

# Literature Update Immunology

Period: 1-31.3.2010

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## **IBD**

Aliment Pharmacol Ther. 2009 Dec 29. [Epub ahead of print]

### **Clinical and economic outcomes in a population-based European cohort of 948 ulcerative colitis and Crohn's disease patients by Markov analysis.**

Odes S, Vardi H, Friger M, Esser D, Wolters F, Moum B, Waters H, Elkjaer M, Bernklev T, Tsianos E, O'Morain C, Stockbrügger R, Munkholm P, Langholz E.

**SUMMARY** Background Forecasting clinical and economic outcomes in ulcerative colitis (UC) and Crohn's disease (CD) patients is complex but necessary. Aim To determine: (1) frequency of treatment-classified clinical states, (2) probability of transition between states, (3) economic outcomes. Methods Newly diagnosed UC and CD patients, allocated into seven clinical states by medical and surgical treatments recorded in serial 3-month cycles, underwent Markov analysis. Results Over 10 years, 630 UC and 318 CD patients had 22,823 and 11,871 cycles. The most frequent clinical outcomes were medical/surgical remission (medication-free) and mild disease (on 5-aminosalicylates, antibiotics, topical corticosteroids), comprising 28% and 62% of UC cycles respectively; 24% and 51% of CD cycles. The probability of drug-response in patients receiving systemic corticosteroids/immunomodulators was 0.74 in UC, 0.66 in CD. Both diseases had similar likelihood of persistent drug-dependency or drug-refractoriness. Surgery was more probable in CD, 0.20, than UC, 0.08. Apropos economic outcomes, surgery was costlier in UC per cycle, but the outlay over 10 years was greater in CD. Drug-refractory UC and CD cases engendered high costs in the cohort. Conclusions Most patients on 5-aminosalicylates, corticosteroids and immunomodulators had favourable clinical and economic outcomes over 10 years. Drug-refractory and surgical patients exhibited greater long-term expenses.

Am J Gastroenterol. 2010 Feb;105(2):395-402. Epub 2009 Oct 27.

### **Genetic analysis in a Dutch study sample identifies more ulcerative colitis susceptibility loci and shows their additive role in disease risk.**

Festen EA, Stokkers PC, van Diemen CC, van Bodegraven AA, Boezen HM, Crusius BJ, Hommes DW, van der Woude JC, Balschun T, Verspaget HW, Schreiber S, de Jong DJ, Franke A, Dijkstra G, Wijmenga C, Weersma RK.

**OBJECTIVES:** Genetic susceptibility is known to make a major contribution to the pathogenesis of ulcerative colitis (UC). Recently, three studies, including a genome-wide association study (GWAS), reported novel UC risk loci. **METHODS:** The top-20 single-nucleotide polymorphisms (SNPs) from the first UC-GWAS were genotyped, as part of the study's replication phase, in 561 UC cases and 728 controls from our Dutch UC study sample. We genotyped eight SNPs identified in two more studies, in these individuals, and replicated all significantly associated SNPs in an additional 894 UC cases and 1,174 controls from our Dutch UC study sample. A combined analysis for all patients (n=1,455) and controls (n=1,902) was performed. Dose-response models were constructed with the associated risk alleles. **RESULTS:** We found 12 SNPs tagging ten loci, including HLA-DRA, IL10, IL23R, JAK2, S100Z, ARPC2, and ECM1, to be associated with UC. We identified 10q26, flagged by the UC-GWAS but not confirmed in its replication phase, as a UC locus and found a trend toward association for GAS7. No association with disease localization or severity was found. The dose-response models show that individuals carrying 11 or more risk alleles have an odds ratio of 8.2 (confidence interval 3.0-22.8) for UC susceptibility. **CONCLUSIONS:** We confirmed the association of multiple loci with UC in the Dutch population and found evidence for association of 10q26 and a trend suggesting association for GAS7. Genetic models show that multiple risk loci in an individual increase the risk for developing UC.

Gut. 2010 Feb;59(2):141-7.

### **Early Crohn disease: a proposed definition for use in disease-modification trials.**

Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ.

No abstract available

Journal of Crohn's and Colitis 2010; 4(1): 106-109

### **Ineffectiveness of infliximab therapy in severe infantile Crohn's disease**, 10 September 2009

Nuray Uslu, Yusuf Usta, Inci Nur Saltik-Temizel, Hulya Demir, Figen Gürakan, Hasan Ozen, Aysel Yüce

No abstract available

Gastroenterology. 2010 Feb 26.

**Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response.**

Turner D, Mack D, Leleiko N, Walters TD, Uusoue K, Leach ST, Day AS, Crandall W, Silverberg M, Markowitz J, Otley AR, Keljo D, Mamula P, Kugathasan S, Hyams J, Griffiths AM.

**BACKGROUND AND AIM::** In the first prospective study of children with severe ulcerative colitis (UC), we aimed to assess outcomes and to identify predictors of non-response to intravenous corticosteroids (IVCS). **METHODS::** 128 children (47% males; 12.9+/-3.9 years) hospitalized for severe UC were enrolled from 10 pediatric centers. Clinical and laboratory data and the Pediatric UC Activity Index (PUCAI) were recorded throughout the admission. Patients were followed for 1-year post discharge. **RESULTS::** 37 (29%; 95%CI 22-37%) children failed IVCS and received, within 10.5+/-6.4 days, cyclosporine (n=1, 3%), colectomy (n=3, 8%) or infliximab (n=33, 89%). Several predictors were associated with IVCS failure, but the best model included number of stools, amount of blood, age, and new-onset disease (OR=1.9 (95%CI 1.1-3.5), OR=2.5 (1.3-4.6), OR=1.2 (1.04-1.36), and OR=0.27 (0.1-0.7), respectively). The PUCAI, followed closely by Travis rule, strongly predicted response when compared with other measures (Seo and Lindgren indices, CRP and fecal calprotectin); P<0.001. Aiming for sensitivity on day 3, PUCAI >45 screened for patients likely to fail IVCS (NPV=94%, PPV=43%; P<0.001). Aiming for specificity on day 5, PUCAI score >70 optimally guided implementation of salvage therapy (PPV=100%, NPV=79%; P<0.001). 25 of 33 children treated with infliximab, responded. Overall cumulative colectomy rate was 9% and 19% by discharge and 1-year, respectively. The day 3 PUCAI score predicted response up to 1 year post discharge (P<0.001; time to salvage therapy). **CONCLUSIONS::** The PUCAI, calculated on days 3 and 5 of steroid therapy, can identify patients requiring salvage therapy. Infliximab is an effective therapy in steroid-refractory pediatric UC.

Am J Gastroenterol. 2010 Jan 26.

**Outcome Following Infliximab Therapy in Children With Ulcerative Colitis.**

Hyams JS, Lerer T, Griffiths A, Pfefferkorn M, Stephens M, Evans J, Otley A, Carvalho R, Mack D, Bousvaros A, Rosh J, Grossman A, Tomer G, Kay M, Crandall W, Oliva-Hemker M, Keljo D, Leleiko N, Markowitz J.

**OBJECTIVES:**Infliximab is effective in treating moderate/severe ulcerative colitis (UC) in adults. The aim of this study was to determine the outcome after treatment with infliximab in pediatric UC.**METHODS:**We performed a multicenter cohort study of 332 pediatric patients with UC enrolled in the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. Children <=16 years of age and newly diagnosed with UC are enrolled in the registry. Disease and medication information are collected prospectively from the treating physician at diagnosis, 30 days, and quarterly thereafter. No interventions were specified, per protocol.**RESULTS:**Of 332 patients, 52 (16%) received infliximab (23% <3 months from diagnosis, 38% 3-12 months, 38% >12 months). Mean age at infliximab initiation was 13.3+/-2.6 (range 6-17) years; 87% of patients had pancolitis. Median follow-up was 30 months. Continuous maintenance (CM) therapy was given in 65%, episodic in 21%, episodic converted to CM in 6%, and insufficient data in 8% of patients. Sixty-three percent of patients were corticosteroid refractory, and 35% were corticosteroid dependent. Concomitant medications at first infliximab infusion included corticosteroids (87%), thiopurines (63%), and 5-aminosalicylates (51%). Corticosteroid-free inactive disease by physician global assessment was noted in 12/44 (27%), 15/39 (38%), and 6/28 (21%) patients at 6, 12, and 24 months, respectively. Kaplan-Meier analysis showed that the likelihood of remaining colectomy free after treatment with infliximab was 75% at 6 months, 72% at 12 months, and 61% at 2 years.**CONCLUSIONS:**In this cohort of children with UC receiving infliximab, corticosteroid-free inactive disease was observed in 38 and 21% of patients at 12 and 24 months, respectively. By 24 months, 61% of patients had avoided colectomy.

