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Biologic Agents for Inflammatory Bowel Disease (The Current, the Future and the Controversy)

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1. Introduction

Inflammatory bowel conditions (IBD) are chronic relapsing diseases. Crohn's disease (CD) is characterised by transmural inflammation due to an imbalance between pro- and anti-inflammatory molecules. Ulcerative colitis (UC) is only a mucosal disease, however one quarter of patients develop fulminating disease and 20% require surgery. Treatment objectives usually include steroid-free remission, decrease in hospitalization and surgery and sustained clinical remission and mucosal healing as well as reduction in the risk of dysplasia and cancer.

The description of the cell signalling cascade over the past 20 years has led to a surge in potential treatments for IBD. It was initially thought that since CD is mediated through the T helper 1 cascade, using specific molecules to block it would be a reasonable approach to potential cure. A multitude of medications and trials later proved this theory to be true. In addition, UC which was thought to be mediated through a different inflammatory cascade (T helper 2) was soon discovered to respond to these newer molecules. In fact several trials showed T helper 1 cells to be prevalent in the serum, stool and mucosa of patients with active UC. The better knowledge of the inflammatory pathways in IBD lead to the development of new targeted therapies with a multitude of actions including inhibition of leukocytes trafficking, inhibition of T cell activation or polarization and inhibition of pro-inflammatory cytokines. Additionally a new technique called humanization was developed through advances in protein engineering and lead to the production of partially humanized and finally fully humanized antibodies.

2. Anti-TNFs

Development of Tumour Necrosis Factor (TNF) agents dramatically changed the course of IBD. They block both soluble and membrane TNF but also fix complement.

2.1 Infliximab

Infliximab is a partially human chimeric molecule introduced in the market before 2000. It was shown to be adequately effective in inducing and maintaining remission in patients with moderate to severe disease (ACCENT 1 & 2). It is a chimeric monoclonal anti-TNF IgG1 antibody and able to block both soluble and membrane TNF and also fix complement. It is

also capable of inducing apoptosis of T-cells and monocytes in a caspase dependant manner [Ten Hove et al. 2002]. It has a proven efficacy in induction and maintenance of remission in patients with refractory luminal and fistulising CD [Hanauer et al. 2002; Present et al. 1999; Targan et al. 1997]. It has also been shown to induce rapid and profound mucosal healing. In the ACCENT 1 trial [Hanauer et al. 2002], IFX induced a clinical response at 5 mg/Kg administered at weeks 0, 2 and 6. It was given every 8 weeks afterwards and assessed at week 54 where a remission rate of 29% was demonstrated compared to the 5% induced in the placebo group. Moreover, mucosal healing was obtained in 44% of patients compared to 18% in the placebo group. The ACCENT 2 study showed that IFX (similar loading and maintenance regimen) improved fistulising disease in 55% and 38% of patients treated respectively with 10 and 5 mg/Kg compared to the placebo group (13%) [Sands et al. 2004]. At week 54, a sustained response was observed in 69% and 46% of patients of the 2 groups compared to placebo (23%).

There is some controversy as to wether the addition of immune-modulators alters the response to IFX. The original ACCENT 1 and 2 trials did not establish the benefit of concomitant therapy. Similarly, the COMMIT study evaluating the addition of methotrexate to IFX regimens for CD failed to demonstrate any benefit [Feagan B et al. 2008]. Others did observe that the addition of immune-modulators prior to IFX does help to maintain duration of response, especially if started more than 3 months before [Rudolph et al. 2008].

The efficacy of IFX in inducing and maintaining remission in 110 children with a diagnosis of CD has been shown in the REACH trial [Hyams et al. 2007] with 88% response and 59% remission rate at week 10 and 64% and 56% at 1 year.

