$10 million (CDN), and a per IBD patient TNFB cost of \$19 412 is higher than the estimated annual cost for standard of care of \$17 107 for CD and \$24 268 for UC.

“Making recommendations requiring TNFBs about anti-TNF α therapies based on less-than-conclusive scientific evidence has ethical implications for physicians...” (CADTH, 2009, page 60).

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