Scand J Gastroenterol. 2009;44(7):774-81.

**Individual medicine in inflammatory bowel disease: monitoring bioavailability, pharmacokinetics and immunogenicity of anti-tumour necrosis factor-alpha antibodies.**

Bendtsen K, Ainsworth M, Steenholdt C, Thomsen OØ, Brynskov J.

Antibody constructs targeting tumour necrosis factor-alpha (TNF) have become important in the management of several chronic immunoinflammatory diseases. Four recombinant anti-TNF drugs are currently approved for clinical use in patients with various chronic inflammatory diseases, three of which are effective in chronic inflammatory bowel disease. These proteins can dramatically lower disease activity and, in some patients, induce remission. Unfortunately, however, not all patients respond favourably to anti-TNF antibodies. For example, patients suffering from Crohn's disease do not benefit from etanercept, and some patients treated with the other anti-TNF constructs either do not respond at all (primary response failure), or they respond initially but have later relapses (secondary response failure) despite increased dosage and/or more frequent administration of the drugs. The reason(s) for these response failures are not clear but inter-individual and even intra-individual differences in bioavailability and pharmacokinetics may contribute. Furthermore, immunogenicity of the drugs, causing patients to develop anti-drug antibodies (ADAs), contributes to treatment failure. Monitoring patients for circulating levels of functional anti-TNF drugs and ADAs is therefore warranted so that treatment can be tailored to the individual patient (individual medicine or personal medicine) in order that effective and economical long-term therapy can be given with minimal risks to the patients.

Int J Colorectal Dis. 2010 Mar;25(3):401-4.

**Preoperative infliximab treatment in patients with ulcerative and indeterminate colitis does not increase rate of conversion to emergent and multistep abdominal surgery.**

Bordeianou L, Kunitake H, Shellito P, Hodin R.

**INTRODUCTION:** A recent study has raised concerns that infliximab treatment, by postponing surgery for ulcerative and indeterminate colitis patients, may result in a greater need for high-risk emergent or multistep surgical procedures (subtotal colectomies). Our aim was to assess whether infliximab exposure affects rates of subtotal colectomy in a large cohort of patients. **METHODS:** We evaluated 171 consecutive patients with ulcerative or indeterminate colitis who had a total proctocolectomy or a subtotal colectomy between 1993 and 2006 for symptoms of unremitting disease. Forty-four patients (25.7%) received infliximab prior to surgery. We compared the surgical procedures employed on these 44 patients to the surgical procedures employed on the 127 non-infliximab patients, using Fisher's exact or Student's t test. **RESULTS:** Infliximab exposure did not appear to affect the rate of emergent surgery (4.5% vs 4.4%,  $p = 0.98$ ), rate of subtotal colectomy (19.2% vs. 18.0%,  $p = 0.99$ ), or rate of ileoanal J pouch reconstruction (53.8% vs. 62%,  $p = 0.98$ ). Nor did it affect intraoperative findings of perforation, toxic megacolon, and active disease. The infliximab and non-infliximab cohorts were similar in age, Charlson Comorbidity Index, concomitant steroid use, and albumin levels, although infliximab patients had higher rates of concomitant exposure to 6-mercaptopurine (34.1% vs 16.6%,  $p = 0.02$ ) and azathioprine (40.9% vs 22.6%,  $p = 0.02$ ). **CONCLUSION:** Infliximab does not appear to increase rates of emergent surgery or multistep procedures in patients undergoing treatment for ulcerative or indeterminate colitis at our institution.

Nat Rev Gastroenterol Hepatol. 2010 Feb;7(2):86-92.

**Top-down therapy for IBD: rationale and requisite evidence.**

D'Haens GR.

Several trials have shown that early treatment of Crohn's disease with immunomodulators and anti-TNF agents leads to a superior clinical outcome, including healing of the mucosa, compared with standard therapy alone. Mounting evidence indicates that mucosal healing is associated with a reduced risk of complications, and a reduced need for surgeries and hospitalizations. In the SONIC trial, a combination of the standard azathioprine immunomodulator therapy and infliximab, an anti-TNF agent, had more potent anti-inflammatory effects than either drug alone in patients with Crohn's disease who had evidence of active inflammation. These findings and those from rheumatoid arthritis trials have prompted the investigation of early initiation of immunomodulator (standard or anti-TNF) therapy for Crohn's disease, in suitable patients, which has led to substantial improvements in disease management. Careful selection of patients is, however, essential given the potential risk of toxic effects from these therapies and the fact that some patients with IBD will have a favorable disease course without them. Identification of suitable patients, however, remains a challenge, as genetic, phenotypic and environmental factors have not yet been identified that can be used for routine assessment and selection is mainly based on clinical criteria.

Nat Rev Gastroenterol Hepatol. 2010 Feb;7(2):110-7.

**Future biologic targets for IBD: potentials and pitfalls.**

Melmed GY, Targan SR.

The treatment of patients with IBD has evolved towards biologic therapy, which seeks to target specific immune and biochemical abnormalities at the molecular and cellular level. Multiple genes have been associated with susceptibility to IBD, and many of these can be linked to alterations in immune pathways. These immune pathways provide avenues for understanding the pathogenesis of IBD and suggest future drug targets, such as the IL-12-IL-23 pathway. In addition, failed therapeutic drug trials can provide valuable information about pitfalls in study design, drug delivery and disease activity assessment. Future biologic drug development will benefit from the early identification of subsets of patients who are most likely to respond to therapy by use of biological markers of genetic susceptibility or immunologic susceptibility.

Drugs. 2010;70(2):109-20.

**Optimizing the use of tumour necrosis factor inhibitors in Crohn's disease: a practical approach.**

Etchevers MJ, Ordás I, Ricart E.

Crohn's disease is a chronic, disabling, inflammatory condition of the gastrointestinal tract that has a segmental distribution and can affect the entire gastrointestinal tract. Treatment of patients with Crohn's disease represents a difficult challenge to physicians. Conventional therapy includes corticosteroids and immunosuppressants. Corticosteroids are highly effective for inducing response and remission, but the results in the long-term are disappointing and are associated with serious adverse events. Immunosuppressants are effective, but have a slow onset of action and are associated with intolerance and adverse events. In the last decade, as a result of a better understanding of the immunopathology of inflammatory bowel disease, novel therapeutic agents have been developed to target crucial components of the inflammatory cascade. Tumour necrosis factor (TNF) inhibitors (infliximab, adalimumab and certolizumab pegol) offer an effective alternative therapy, and are widely used in clinical practice for the management of Crohn's disease and ulcerative colitis. This article focuses on the latest evidence-based data on clinical effectiveness, mucosal healing, immunogenicity, dose optimization for induction and maintenance of response and remission, and step-up versus top-down approaches of the available TNF inhibitors for the treatment of Crohn's disease.

Med Sci Monit. 2010 Feb;16(2):P11-6.

**Early onset steroid-dependent ulcerative colitis is a predictor of Azathioprine response: a longitudinal 12-month follow-up study.**

Chebli LA, Felga GG, Chaves LD, Pimentel FF, Guerra DM, Gaburri PD, Zanini A, Chebli JM.