Subsequent to the marketing of IFX for CD in the United States in 1998 there were several reports of "open label" use of IFX for refractory, moderate to severe UC in out-patients settings [Gornet et al. 2003; Su et al. 2002; Chey et al. 2001]. There were no standardized administration schedules and most patients received a single infusion. The first randomized placebo controlled trial was reported in 2003; it enrolled patients with corticosteroid refractory disease to receive IFX at 5 mg/Kg at weeks 0 and 2. Results showed no statistical difference with placebo regarding clinical or endoscopic remission [Probert et al. 2003]. However, two large multi-center, placebo-controlled randomized trials were performed to clarify the role of IFX in refractory UC. The ACT 1 and 2 were designed to evaluate both induction and maintenance effect. They studied the efficacy of IFX at a dose of 5 mg or 10 mg/Kg administered at week 0, 2 and 6 in moderate to severe UC compared to placebo during 54 weeks (ACT 1) or 30 weeks (ACT 2) [Rutgeert et al. 2005]. Week 8 clinical response was 61 and 69% in patients treated with 5 mg and 10 mg/Kg respectively versus 29 and 37% in the placebo group. At the conclusion of 54 weeks in ACT 1 and 30 weeks in ACT 2, clinical remissions were observed in 35% in the IFX group compared to 15% in the placebo group. Furthermore, additional pre-defined end-points including "mucosal healing" and "steroid free remissions" were reported with significant benefit. Follow up of these cohorts also reported a drop in the rate of colectomy (67%) versus placebo (27%) [Janerot et al. 2005].

Clinical series in pediatric patients with moderate to severe refractory UC have described very similar results to series enrolling adult patients with approximately 50% of patients avoiding colectomy within 5 years of initiating IFX [Hyams et al. 2010; Russo et al. 2009; Wilhelm et al. 2008; Jakobovits et al. 2007].

In the settings of severe-fulminant UC, cyclosporine has been (although controversial) described as salvage therapy for patients who have failed a course of intravenous steroids

[McDonald et al. 2005; Hanauer et al. 2005]. A placebo controlled trial comparing IFX to placebo in hospitalized patients with severe UC not responding to conventional therapy was conducted [Janerot et al. 2005]. Patients admitted, who didn't respond to IV steroids within 4 or 7 days (depending on their initial status) received a single infusion of IFX, 4-5 mg / Kg or placebo with the primary endpoint of colectomy 3 months after randomization. 7 out of 14 patients in the IFX group versus 14 out of 21 in the placebo group underwent colectomy. The debate between uses of cyclosporine or IFX for patients with fulminant UC has been complicated by the complexity of monitoring cyclosporine IV compared to the ease of giving IFX [Janerot et al. 2006].

Additional questions remain regarding the need for long term dosing after anti-TNF induction therapy as ACT studies did not evaluate the long term responses and one may speculate that doses may need adjustment on the long term [Danese et al. 2008; Kohn et al. 2007].

Some patients were noted to develop anti-drug antibodies and this increased the risk of potential hypersentivity reactions (acute and delayed) as well as secondary loss of response [Hanauer et al. 2004; Baert et al. 2003]. Episodic treatment was coupled with a higher rate of anti-drug antibodies (30 – 60%) compared to patients receiving a scheduled protocol (7 – 10%) [Hanauer et al. 2004]. This risk seems to be lower if patients are treated with concomitant immune-suppressive agents. ACCENT 1 and 2 showed and acceptable tolerability profile with a low rate of serious side effects. Development of active tuberculosis in patients with latent tuberculosis was observed [Keane et al. 2001]. Therefore the presence of latent tuberculosis has to be evaluated before treatment [Rutgeerts et al. 2004]. The TREAT trial showed similar mortality rates in IFX and placebo group [Lichtenstein et al. 2006].

This drug received FDA approval in 1998 for use in patients with moderate to severe CD and in those with fistulising disease. Currently we have a decade of experience with it and a massive number of patients and trials detailing its efficacy, long term benefits and adverse effects. The use in UC was advocated later, it received FDA approval for use in moderate to severe disease patients in 2006.