**BACKGROUND:** Studies assessing the efficacy of azathioprine (AZA) in steroid-dependent ulcerative colitis (UC) are scarce. The aim of this study was to assess the long-term efficacy and safety of AZA in patients with steroid-dependent UC, as well as factors associated with sustained response. **MATERIAL/METHODS:** In this prospective observational study 46 adult subjects with steroid-dependent UC were included for AZA therapy during a 12-month period. AZA dosage was adjusted according to clinical response and occurrence of adverse events. Steroid therapy was tapered according to protocol. The primary endpoint was the rate of steroid-free remission to AZA at the end of 12 months. Secondary endpoints included clinical relapse, cumulative steroid dose and safety of treatment. **RESULTS:** On an intention-to-treat basis, the proportion of patients remaining in steroid-free remission at the end of 12 months was 0.54. The median time until complete steroid withdrawal was 5 months. A significant decrease in the relapse rate and in requirement for steroids were observed during 12 months on AZA compared with the prior year ( $P=0.000$ ). Demographic, dose of AZA, steroid use, and disease-related data did not correlate with remission. Only disease duration <24 months was associated to steroid-free remission ( $P=0.03$ , OR 3.60 95% CI 1.95-9.74). Serious adverse events related to AZA were uncommon. **CONCLUSIONS:** AZA demonstrated sustained efficacy for maintenance of clinical remission without steroids and steroid sparing through 12 months of therapy in steroid-dependent UC. Patients with early onset UC are those who most probably will achieve sustained steroid-free remission while on AZA.

Clin Ther. 2010 Feb;32(2):238-245.

**Self-reported frequency and severity of disease flares, disease perception, and flare treatments in patients with ulcerative colitis: Results of a national internet-based survey.**

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Bolge SC, Waters H, Piech CT.

**Objectives:** The purpose of this study was to better understand the characteristics and patterns of treatment of flares of ulcerative colitis (UC) from the patient's perspective. A secondary objective was to determine the predictive value of disease characteristics, particularly disease flares, on current use of biologic therapy. **Methods:** Study participants were recruited from an Internet panel of self-identified individuals with inflammatory bowel disease (UC or Crohn's disease). The present analysis was limited to individuals who reported having a diagnosis of UC, were aged  $\geq 18$  years, resided in the United States, and could speak and write English. Cross-sectional data (demographic characteristics, insurance coverage, incidence of flares, patient experiences, treatment patterns) were collected via a self-reported Internet-based questionnaire during the third quarter of 2008. **Results:** A total of 505 individuals with UC completed the survey (72.7% female; 16.6% non-white; 37.2% college graduates; mean [SD] age, 48.6 [2.8] years). The mean time since the diagnosis of UC was 11.9 (10.1) years, and 76.6% of respondents characterized their disease as controlled. Overall, 27.9% of the sample reported  $\geq 1$  flare per week, and an additional 25.1% reported  $\geq 1$  flare per month. Most disease flares (76.5%) lasted  $\leq 7$  days and were classified as moderate in severity (51.9%). Among those reporting  $\geq 1$  flare per week, 30.5% classified their overall disease severity as mild, 56.0% as moderate, and 13.5% as severe. The majority of respondents with  $\geq 1$  flare per week currently used 5-aminosalicylic acids (5-ASAs) (41.1%) or corticosteroids (49.6%), whereas 19.1% used immunomodulators and 17.0% used biologics. Disease flares were most commonly treated by increasing the dose of the current medication (60.4%) or adding a corticosteroid to the treatment regimen (34.5%). **Conclusions:** More than half of these individuals with UC reported experiencing disease flares  $\geq 1$  time per week or month. The majority reported using 5-ASAs or corticosteroids as maintenance medications and increasing the dose or adding corticosteroids to control flares in the short term.

Expert Rev Gastroenterol Hepatol. 2010 Feb;4(1):81-9.

**Joint involvement in inflammatory bowel disease: managing inflammation outside the digestive system.**

De Vos M.

Joint inflammation is present in approximately 30% of patients with inflammatory bowel disease. Peripheral arthritis can frequently be controlled by an optimal treatment of the gut inflammation in association with short-term use of NSAIDs. Recurrent inflammation requires the use of sulfasalazine. More therapy-resistant forms and axial arthropathy can be treated with anti-TNF drugs, predominantly infliximab and adalimumab. An intensified multidisciplinary approach in research and in the clinic may help to unravel the question of why common etiopathogenic mechanisms ultimately lead to different disease phenotypes. Animal models may help to identify the most promising therapeutic strategies including in the near future modulation of adhesion molecules, costimulatory molecules and the Th17 pathway.

Current Drug Targets 2010; 11(2): 136-7

**Editorial: Hot topic: Anti TNF- $\alpha$  Treatment for Crohn's Disease: "Menage A Trois"**

Danese S

No abstract available.

Curr Drug Targets. 2010 Feb 1;11(2):138-42.

**Efficacy of anti-TNF in Crohn's Disease: How Does it Work?**

Chowers Y, Allez M.

Several TNF antagonists, mainly monoclonal antibodies, have shown to be efficacious in the therapy of Crohn's disease. Despite the fact that they have been used for over a decade, their precise mechanism of action is still a matter of investigation. The effects of anti-TNF agents are mediated by multiple mechanisms including direct neutralization of soluble TNF and interaction with membrane-bound TNF. Anti-TNF agents may act by reduction of proinflammatory cytokine levels, elimination or clearance of active inflammatory cells from inflamed tissue which can conceptually be achieved by a number of mechanisms including apoptosis induction, antibody and complement mediated cytotoxicity and inhibition of cell migration into the intestinal tissue. Regulatory events both in the cellular and intracellular levels

probably play a role as well. Finally, effects of anti-TNF agents may vary according to their physical contact with TNF leading to different binding avidities, conformational changes and variable downstream effects. These effects may also be influenced by structural differences in the non-TNF binding domain which affects the ability of each drug to interact with the immune system. Our understanding of these mechanisms of action is limited by the fact that much of the data was obtained using artificial in vitro systems of which their relevance to the in vivo situation is uncertain.

Curr Drug Targets. 2010 Feb 1;11(2):143-7.

**Anti-TNF and Crohn's Disease: When Should We Start?**

Fidder HH, Hommes DW.

The natural course of Crohn's disease is characterized by the progression from primarily inflammatory disease to a complicated stricturing or penetrating disease. This irreversible complications lead to repeated surgery and considerable disability. It may therefore be argued that a window of opportunity for intensive treatment exists early in the disease course. Healing of the mucosa has been shown to be a strong predictor of improved outcome of Crohn's disease on the long-term, in terms disease control, hospitalizations, and surgery. Anti-tumor necrosis factor (TNF)-alpha therapy has shown to be a strong inducer of mucosal healing and it may be argued that early treatment with anti-TNF's and/or immunomodulators may be the preferable approach in selected patients. The main concern with such strategies is safety, especially the risk of lymphoma's and infections. This paper aims to review the existing data regarding the benefits and disadvantages of inverting the classic step up therapeutic paradigm.

Curr Drug Targets. 2010 Feb 1;11(2):148-51.

**Anti-TNF and Crohn's Disease: When Should We Stop?**

Louis E, Belaiche J, Reenaers C.

When to stop anti-TNF therapy in Crohn's disease (CD)? This is a very important question both for patients and physicians. There is no published evidence to clearly and definitely answer this question. However data on natural history of CD, long term safety of biologics, outcome after immunosuppressors (IS) cessation and some preliminary studies on biologics cessation may help us to discuss this topic. One could argue that there is currently no good reason to stop anti-TNF therapy in a patient who is in stable remission and tolerate this drug very well. The decision to stop an anti-TNF treatment is thus currently based on a compromise between the benefits/risks and cost of such long term treatment. While it appears now clearly that prolonged anti-TNF therapy is associated with favourable outcome with sustained remission, reduced surgeries and hospitalisation as well as absence of significant increase in mortality or cancers, the cost-effectiveness which is probably favourable for short and mid-term treatment (up to one year), may be less optimal for very long term treatment. In this perspective however, prospective studies should be performed to adequately assess long term evolution, disease outcome, safety and global cost of strategies based on treatment reduction with IS maintenance alone or even full treatment cessation.

Curr Drug Targets. 2010 Feb 1;11(2):152-5.