2.2 Adalimumab

Adalimumab (ADA) is a fully humanized monoclonal anti-TNF and therefore immunogenicity is very low. The CLASSIC 1 trial was the first multi-center randomized double blind controlled trial studying the response to ADA in 299 moderate-severe CD patients naïve to anti-TNF therapy [Hanauer et al. 2006). They received induction therapy with ADA 40 mg/20 mg, 80 mg/40 mg, 160 mg/80 mg or placebo, at weeks 0 and 2. The primary endpoint was remission at week 4. Rates seen in the 160 mg/80 mg group was 36% versus 12% for the placebo group. Clinical response was significantly higher in both groups of ADA with higher dosing regimen. 55 patients from the CLASSIC 1 trial were enrolled in the CLASSIC 2 study [Sandborn et al. 2007]. This study showed remission maintained at week 54 in 74%, 83% and 44% of the patients treated respectively with ADA 40 mg every 2 weeks, every week and placebo. Data from the CHARM trial [Colombel et al. 2007], conducted in CD patients with the same clinical characteristics, randomized to receive ADA 40 mg QOW, 40 mg weekly or placebo after an open label induction regimen of ADA 80 mg/40 mg, support in a large cohort (854 patient) the fact that this drug is more effective than placebo for maintaining clinical remission at week 26 (40%, 47% versus 17% in placebo). No significant difference was found between the dosage of 40 mg QOW and 40 mg QW. Interestingly, the response rate was higher in patients who had never received other anti-TNFs before. There is no randomized controlled trial studying ADA in fistulizing CD,

but the presence of a fistula was not an exclusion criteria in the CHARM trial and post hoc data have been published. Complete fistula closure was seen in 36% of patients treated with ADA every other week, 46% in those treated weekly and 14% in the placebo group [Colombel et al. 2009]. In an open label single arm trial , the CHOICE, 673 CD patients who were IFX primary non-responders (17%) or initial responders (83%), were enrolled and treated with ADA (induction dose 160/80 mg and maintenance dose 40 mg QOW). At baseline 88 patients (13%) had at least one draining cutaneous fistula. Complete fistula healing was achieved by 34 patients (39%) at the last visit (dates from week 4 to week 36) [Lichtiger et al. 2010]. Improvements in quality of life and work productivity were sustained all throughout, as well as the group of non-responders. The GAIN study reported the first data on ADA use in IFX intolerant or secondary non-responder patients [Sandborn et al. 2007]. 301 patients enrolled showed remission in 21% at week 4 (standard induction and maintenance doses) compared to only 7% in the placebo group. The safety of ADA was comparable to that of IFX. Remission rate was 39% at 6 months and 29% at one year. Data on the efficacy of ADA on primary non-responders to IFX are limited. In the large cohort of the open label CARE study, about one quarter of patients were primary non-responders to IFX [Lofberg et al. 2011]. The percentage of patients in remission was 43% at week 4 and increased to 52% at week 20. Remission was significantly different between IFX-naïve compared to IFX-exposed patients (62% vs 42%). A systematic review including all open-label cohorts that evaluated the efficacy of ADA in IFX primary and secondary non-responders was published. Among the 15 studies included, 1810 CD patients with previous IFX exposure were identified. Short term clinical response (week 4) ranged from 41% to 83%. Long term clinical remission (12 months) ranged from 19% to 68%. The authors concluded that the variability was because of differences in the study design and baseline characteristics of the patients included in the studies [Ma et al. 2009].

Regarding "mucosal healing", the EXTEND study included 135 patients with moderate-severe ileo-colonic CD and baseline mucosal ulceration [Colombel et al. 2010]. After induction 129 patients enrolled were randomized to maintenance. The primary endpoint was deep remission and mucosal healing as evidenced by the absence of mucosal ulceration at week 12 and 52. A highly statistical difference was noted at 52 weeks between the 2 groups (19% vs 0%).

The RESEAT trial is the largest multi-center experience using ADA for pediatric CD [Rosh et al. 2009]. 115 children included were shown to have clinical response rates at 3, 6 and 12 months of 65%, 71% and 70%. Similarly, clinical remission was 32%, 43% and 49%.