**How to Manage Loss of Response to Anti-TNF in Crohn's Disease?**

Reinisch W.

Despite the fact that anti-TNF alpha antibodies are well-tolerated and highly effective in Crohn's disease 25% to 40% of patients who initially benefited from treatment are developing intolerable adverse events or are losing their response during maintenance therapy. The molecular mechanisms of loss of response are not fully understood, but clinician face this clinical problem. The aim of this paper is to review the clinical strategies to face anti-TNF alpha antibodies in Crohn' disease.

Curr Drug Targets. 2010 Feb 1;11(2):156-75.

**Efficacy of TNF Antagonists Beyond One Year in Adult and Pediatric Inflammatory Bowel Diseases: A Systematic Review.**

Oussalah A, Danese S, Peyrin-Biroulet L.

The introduction in the mid-1990s of tumor necrosis factor (TNF) antagonists changed the treatment of inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis (UC) refractory to conventional medications (corticosteroids, immunomodulators). This review summarizes current data on the long-term efficacy and safety of anti-TNF therapy in IBD beyond 1 year. We searched Medline, the Cochrane Library, Embase, and Ovid Medliner for relevant studies. Infliximab, adalimumab and certolizumab are effective in maintaining clinical remission in luminal Crohn's disease. Infliximab and adalimumab are also effective in maintaining long-term fistula closure in Crohn's disease. Only infliximab has been evaluated in UC in the long term, with similar data on its effectiveness than in CD. In addition to the maintenance of clinical remission, TNF antagonists have the ability to maintain long-term mucosal healing, resulting in a reduced risk of surgery. With 2010 on the horizon, we have no good reasons to stop anti-TNF therapy in IBD patients because of its efficacy in maintaining remission and a risk-benefit ratio that remains in its favor. It is now clear that patients in deep remission, comprising clinical, biological, and endoscopic remission, are at lower risk of relapse after withdrawal of anti-TNF therapy.

Curr Drug Targets. 2010 Feb 1;11(2):176-8.

#### **Concomitant Use of Immunomodulators with Anti-TNF in Crohn's Disease: Yes or No?**

Meier J, Sturm A.

Today up to 40% of Crohn's disease patients receive a concomitant therapy of TNF blockers in combination with thiopurines or methotrexate. Although data of prospective controlled trials are rare, some recently published studies indicate a more rapid onset of remission and increased mucosal healing following concomitant therapy in short term. However, data confirming the need or benefit of concomitant immunosuppressive therapy once remission has been reached remains unknown. Concomitant therapy lowers TNF-alpha induced immunogenicity, but the question of whether ATI formation also lowers the efficiency of TNF-alpha antagonists has not yet been answered to a level that would justify the use of concomitant immunosuppression. Knowing that immunosuppression increases the risk for opportunistic infections and lymphomas the potential risks and of concomitant therapy must be well balanced against the benefit. This article aims to interpret the available data on the efficiency, immunogenicity, and safety of concomitant therapy in patients under anti-TNF therapy.

Curr Drug Targets. 2010 Feb 1;11(2):219-26.

#### **Anti-TNF's for Postoperative Recurrence in Crohn's Disease: The If's and How's.**

Sorrentino D, Paviotti A, Fiorino G.

Recurrence of Crohn's disease (CD) is extremely frequent after surgery and its prevention remains a fundamental problem in the medical management of these patients. As of today, none of the medications traditionally used to treat the spontaneous disease (i.e. mesalamine, steroids, immunosuppressives and antibiotics) has shown a clear benefit. Recent data, coming from our center and from a small RCT do indicate that infliximab is extremely effective in preventing this complication in the large majority of patients. While additional, larger studies may be desirable, the strength and consistency of the available data suggest that future trials may merely confirm these observations. A number of issues however remain to be solved and include the long term strategy in patients treated for years with infliximab, whether treating early endoscopic lesions may be as effective as preventing them and whether immunosuppressives should be used together with infliximab. A thorough understanding of the mechanisms by which infliximab appears so effective in the postoperative setting may provide us with essential information regarding patients' management and, ultimately, highlight the molecular mechanisms at the very basis of Crohn's disease.

Curr Drug Targets. 2010 Feb 1;11(2):227-33.

#### **Mucosal Healing and Anti TNFs in IBD.**

van Assche G, Vermeire S, Rutgeerts P.

Mucosal healing has been incorporated in the assessment of treatment efficacy in ulcerative colitis, but in Crohn's disease this concept has only emerged after biological therapies have been evaluated in clinical trials. Systemic steroids don't induce mucosal healing in Crohn's disease, but purine analogues and anti TNF agents have a potential to heal mucosal ulcerations. Evidence for mucosal healing has now been provided for the anti TNF agents infliximab, adalimumab and certolizumab. For infliximab mucosal healing is associated with a reduction in hospitalizations and surgeries. On the contrary, the benefit of treating

patients with IBD more intensively until they achieve mucosal healing has not been proven. In clinical practice assessing mucosal healing should be considered in patients with persistent symptoms despite adequate therapy and when treatment discontinuation is being considered.

Curr Drug Targets. 2010 Feb 1;11(2):249-60.

**Emerging Biologics in the Treatment of Inflammatory Bowel Disease: What is Around the Corner?**

Fiorino G, Rovida S, Correale C, Malesci A, Danese S.

Inflammatory bowel diseases (IBD) are idiopathic chronic inflammations: the etiology of Crohn's disease (CD) and ulcerative colitis (UC) is still largely unknown. Environmental and genetic factors in combination with the microbial flora or specific microorganisms trigger an event, leading to the activation of an intestinal immune response. Immune and non-immune cells create a cross talk via the secretion of soluble mediators and expression of cell adhesion molecules, resulting in further cell activation. Mediators such as cytokines and chemokines play a role in cell recruitment and polarization, intercellular signal amplification or activation and differentiation. Considering these aspects, medical management of inflammatory bowel disease has changed considerably over the past decade. Advances in biotechnology has allowed for the introduction of many biologic therapies, other than anti-TNF therapies. Many of these drugs showed clinical benefit for induction and maintenance therapy, both in UC and CD. Although numerous, at present only monoclonal anti-TNF antibodies are currently available worldwide. Other biological agents have been tested or are under evaluation. This paper systematically reviews the mechanism-of-action, efficacy, short-term and, where available, long-term safety of biological agents that have been approved for the treatment of IBD or are under evaluation which target different molecules other than tumor necrosis factor alpha (TNF-alpha).

Inflamm Bowel Dis. 2010 Apr;16(4):620-9.

**Prospective randomized open-label multicenter phase I/II dose escalation trial of visilizumab (HuM291) in severe steroid-refractory ulcerative colitis.**

Baumgart DC, Targan SR, Dignass AU, Mayer L, van Assche G, Hommes DW, Hanauer SB, Mahadevan U, Reinisch W, Plevy SE, Salzberg BA, Buchman AL, Mechkov GM, Krastev ZA, Lowder JN, Frankel MB, Sandborn WJ.

**BACKGROUND:** Visilizumab is a humanized IgG(2) monoclonal anti-CD3 antibody. We evaluated its safety and dose response in severe intravenous steroid-refractory ulcerative colitis (UC). **METHODS:** In all, 104 patients were treated. In Stage I, 73 patients were randomly assigned to receive intravenous visilizumab 5, 7.5, 10, or 12.5 microg/kg/day for 2 consecutive days. In Stage II, 33 patients received visilizumab at the optimal clinical dose (OCD) of 5 microg/kg/day for 2 days. Symptomatic response and remission were defined by the modified Truelove-Witts severity index. Clinical response and remission were defined by the Mayo score. **RESULTS:** The rates of symptomatic response at day 15 in the 5, 7.5, 10, or 12.5 microg/kg dose groups were 71%, 70%, 50%, and 61%, respectively, in Stage I and in 54% in Stage II. The symptomatic remission rates were 35%, 5%, 22%, and 11% in Stage I and 18% in Stage II. The rates of clinical response at day 30 in the 5, 7.5, 10, or 12.5 microg/kg dose groups were 71%, 65%, 50%, and 67%, respectively, in Stage I and 55% in Stage II. The clinical remission rates were 6%, 5%, 0%, and 11% in Stage I and 6% in Stage II. All patients experienced adverse events. Serious adverse events included abdominal abscess, cytomegalovirus infection, atrial fibrillation, herpes zoster, and esophageal candidiasis. **CONCLUSIONS:** Treatment with visilizumab induced symptomatic response and clinical response. Results with 5 microg/kg/day were similar to those observed with higher doses.