Preliminary data from open-label trials showed efficacy of ADA in mild-moderate UC with loss of response or poor tolerability to IFX [Trinder and Lawrance 2009]. Until now, the only randomized placebo-controlled double blind trial was an 8 week multi-center study, conducted in North America and Europe, it included patients with moderately to severely active UC [Reinisch et al. 2011]. All patients were naïve to IFX and failed or didn't tolerate conventional treatment. Standard ADA dosing was used and the primary endpoint was clinical remission at week 8. No significant difference was found in clinical remission, response and mucosal healing in the three arms. However, a difference was noted regarding rectal bleeding score and physician global assessment. Recently a small randomized trial assessed the long term efficacy of ADA in patients with UC. Clinical response and remission were assessed at weeks 4 and 12. The proportion of patients who continued on ADA and those who remained colectomy free were noted over the long term. Clinical response was achieved in 53% and 60% at week 4 and 12 respectively and remission in 10% and 27%. After a 48 week follow up, 50% of patients were still on ADA and only 20% underwent

colectomy. All patients who achieved clinical response at week 12 were colectomy free at 1 year [Taxonera et al. 2011]. Data on efficacy should be confirmed by large prospective trials.
The safety profile of ADA in global clinical trials in CD patients was comparable to that of IFX. Analysing the largest trial of ADA in CD, the types and frequency of adverse events and serious adverse events were similar to placebo in both induction and maintenance phases [Colombel et al. 2009]. In the all exposed patients from the main trials, 56 patients (1.8%) had opportunistic infections. The most frequently reported serious adverse event was serious infection (5.8%). Low incidences of malignancies were reported in the CD trials. Four deaths were recorded, in particular only one of these was related to ADA therapy [Colombel et al. 2009].
This medication was rewarded FDA approval for use in patients with CD in 2007. Although data from the open label trials showed it is also efficacious in UC but large prospective trials results are still pending and so is the FDA approval.

2.3 Certolizumab Pegol

Certoluzimab Pegol is the third medication in this family and involves the addition of two polyethylene glycols to the antibody fragment rendering its plasma half-life longer. The preliminary placebo-controlled phase II trial studied certolizumab at different doses (100, 200 and 400 mg) at weeks 1, 4 and 8 in patients with moderate – severe CD [Schreiber et al. 2005]. All doses produced benefit at week 2 but at week 10 the optimal dose was discovered to be 400 mg. The PRECISE 1 and 2 trials used an induction dose of 400 mg at week 0, 2 and 4 and then every 4 weeks. The trial showed response by two thirds of patients at week 6 in comparison to placebo but no significant improvement in remission at weeks 6 and 26 [Sandborn et al. 2007; Schreiber et al. 2007].

3. Adhesion molecules

In CD there is continuous release of pro-inflammatory cytokines and persistent recruitment of leukocytes into the gastrointestinal tissue. Interference with the mechanism of regulation of this trafficking would reasonably be an attractive therapeutic strategy. Much of this leukocyte trafficking is mediated through a large family of transmembrane proteins including integrins, selectins, chemokines and their associated ligands [Springer et al. 1994]. This on-going and persistent recruitment of leukocytes into gut tissue is of paramount importance in maintaining and perpetuating the inflammation associated with IBD. Adhesion molecules are located at the surface of endothelial cells and play a crucial role in the migration of leukocytes from blood vessels to intestinal tissues.

3.1 Natalizumab

Natalizumab is a humanized monoclonal antibody inhibiting the migration and adhesion of leukocytes into inflamed tissues. This humanization resulted in an antibody that is 95% human, with a potential for lower immunogenicity, increased half-life, and the ability for repeated administration while maintaining potency [Kent et al. 1995; Leger et al. 1997].
In CD, the initial pilot study was a small, randomized, placebo-controlled trial conducted in 30 patients with mild to moderate active disease, randomized to receive either Natalizumab 3 mg/Kg as a single intravenous infusion, or placebo [Gordon et al. 2001]. At week 2 the mean drop in CDAI (Crohn's disease activity index) was significantly higher in the treatment group compared to placebo. The phase III study program consisted of evaluating

Natalizumab as induction therapy for CD [Sandborn et al. 2005]. The ENACT 1 trial randomized patients to receive either Natalizumab 300 mg of placebo at weeks 0, 4 and 8. Both response and remission were not statistically significant between the 2 groups, which was disappointing. However, subgroup analysis showed a significant difference in patients with baseline elevated CRP and those on concomitant immune-modulators. Similarly there was also a significant difference in both endpoints in patients previously treated with anti-TNFs. The mixed results of the ENACT 1 trial lead to the design of a second induction trial, ENCORE [Targan et al. 2007]. It involved only patients with elevated CRP and moderate – severe CD. The primary endpoint was response through week 12. Both rates of response and remission were significantly higher in the Natalizumab group (48% and 26%) compared to the placebo group (32% and 16%). These rates were substantially higher starting week 4, thus demonstrating the efficacy of Natalizumab for induction of remission in selected CD patients. The ENACT 2 involved 339 patients who had a response in ENACT 1, they were randomized to receive 300 mg of natalizumab or placebo every 4 weeks for 12 months [Sandborn et al. 2005]. 61% of patients treated with Natalizumab had a sustained response through week 36 compared to 28% in the placebo group. The remission rate was 44% versus 26%. Serious adverse events were similar in both groups.

A pilot study of Natalizumab in UC showed no major adverse events [Gordon et al. 2002].

In phase I and II trials, the occurrence of adverse events ranged from 9% - 12%, with the most frequent being headache and abdominal pain [Gordon et al. 2001; Ghosh et al. 2003]. Similarly in the ENACT 1 and 2 trials adverse events were reported in comparable frequency between both groups. Influenza like symptoms were reported more frequently in patients receiving Natalizumab. Acute infusion reactions were reported in 11% and 7% in both trials and antibody detected were less than 10%. Although deemed safe Natalizumab was associated with progressive multifocal leukoencephalopathy (PML), a fatal opportunistic infectious brain disorder induced by the JC virus [Van Assche et al. 2005]. This complication has also been described in six patients treated for multiple sclerosis. A follow up of more than 3000 patients who received Natalizumab in different clinical trials showed no additional cases. As of June 2007, more than 10,000 patients had received the drug for multiple sclerosis with no new reports of PML.

In January 2008, the FDA approved the use of Natalizumab in the treatment of patients with moderate – severe CDwho have failed or cannot tolerate available therapies including anti-TNFs.

3.2 Vedolizumab

Due to the major adverse events associated with Natalizumab, newer selective adhesion molecules inhibitors are in development. Vedolizumab (MLN-02) is one of those new agents; it is a humanized antibody directed against integrin α4β7. It has been studied in 181 patients with active ulcerative colitis [Feagan et al. 2005]. The difference in clinical response at week 6 was significantly different between groups: 33% (0.5 mg/Kg), 32% (2 mg/Kg), and 14% (placebo). The phase II, double blind, placebo-controlled, dose finding trial has been reported [Feagan et al. 2003]. 185 patients were randomized to receive either one of 2 doses (0.5 mg/Kg or 2 mg/Kg) Vedolizumab or placebo at day 1 and 29. The study failed to show a difference in response between the groups, however remission rate on day 57 in the 2 mg/Kg group (37%) was statistically superior than both groups. But since dynamic data showed that the receptors were not completely saturated, it is possible that the appropriate dose was not studied yet.

4. New molecules

Interleukin 12 is one of those many cytokines that drive the inflammatory response. It is found in high amounts and concentrations in the bowel walls of patients with CD [Gately et al. 1998]. Administration of recombinant anti-IL 12 has been shown to inhibit colitis in mice [Davidson et al. 1998]. Currently two fully humanized IgG1 monoclonal antibodies have been developed: ABT-874 and CNTO 1275 (Ustekinumab). A randomized controlled study of 79 moderate – severe CD patients treated with ABT-874 (1 or 3 mg/Kg) was done. Response was 75% in the group with the higher dose compared to 25% in the placebo group [Mannon et al. 2004]. A high proportion of patient included developed injection-site reactions, but only 3 out of 79 patients developed anti-drug antibodies. Recently a double blind trial studied the efficacy of ustekinumab [Sandborn et al. 2008]. Response rates versus placebo were 53% and 30% respectively at weeks 4 and 49% and 40% respectively at week 8. In the subgroup of patients exposed previously to IFX, clinical response to ustekinumab was again significantly higher than placebo.

Visiluzimab is a humanized anti-CD3 monoclonal antibody. An open label phase I trial included 32 severe steroid-refractory UC patients. They received Visiluzimab at 10 or 15 μg/Kg, intravenously on 2 consecutive days. The remission rate (66%) and response rate (87%) were both acceptable as well as the adverse events. However, development of this compound has been halted due to transient elevation of blood EBV-DNA noted in some patients [Plevy et al. 2007].