Inflamm Bowel Dis. 2010 Apr;16(4):645-50.

**A new tool to measure the burden of Crohn's disease and its treatment: do patient and physician perceptions match?**

Wilcox AR, Dragnev MC, Darcey CJ, Siegel CA.

**BACKGROUND:** Health-related quality of life (HRQOL) is difficult to efficiently measure in the clinic setting. Our aim was to develop and test a simple tool to measure the burden of Crohn's disease (CD) and its treatment and to compare how patients and their physicians perceive the impact of CD on HRQOL. **METHODS:** A cross-sectional, self-administered questionnaire was distributed to patients with CD. The questionnaire included a feeling thermometer to measure disease and treatment burden, which was compared to the Short Inflammatory Bowel Disease Questionnaire (SIBDQ). At that visit, the

patient's physician completed a questionnaire containing the feeling thermometer and the Harvey Bradshaw index (HBI). Nonparametric tests were used to report results. RESULTS: In all, 113 surveys were completed. The median age of respondents was 40 years and 68% were female. Using the feeling thermometer (scale 0-100), patients reported their current health as a median of 70 (interquartile range [IQR] 50-80) and their disease specific burden as 20 (IQR 10-40). Treatment-specific burden was 6.9 (IQR 1.3-20). Physicians perceived their patients' current health as a median of 71.3 (IQR 57.5-90) with a disease burden of 12.5 (IQR 5-30). Spearman's rho between the burden of symptoms measured by the feeling thermometer and the SIBDQ was -0.71. The correlation between patient and physician perception of current health was 0.73. CONCLUSIONS: Two questions using the feeling thermometer provide a quick and accurate assessment of the burden of CD on patients. Physicians' perception of the burden of disease was similar to their patients.

Inflamm Bowel Dis. 2010 Apr;16(4):651-6.

**Assessing disease activity in ulcerative colitis: patients or their physicians?**

Turner D, Griffiths AM, Mack D, Otley AR, Seow CH, Steinhart AH, Silverberg MS, Hyams J, Guyatt GH.

BACKGROUND: We aimed to determine the optimal approach to assess disease activity (i.e., biological inflammation) in ulcerative colitis (UC) by comparing patients' and physicians' rating of the disease. METHODS: This was a prospective, multicenter, double-cohort study. The first cohort was composed of 94 children with UC (parent proxy when required) and their physicians who provided independent clinical report and global assessment of disease, rated on a 100 mm visual analog scale. Constructs of disease activity (including mucosal inflammation, laboratory tests, Mayo score, and the Pediatric UC Activity Index), were scored by an independent blinded physician and used to compare validity of the assessment. Of the 94 children, 43 were seen at a follow-up visit and provided a global rating of change in disease activity. To ascertain whether age influences assessment accuracy, a second cohort of 86 adult UC patients were analyzed in a similar way. RESULTS: In both cohorts the physician global assessment had higher correlations with all constructs of disease activity than did the patient' global assessment (for colonoscopic score  $r = 0.76$  vs.  $r = 0.29$ ,  $P = 0.002$ ). Even with abdominal pain, a subjective item, the physician's rating had higher correlation than the patient's rating. Similarly, the physician rating of change better reflected change in disease activity than that of the patient rating. CONCLUSIONS: For indirect measurement of biological activity on the basis of symptoms and signs, clinician assessments are superior to those of patients. Patient assessments, physician assessments, and direct measurement of disease activity provide complementary information in clinical research.

Inflamm Bowel Dis. 2010 Apr; 16(4):714-5.

**Body mass index and disease activity at treatment initiation: potential new predictors of response to azathioprine therapy in IBD.**

Sokol H, Beaugerie L.

No abstract available

Dig Dis Sci. 2010 Mar;55(3):747-53. Epub 2009 Mar 31.

**Adalimumab treatment in children with refractory Crohn's disease.**

Rosenbach Y, Hartman C, Shapiro R, Hirsch A, Avitzur Y, Shamir R.

Information on safety and efficacy of adalimumab in children with Crohn's disease (CD) is limited. We present a case-series of 14 children with severe CD treated with adalimumab during a 3.5-year period. Fourteen children (nine boys, five girls), aged 13.9 years (range 1.9-19.1) were treated with adalimumab during 12.5 months (range 7-42). All had steroid or immunosuppression-drugs refractory disease. Ten patients (71%) had been previously treated with infliximab, 13/14 were treated with different immunosuppressive drugs and all were steroid-dependent or resistant. Seven children (50%) showed full clinical response and 5/14 (35%) improved partially. Two children (15%) had loss of response after a period of transient improvement. Adalimumab treatment enabled complete steroids withdrawal in 8/14 (57%) of steroid-dependent children. Currently, five children are in complete remission with adalimumab monotherapy for a median 14 months (range 9-24). Adalimumab may induce and maintain remission in children with severe, refractory CD. Prospective safety and efficacy confirmation of this data in children is necessary.

Current Drug Targets 2010; 11: 187-197

**Anti-TNF and Fistulising Perianal Crohn's Disease: Use in Clinical Practice**

Bourikas, Leonidas A.; Koutroubakis, Ioannis E.

No abstract available

Nat Genet. 2010 Apr;42(4):292-4. Epub 2010 Mar 14.

**Genome-wide association study for ulcerative colitis identifies risk loci at 7q22 and 22q13 (IL17REL).**

Franke A, Balschun T, Sina C, Ellinghaus D, Häsler R, Mayr G, Albrecht M, Wittig M, Buchert E, Nikolaus S, Gieger C, Wichmann HE, Sventoraityte J, Kupcinskis L, Onnie CM, Gazouli M, Anagnou NP, Strachan D, McArdle WL, Mathew CG, Rutgeerts P, Vermeire S, Vatn MH; and the IBSEN study group, Krawczak M, Rosenstiel P, Karlsen TH, Schreiber S.

We performed a genome-wide association analysis of 1,897,764 SNPs in 1,043 German ulcerative colitis (UC) cases and 1,703 controls. We discovered new associations at chromosome 7q22 (rs7809799) and at chromosome 22q13 in IL17REL (rs5771069) and confirmed these associations in six replication panels (2,539 UC cases and 5,428 controls) from different regions of Europe (overall study sample  $P(\text{rs7809799}) = 8.81 \times 10^{-11}$  and  $P(\text{rs5771069}) = 4.21 \times 10^{-8}$ , respectively).

J Gastroenterol. 2010;45(1):24-9. Epub 2009 Oct 2.

**Prospective clinical trial: enteral nutrition during maintenance infliximab in Crohn's disease.**

Yamamoto T, Nakahigashi M, Umegae S, Matsumoto K.

**PURPOSE:** Hitherto, the efficacy of enteral nutrition (EN) on clinical outcomes during biological maintenance therapy in Crohn's disease (CD) has not been investigated. This prospective study was to assess the efficacy of EN on the maintenance rate of clinical remission in patients with quiescent CD receiving infliximab as maintenance therapy. **METHODS:** Fifty-six patients who achieved clinical remission with infliximab induction therapy received infliximab as maintenance therapy (5 mg/kg, every 8 weeks). Thirty-two of the 56 patients received concomitant EN: elemental diet infusion during night-time and a low fat diet during daytime (EN group), while the remaining 24 patients received neither nutritional therapy nor food restriction (non-EN group). All patients were followed for 56 weeks; CD activity index (CDAI) was assessed and  $\text{CDAI} < 150$  was defined as clinical remission. **RESULTS:** During the 56-week observation, the mean CDAI was not significantly different between the 2 groups. Seven patients in the EN group ceased EN therapy because they maintained complete remission. On an intention-to-treat basis, 25 patients in the EN group (78%) and 16 patients in the non-EN group (67%) remained in clinical remission during the 56-week observation ( $P = 0.51$ ). **CONCLUSIONS:** The outcomes of this prospective study showed that concomitant EN during infliximab maintenance therapy does not significantly increase the maintenance rate of clinical remission in patients with CD.