IL-6 is a molecule that promotes inflammation by playing a key role in the apoptosis resistance of T cells in CD, it acts in synergy with IL-12 [Yen et al. 2006]. Preliminary studies for blocking IL6 showed potential in decreasing colitis in mice. Tocilizumab a recombinant anti-IL 6 showed efficacy at week 12 both in induction of response and remission in 36 patients with moderate-severe CD. Intravenous doses of 8 mg/Kg every 2 weeks and every 4 weeks were given. The response was higher in the group treated every 2 weeks, no major adverse events were noted [Ito et al. 2004].

Il-10 is an anti-inflammatory cytokine whose production is reduced in patients with CD. IL-10 deficient mice develop transmural inflammation of the gut. This can be prevented by administering recombinant IL-10 [Kuhn et al. 1993]. However, when tested clinically no efficacy was observed and multiple side effects occurred [Fedorak et al. 2000].

Problems caused by epithelial permeability have been implicated in the pathophysiology of CD. This is usually threatened during inflammation because of severe damage to the bowel wall. Epidermal growth factor (EGF) has been suggested to be involved in preserving mucosal integrity and the regeneration of cells [Beck and Podolsky 1999]. Initially a recombinant EGF was formulated and tested in 24 patients with moderate – severe UC. This randomized placebo-controlled trial showed remission in 83% of patients versus 8% in the placebo group [Sinha et al. 2003].

Granulocyte-macrophage colony stimulating factor (GM-CSF) can be used for the treatment of disorders due to neutrophil dysfunction. A phase II trial included 124 CD patients and showed Sargramostin (GM-CSF) to be effective in inducing remission, the actual mechanism is still unknown [Korzenik et al. 2005]

5. The controversy

In general biologic agents have succeeded where conventional therapy has failed; they have changed the natural history of inflammatory bowel disease. Several prospective trials have

already shown a decrease in hospitalization and surgery in these patients over time. A new marker of response has been gaining more momentum and significance: mucosal healing was discovered to be of prime importance in the prognosis of IBD patients. For instance in UC the presence of mucosal healing 1 year after diagnosis was associated with a significant decrease in the rate of colectomies up to 5 years later. In CD patients it was associated with a substantial drop in the need for corticosteroids. In IBD, mucosal healing data are available for steroids, azathioprine, methotrexate, infliximab, certoluzimab pegol and adalimumab. Evidence points clearly to the superiority of biologic agents in that respect.

With this new era of treatment options dawning, the clinicians are faced with the dilemma of rightfully placing these new medications in the conventional protocol of standards of care. When should we start these drugs? Which patients should be selected to receive them? How can we stratify patients to receive them? All of these questions are covered by evidence, however the answers so far are not very clear. The therapeutic approach to patients with CD depends on the clinical presentation and the potential for complications. Several tools are available, mainly through retrospective studies that may aid in predicting a more aggressive course of disease. These parameters include a younger age at diagnosis, active smoking, extensive small bowel disease, deep colonic ulcers, perianal disease and the initial need for corticosteroids. Many clinicians still apply a stepwise approach in managing CD starting from mesalamine, antimicrobials or budesonide moving to more toxic medications like corticosteroids and immuno-suppressants (azathioprine, 6MP, tacrolimus and methotrexate). Biologic agents have generally been used only after intolerance to or failure of this therapy. This escalating approach is called the "step up approach". However, there is increasing evidence that a strategy of earlier use of potent immuno-suppressants and namely biologic agents maybe the optimal approach in selected patients. The key to understanding this theory lies in the natural history of CD. Patients usually evolve in a steady progressive fashion from easily treatable inflammatory lesions towards irreversible fibrotic disease such as strictures and fistulae. A large load of evidence is currently present to support what is now called the "top down therapy" ranging from randomized trials (SONIC, CHARM) to sub-analysis (REACH, ACCENT, PRECISE). Unlike CD where longer duration usually means problems for patients, the same cannot be said for UC. One important long term issue here is dysplasia prevention. Theoretically the premise still holds, however although evidence does support the use of amino-salicylates in this regard, it is still lacking for biologics and therefore at present there is little rationale for a top down approach in managing UC.

A third factor playing a major role in the confusion for the use of biologics is their side effects. A multitude of cohorts have shown their potential for serious adverse events ranging from severe infections to life threatening allergic reactions and anaphylaxis. Although they fare well in comparison to conventional immuno-suppressants and corticosteroids, mounting evidence has shown that combination therapy may carry a dramatic toll on the patients. In a CD registry in the US (TREAT); that involved more than 6000 patients it was found that steroid treatment was associated with increased risk of serious infection and mortality, OR of 2.5 and 1.9 respectively. This was statistically significant when compared to both IFX and immune-suppressants [Lichtenstein, 2006]. Another study examined wether treatment of CD or UC patients with immune-suppressant medications was associated with an increased risk of death in the era prior to anti-TNF treatment. It showed that patient with IBD, particularly those with CD, have an increased mortality risk that may be even higher among those receiving steroids [Lewis, 2008]. One of their most controversial effects is their theoretical potential for increasing the risk for cancer.

We already know that IBD per say increases the chance of developing colon cancer; for instance based on stratified pooled data the risk of developing colon cancer in UC patients increases steadily with the length of disease. It is 2% by 10 years, 8% by 20 and an exponential 18% by 30 years of disease [Eaden, 2001]. Another prospective, observational, non-randomized, parallel-group, post-marketing safety surveillance registry (ENCORE) was launched in 8 European countries to collect long-term (5-year) safety data in patients with CD treated with infliximab (IFX) or non-biologic therapies. Additionally, data on efficacy and health economics were also obtained. As of May 2007, 842 patients received non-biologic therapy, and 1166 received IFX with a median follow-up of 12.7 and 13.2 months, respectively. A total of 122 subjects switched from non-biologic therapy to IFX therapy. Follow-up patient years were 1016 for patients on non-biologic therapy and 1506 for patients on IFX therapy. Mean disease time since first diagnosis was 8 years for patients in the non-biologic therapy group and 9.1 years in the IFX group. The number of hospitalizations, need for narcotic analgesics, and treatment with methotrexate and azathioprine were greater at baseline for patients in the IFX group. More corticosteroids, sulfasalazine/5-ASA, and other Crohn's disease medications were used in the non-biologic therapy group at baseline. Patients placed in the IFX group initially had a higher mean Harvey-Bradshaw severity score (8.4 compared to 6.3 in the non-biologic therapy group), more infections requiring antibiotics, and/or (draining) fistulae. This indicates that patients in the IFX group had more active and severe disease at baseline compared to those on non-biologic treatment. The incidence of overall adverse events was 53.7% in the IFX group compared to 41.2% in the non-biologic therapy group and the occurrence of Crohn's disease related AEs was higher in the IFX group than in non-biologic group (12.9% *vs* 8.05%). As previously shown, the incidence of serious infections was slightly higher in the IFX group than in the non-biologic therapy group (2.8% *vs* 1.7 %). Events like congestive heart failure, malignancies, and death were observed at an event rate of less than 1 percent, and treatment with IFX was not a predictor of risk for these events. No new safety signals in those treated with IFX were presented in this interim data analysis of the 5 year ENCORE registry, long-term follow-up on approximately 2000 Crohn's Disease patients [Colombel 2008]. A 4-fold increased risk in lymphoproliferative disorders (LPD) was reported in a recent meta-analysis of IBD patients receiving thiopurines that pooled data mainly originating from tertiary centers. The main objective of the cross-sectional, nationwide French CESAME cohort was to determine prospectively the risk of LPD associated with the use of immunosuppressive therapy (IT) in IBD, at a population level. Between May 2004 and May 2005, 821 French gastroenterologists (322 and 497 in hospital and private practice, respectively) included 20,802 IBD patients (60% with CD and 40% with UC or indeterminate colitis (IC)) into the cohort. At inclusion, 35.3% of the patients were receiving an IT (thiopurines (AZA, 29.8%), and/or methotrexate (3.5%), and/or an anti-TNF agent (4.8%)), 10.0% had previously been treated with IT, and 54.7% were naïve to any IT. Investigators had to report up to December 2007 the incident cases of cancers. Only LPD with a minimal 3-month interval between the inclusion and the time of histologic diagnosis were taken into account. Clinical and histologic characteristics of LPD were reviewed for validation. LPD were considered as EBV-associated in the case of high systemic EBV viral load (by PCR) and/or presence of viral RNA or proteins in neoplastic tissues. One case of Hodgkin's disease and 16 cases of non-Hodgkin's LPD (NH-LPD) were reported. Compared with the general population, the standardized incidence ratio (SIR) of LPD was 1.86 (95% CI 1.08–2.97; p=0.03). For Hodgkin's disease and NH-LPD, respectively, SIR were 0.7 (95% CI 0.01–3.92; p=0.82) and 2.07 (1.2–3.3; p=0.01). Among the