## **Safety**

J Infect. 2010 Feb 19. [Epub ahead of print]

**Listeria Endocarditis In A Patient With Psoriatic Arthritis On Infliximab: Are Biologic Agents As Treatment For Inflammatory Arthritis Increasing The Incidence Of Listeria Infections?**

Kelesidis T, Salhotra A, Fleisher J, Uslan DZ.

The use of anti-tumor necrosis factor agents such as infliximab as treatment modalities of inflammatory joint diseases has widely spread over the past few years. However, increasing numbers of reports of infectious complications during TNF- $\alpha$  blockade have also highlighted the fact that an increased rate of sometimes life-threatening complications may be the price paid for superior therapeutic efficacy. We report the first case report of Listeria endocarditis associated with infliximab use and the second published case of Listeria infection associated with infliximab in patients with psoriatic arthritis. We also summarize the literature regarding the association of Listeria infection with use of infliximab. Further studies are needed to elucidate the contribution of anti-TNF- $\alpha$  therapy to development of listeriosis. Physicians should be aware of the possibility of Listeria infection in individuals receiving anti-TNF therapy.

Joint Bone Spine. 2010 Feb 18. [Epub ahead of print]

**Safety of rituximab in rheumatoid arthritis patients with a history of severe or recurrent bacterial infection: Observational study of 30 cases in everyday practice.**

Toussiro E, Pertuiset E, Sordet C, Augé B, Wendling D, Pallot-Pradès B, Collet P, Lohse A, Balblanc JC.

**OBJECTIVES:** To report our experience with rituximab therapy in patients with rheumatoid arthritis (RA) and a history of severe or recurrent bacterial infections. **PATIENTS AND METHODS:** Retrospective observational study in five rheumatology departments experienced in the use of biotherapies. Patients were included if they had RA and a history of severe or recurrent bacterial infection (requiring admission and/or intravenous antimicrobial therapy) that contraindicated the introduction or continuation of TNFalpha antagonist therapy. **RESULTS:** Of 161 RA patients given rituximab in the five study centers, 30 met the inclusion criteria, 23 females and seven males with a mean age of 58.4+/-11.8 years and a mean disease duration of 11.4+/-13.9 years. Among them, 22 had rheumatoid factors and 21 had received TNFalpha antagonist therapy (one agent in 15 patients, two in five patients and three in one patient). Prior infections were as follows: septicemia, n=2; lower respiratory tract infection or lung abscess, n=12; prosthesis infection, n=3; septic arthritis, n=3; endocarditis, n=1; pyelonephritis, n=2; osteitis, n=4; and various skin infections (erysipelas, cellulitis or skin abscess), n=6. Of these 33 infections, 21 occurred during TNFalpha antagonist therapy. During rituximab therapy, all patients received concomitant glucocorticoid therapy (mean dosage, 12+/-7.9mg/day). The number of rituximab cycles was one in 13 patients, two in seven patients and three or more in 10 patients. Mean time from the single or last serious infection and the first rituximab infusion was 20.1+/-18.7 months. Mean follow-up since the first rituximab infusion was 19.3+/-7.4 months. During follow-up, six (20%) patients experienced one infection each. Immunoglobulin levels after rituximab therapy were within the normal range. **CONCLUSION:** Rituximab therapy was well tolerated in 24 (80%) of 30 patients with RA and a history of severe or recurrent bacterial infection. In everyday practice, rituximab therapy seems safe with regard to the recurrence of infectious episodes. However, longer follow-ups are needed.

Biologics. 2010 Feb 4;4:1-4.

**Safety of etanercept in elderly subjects with rheumatoid arthritis.**

Lurati A, Marrazza M, Angela K, Scarpellini M.

**OBJECTIVE:** To report side effects seen in a clinical cohort of patients aged >65 years with rheumatoid arthritis (RA) treated with the tumor necrosis factor-alpha TNF-alpha blocker etanercept and to compare the side effects rate with patients aged <=65 years. **METHODS:** All patients with RA that started etanercept and who were referred to our rheumatology unit from November 2005 to March 2009 were included in this study and prospectively followed to collect side effects related to therapy. **RESULTS:** ONE HUNDRED THREE PATIENTS WERE ENROLLED: 41 (37 females, 4 males) aged >65 years and 62 (40 females, 22 males) aged <65 years. In the patients aged >65 years, the safety profile (defined as rate of side effects) of etanercept was similar to that in patients aged <=65 years (P > 0.05) and the survival curves between the groups were similar (P > 0.05). **CONCLUSIONS:** In our three-year experience, the anti-TNFalpha agent etanercept has been well tolerated and safe in elderly patients. The risk of side effects in these patients was no greater than in subjects aged <=65 years. However, such inhibitors are associated with various and numerous side effects and elderly patients with RA should be carefully monitored to limit the risk of side effects during anti-TNFalpha therapy as much as possible.

Nat Rev Rheumatol. 2010 Mar;6(3):165-74. Epub 2010 Feb 9.

**Tumor necrosis factor blockade and the risk of viral infection.**

Kim SY, Solomon DH.

Tumor necrosis factor (TNF) blockers are widely used to treat rheumatoid arthritis and other chronic inflammatory diseases. Many studies have demonstrated an increased risk of opportunistic infections such as tuberculosis and fungal infection in patients treated with TNF blockers, which is thought to be related to the primary role of TNF both in host defense and in the immune response. Little is known, however, about the association between TNF blockade and the development of viral infection. Owing to the critical role of TNF in the control of viral infection, depletion of this cytokine with TNF blockers could facilitate the development or reactivation of viral infection. A number of large observational studies have found an increased risk of herpes zoster in patients receiving TNF blockers for the treatment of rheumatoid arthritis. This Review draws attention to the risk of several viral infections, including HIV,

varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and human papillomavirus, in patients receiving TNF-blocking therapy for chronic inflammatory conditions. In addition, implications for clinical practice and possible preventative approaches are discussed.

Nat Rev Rheumatol. 2010 Mar;6(3):126-7.

**Therapy: Assessing cancer risk of cytokine inhibitors in RA.**

Strangfeld A, Zink A.

No abstract available

J Rheumatol. 2010 Mar;37(3):558-67. Epub 2010 Jan 28.

**Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials.**

van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann R, Furst DE, Macey K, Sweetser M, Kelman A, Rao R.

**OBJECTIVE:** To evaluate the longterm safety of rituximab in clinical trials in patients with rheumatoid arthritis (RA). **METHODS:** Pooled analysis of safety data, including adverse events (AE) and infections, from patients treated with rituximab in combination with methotrexate in a global clinical trial program. **RESULTS:** A total of 2578 patients with RA received at least 1 course of rituximab. Safety analyses were based on 5013 patient-years of rituximab exposure. The most frequent AE was infusion-related reactions (25% of patients during the first infusion of Course 1). Less than 1% of infusion-related reactions were considered serious. Rates of AE and serious AE (SAE; 17.85 events/100 patient-yrs, 95% CI 16.72, 19.06) were stable following each course. The overall serious infection rate was 4.31/100 patient-years (95% CI 3.77, 4.92). Infections and serious infections over time remained stable across 5 courses at 4-6 events/100 patient-years. Compared with other patients with RA and with the general US population, there was no increased risk of malignancy. **CONCLUSION:** In this longterm safety update in RA clinical trial patients, rituximab remained well tolerated over multiple courses. SAE and infections remained stable over time and by treatment course.

Clin Gastroenterol Hepatol. 2010 Mar;8(3):268-274.

**Increased Risk for Non-Melanoma Skin Cancer in Patients With Inflammatory Bowel Disease.**

Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD.

**BACKGROUND & AIMS:** Patients with inflammatory bowel disease (IBD) might be at increased risk for certain malignancies. We evaluated the risk of non-melanoma skin cancer (NMSC) in patients with IBD and determined how immunosuppressive and biologic medications affect this risk. **METHODS:** We performed retrospective cohort and nested case-control studies by using administrative data from PharMetrics Patient Centric Database. In the cohort study, 26,403 patients with Crohn's disease (CD) and 26,974 patients with ulcerative colitis (UC) were each matched to 3 non-IBD controls. NMSC risk was evaluated by incidence rate ratio (IRR). In the nested case-control study, 387 CD patients and 355 UC patients with NMSC were each matched to 4 IBD patients without NMSC by using incidence density sampling. Conditional logistic regression was used to determine the association between specific IBD medication use and NMSC. **RESULTS:** In the cohort study, the incidence of NMSC was higher among patients with IBD compared with controls (IRR, 1.64; 95% confidence interval [CI], 1.51-1.78). In the nested-case control study, recent thiopurine use ( $\leq 90$  days) was associated with NMSC (adjusted odds ratio [OR], 3.56; 95% CI, 2.81-4.50), as was recent biologic use among patients with CD (adjusted OR, 2.07; 95% CI, 1.28-3.33). Persistent thiopurine use ( $>365$  days) was associated with NMSC (adjusted OR, 4.27; 95% CI, 3.08-5.92), as was persistent biologic use among patients with CD (adjusted OR, 2.18; 95% CI, 1.07-4.46). **CONCLUSIONS:** Patients with IBD, especially those who receive thiopurines, are at risk for NMSC. Appropriate counseling and monitoring of such patients with IBD are recommended.

Nat Rev Gastroenterol Hepatol. 2010 Feb;7(2):93-101.

**Optimizing the safety of biologic therapy for IBD.**

de Silva S, Devlin S, Panaccione R.

The introduction of biologic therapy for the treatment of IBD has substantially changed its management. The safety concerns associated with biologic therapies include the increased risk of infection, autoimmunity, development of lymphoma and demyelinating disease, and the risk of worsening heart

failure. There are several strategies for minimizing the risks associated with biologic therapies. Pretreatment strategies include taking a proper history from the patient, physical examination of the patient, screening for latent tuberculosis and ruling out sepsis. Vaccination of patients against vaccine preventable diseases is also recommended. During treatment, patients should be closely monitored and any symptoms that develop should be dealt with early. Education of physicians and patients is also important to allow the early detection of any adverse events.

Eur Rev Med Pharmacol Sci. 2010 Jan;14(1):47-55.

**Safety and effectiveness of infliximab for inflammatory bowel diseases in clinical practice.**

Tursi A, Elisei W, Brandimarte G, Giorgetti G, Penna A, Castrignano V.

**BACKGROUND AND OBJECTIVES:** Our aim was to assess the efficacy and safety of infliximab (IFX) in clinical practice in three Primary Care, Hospital Centers. **MATERIAL AND METHODS:** From September 2004 to December 2008 62 patients (28 males, 34 females, mean age 30.25 years, range 15-55 years), affected by ulcerative colitis (UC) (23 pts) or by Crohn's disease (CD) (39 patients) were treated. Clinical efficacy, safety, mucosal healing and quality of life were assessed both in UC and CD. **RESULTS:** A total of 746 infusions were performed. IFX was administered for a mean of 26 months (range 8-44 months). 33/39 (84.61%) pts with CD were in remission under treatment with IFX for a mean time of 19 months (range 12-44 months). Mean Crohn Disease Activity Index (CDAI) score decreased from 295 (range 258-346) to 136 (range 98-136) ( $p < 0.005$ ). Inflammatory Bowel Disease Quality of Life (IBDQL) improved from 48 (at entry) to 198 (at the end of the study) ( $p < 0.005$ ). 20/23 (86.95%) patients with UC were in remission under treatment with IFX for a mean of 18 months (range 8-34 months). Mean Disease Activity Index (DAI) decreased from 11 (range 9-12) to  $< 3$  (range 2-3) ( $p < 0.05$ ). Mean Mayo Subscore for Endoscopy decreased from 3 to  $< 1$  (range 0-1). IBDQL improved from 56 (at entry) to 194 (at the end of the study) ( $p < 0.005$ ). Only 5 patients (8.06%) experienced side-effects. **CONCLUSIONS:** Long-term outpatients treatment with IFX seems to be safe and effective in managing patients affected by IBD in clinical practice.

Nat Rev Gastroenterol Hepatol. 2010 Mar;7(3):174-7.

**Rash induced by anti-tumor necrosis factor agents in an adolescent with Crohn's disease.**

Conklin LS, Cohen B, Wilson L, Cuffari C, Oliva-Hemker M.

**Background.** A 17-year-old white male with Crohn's disease who was receiving maintenance infusions of the anti-tumor necrosis factor (TNF) agent, infliximab, presented with a new-onset psoriasiform skin rash. The rash was not responsive to topical or oral corticosteroids and worsened after infliximab infusions and after subsequent administration of a second anti-TNF drug, adalimumab. **Investigations.** Full medical history and physical examination, including assessment of the morphology of rash and the temporal correlation with administration of anti-TNF agents. **Diagnosis.** Anti-TNF-agent induced psoriasiform skin rash. **Management.** Discontinuation of anti-TNF therapy. The patient opted to have his gastrointestinal symptoms treated with oral mesalazine and metronidazole.

Curr Drug Targets. 2010 Feb 1;11(2):179-86.

**Is There an Increased Risk of Lymphoma and Malignancies Under Anti-TNF Therapy in IBD?**

Lakatos PL, Miheller P.

Tumour necrosis factor alpha (TNF-alpha) inhibitors ensure valuable treatment advantages for patients with inflammatory bowel diseases (IBD) by offering a more targeted anti-inflammatory therapy. In contrast, there is concern that it might increase the risk of long-term complications including infections and the risk for malignancies and non-Hodgkin's lymphoma (NHL). Although the results from hospital- and population-based studies are conflictive, the results of a meta-analysis suggest that patients receiving purine analogues for the treatment of IBD have a lymphoma risk 4-fold higher than expected. Analyses of lymphoma risk in patients receiving biologic agents directed against tumor necrosis factor-alpha are confounded by concomitant use of immunosuppressive agents in most of these patients. Nevertheless, in a recent meta-analysis, a 3-fold increased risk of NHL was found in patients with previous immunomodulator exposure, while scattered case reports point to the potentially increased risk of a rare form of NHL (Hepatosplenic T-cell lymphoma) with the use of azathioprine-anti-TNF combination. The absolute rate of these events remains, however, low and should be weighed against the substantial benefits associated with treatment. In contrast, data obtained from observational studies and

registries did not show an increased risk for solid tumours or lymphoma in patients with anti-TNF exposure. The aim of this review is to summarize the available evidence on the association between malignancy and anti-TNF treatment in IBD.

Curr Drug Targets. 2010 Feb 1;11(2):198-218.

**How to Manage the Infectious Risk under Anti-TNF in Inflammatory Bowel Disease.**

Culver EL, Travis SP.

The advent of biological therapy has had a significant impact on the management of patients with inflammatory bowel disease. Nevertheless, anti-TNF-alpha agents are still used with caution, driven by concerns about the risk of infection. Stringent post-marketing surveillance programmes and registries have allowed early recognition of problems, highlighting an increased risk of infectious complications. Although the focus is on biological drugs, other immunomodulators have been less well scrutinised and similarly carry considerable risks of infection. It remains unclear whether the risk of infection from anti-TNF therapy is any different from conventional immunomodulators such as azathioprine or methotrexate, although it appears to be less than that ascribed to corticosteroids. The majority of patients on anti-TNF agents are on concomitant immunosuppressive medication, which makes ascribing risk to a specific drug more difficult. The risk of life-threatening opportunistic infections associated with anti-TNF therapy has obliged us to re-consider methods of prevention of infection and to develop guidelines for risk-stratification of patients with a diagnosis of inflammatory bowel disease. This encompasses vaccination and chemoprevention, appropriate treatment of underlying infection, patient education, travel advice and careful monitoring whilst on anti-TNF therapy. Contingency planning is essential. Implementing these preventative strategies will have an appreciable impact on the organisation of care and on current clinical practice.