16 cases of NH-LPD, 3 occurred in patients naïve to IT. One fatal case occurred in a patient who previously received AZA. The 12 remaining cases (5 deaths) occurred in patients receiving AZA at the time of diagnosis of NH-LPD. Among these, 11 could be tested for EBV; 7 were EBV-associated, including 1 fatal case of brain LPD, 1 fatal case of intestinal large ß-cell lymphoma, and 2 fatal cases of early post-mononucleosis LPD. These interim results of the CESAME cohort suggest an overall increased risk of LPD in IBD. The excess risk appears to be related to immunosuppressive therapy since 13 of the incident cases of LPD occurred in patients receiving AZA, with a fatal issue in almost half of the cases, and a frequent association with EBV infection [Kandiel, 2005 & Beaugerie 2008]. There is concern that anti-TNF agents may be associated with an increased risk of lymphoma: This study aimed to determine the rate of non-Hodgkin's lymphoma (NHL) in adult CD patients who have received anti-TNF therapy, and to compare this to the expected rate in the Surveillance Epidemiology & End Results (SEER) registry and to estimates from a meta-analysis of patients with IBD treated with immunomodulators. This meta-analysis included randomized controlled trials, cohort studies, or case series of consecutive adult CD patients, with a minimum median follow-up time of 48 weeks, reporting adverse effects of treatment with infliximab, adalimumab, or certolizumab pegol. Twenty-six studies involving 8843 patients were included. Ten cases of NHL were reported for a rate of 5.5 per 10,000 patient-years for anti-TNF-treated patients. Compared to the expected rate of NHL in the SEER database, the incidence rate ratio (IRR) was 2.88 (95% CI 1.19–6.50). Compared to the rate of NHL in CD patients treated with immunomodulators alone, the IRR was 1.50 (95% CI 0.43–6.57). Excluding studies with a high drop-out rate yielded a rate of lymphoma of 9.4 per 10,000 patient-years. When compared to the general population or to CD patients treated with immunomodulators alone, patients treated with anti-TNF agents were found to have an increased risk of NHL. This increased risk could be a result of the anti-TNF treatment, the severity of the underlying disease, or other factors. While the absolute event rate is low, understanding this increased risk will assist providers and patients in making decisions about anti-TNF treatment for CD [Siegel 2008]. Cohorts from European and American polls are still on-going to report incidences of adverse events but so far physicians are still moderately cautious with their use.

6. Conclusion

In general the last 10 years have seen a significant surge in new medications and options for treatment. This coincided with a parallel change in protocols and patient approach. The future management to IBD will be based on accurate risk assessment and secondary phenotypic predictions based on clinical, serologic and genetic profiling. In defining the potential therapeutic benefit of each new biologic agent, it will be important to further delineate risk profiles so that the benefits can be fairly weighed against the potential unwanted effects. Undoubtedly, the number of new strategies will continue to expand, the years ahead will be exciting for investigators and enormously promising for patients.

7. References

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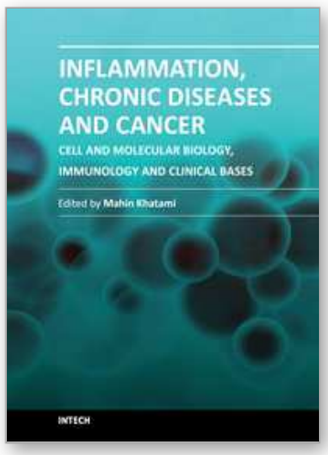

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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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