Curr Drug Targets. 2010 Feb 1;11(2):234-41.

**Anti-TNF Antibody Therapy for Inflammatory Bowel Disease During Pregnancy: A Clinical Review.**

El Mourabet M, El-Hachem S, Harrison JR, Binion DG.

The incidence of inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis) is highest during the peak reproductive years, hence the increased concern with the safety of IBD drugs during pregnancy. Over the past 11 years, anti-TNF-alpha antibody therapy has emerged as a treatment approach for refractory IBD patients who have failed to achieve or maintain remission with corticosteroids and immunomodulator agents. The TNF-alpha inhibitors (anti-TNFs; infliximab, adalimumab, certolizumab pegol) have proven successful in inducing and maintaining remission of moderate-to-severe IBD, but recommendations for the use of these compounds during pregnancy have lacked consensus. Balanced against the potential risk of these drugs on the fetus is the well-established fact that high disease activity has been found to poorly affect pregnancy outcomes in IBD, and the potential use of anti-TNF agents may control disease flare and severity during pregnancy. Concerns regarding the effect of anti-TNFs on the pregnancy and fetus have been assuaged by registry data which has demonstrated an overall positive safety record. Both the U.S. Food and Drug Administration and the European Crohn's and Colitis Organization categorize anti-TNF agents as safe during pregnancy. New knowledge regarding the physiologic timing of placental transfer of therapeutic antibody subclasses and pegylated antibody fragments from the mother into the fetus has also helped to allay concerns. This review will examine the present state of knowledge regarding the use of anti-TNFs in pregnant women with IBD.

Ann Rheum Dis. 2009 Oct 22.

**Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR).**

Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, Symmons DP.

**BACKGROUND:** The risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA) is thought to be increased following anti-TNF therapy, with a proposed differential risk between the anti-TNF drugs etanercept (ETA), infliximab (INF) and adalimumab (ADA). We aimed to compare directly the risk between drugs, to explore time to event, site of infection and the role of ethnicity. **METHODS:** and findings: Using data from the British Society for Rheumatology Biologics Register (BSRBR), a national prospective observational study, we compared TB rates in 10712 anti-TNF treated patients (3913 ETA, 3295 INF, 3504 ADA) and 3232 patients with active RA treated with traditional disease-modifying anti-

rheumatic drugs. RESULTS: To April 2008, 40 cases of TB were reported, all in the anti-TNF cohort. The rate of TB was higher for the monoclonal antibodies ADA (144 events/ 100,000 person years (pyrs)) and INF (136/100,000 pyrs) than ETA (39/ 100,000 pyrs). After adjustment, the incidence rate ratio compared to ETA-treated patients was 3.1 (95% CI 1.0, 9.5) for INF and 4.2 (1.4, 12.4) for ADA. The median time to event was lowest for INF (5.5 months) compared to ETA (13 months) and ADA (18.5 months). 13/40 cases occurred after stopping therapy. 25/40 (62%) cases were extra-pulmonary, of which 11 were disseminated. Patients of non-white ethnicity had a six-fold increased risk of TB compared to white patients treated with anti-TNF therapy. CONCLUSION: The rate of TB in patients with RA treated with anti-TNF therapy was 3-4 fold higher in patients receiving INF and ADA compared to ETA.

JEADV 2010, 24 (Suppl. 2), 23-30

**Cardiovascular risk factors in patients with plaque psoriasis: a systematic review of epidemiological studies**

S Prey, C Paul, V Bronsard, E Puzenat, P-A Gourraud, S Aractingi, F Aubin, M Bagot, B Cribier, P Joly, D Jullien, M Le Maitre, M-A Richard-Lallemand, J-P Ortonne

JEADV 2010, 24 (Suppl. 2), 31-35

**Assessment of risk of psoriatic arthritis in patients with plaque psoriasis: a systematic review of the literature**

S Prey, C Paul, V Bronsard, E Puzenat, P-A Gourraud, S Aractingi, F Aubin, M Bagot, B Cribier, P Joly, D Jullien, M Le Maitre, M-A Richard-Lallemand, J-P Ortonne

J Am Acad Dermatol. 2010 Apr;62(4):706.

**Concern regarding the safety of tumor necrosis factor-alfa antagonists in pregnancy.**

Miner A.

No abstract available

Inflamm Bowel Dis. 2010 Apr;16(4):550-1.

**TNF-alpha is an important pathogenic factor contributing to reactivation of cytomegalovirus in inflamed mucosa of colon in patients with ulcerative colitis: lesson from clinical experience.**

Nakase H, Chiba T.

No abstract available

J Invest Dermatol. 2010 Apr;130(4):917-9.

**Psoriasis is not a useful independent risk factor for cardiovascular disease.**

Stern RS.

Since Gelfand's 2006 publication, the hypothesis that psoriasis is a risk factor for myocardial infarction (MI) and cardiovascular disease (CVD) has drawn substantial attention (Gelfand et al., 2006). Makers of biologic therapies for psoriasis, whose products cost \$15,000 to \$25,000 per patient treated per year, are prominent sponsors of symposia and publications that have advanced this hypothesis (Strober et al., 2008; Friedewald et al., 2008). A company-supported clinical trial testing the hypothesis that tumor necrosis factor (TNF) inhibitor therapy of psoriasis may also reduce cardiovascular risk is under way (ClinicalTrials.gov, 2007). In this issue, Wakkee et al. provide additional evidence that it is unlikely that either psoriasis or severe psoriasis is a relevant risk factor for MI. Even if--after accounting for confounding and bias--psoriasis is significantly associated with CVD risk, psoriasis is unlikely to be a clinically useful independent risk factor for CVD.

J Invest Dermatol. 2010 Apr;130(4):919-22.

**Psoriasis and cardiovascular risk: strength in numbers.**

Gelfand JM, Azfar RS, Mehta NN.

In this issue, Wakkee and colleagues report a self-described exploratory cohort study and conclude that psoriasis may not be an independent risk factor for ischemic heart disease (IHD) hospitalization and that

there is only a slight and borderline increased risk of ischemic heart disease among psoriasis patients. This negative result should be interpreted in light of the study's limitations, the complex relationship among levels of psoriasis severity, patient age, and cardiovascular (CV) risk, and the context of the rapidly growing literature.

J Invest Dermatol. 2010 Apr;130(4):962-7. Epub 2009 Oct 8.

**Psoriasis may not be an independent risk factor for acute ischemic heart disease hospitalizations: results of a large population-based Dutch cohort.**

Wakkee M, Herings RM, Nijsten T.

Although psoriasis has been associated with components of the metabolic syndrome, its association with myocardial infarction is less clear. A cohort study was conducted using hospital and pharmacy records of 2.5 million Dutch residents between 1997 and 2008. The risk of ischemic heart disease (IHD) hospitalizations was compared between psoriasis patients and a matched reference cohort. Additional adjustments were made for healthcare consumption and use of cardiovascular drugs. A total of 15,820 psoriasis patients and 27,577 reference subjects were included, showing an incidence rate of 611 and 559 IHD per 100,000 person-years, respectively ( $P=0.066$ ). The age- and gender-adjusted risk of IHD was comparable between both cohorts (hazard ratio (HR)=1.10, 95% confidence interval 0.99-1.23). Before cohort entry, psoriasis patients used more antihypertensive, antidiabetic, and lipid-lowering drugs and were more often hospitalized. Adjusting for these confounders decreased the HR for IHD, but it remained comparable between both populations. There was no different risk of IHD between the subgroup of patients who only used topicals versus those who received systemic therapies or inpatient care for their psoriasis. This study, therefore, suggests that psoriasis is not a clinically relevant risk factor for IHD hospitalizations on the population level.

Ann Rheum Dis. 2010 Apr;69(4):654-9. Epub 2009 May 12.

**Rheumatoid arthritis, treatment with corticosteroids and risk of malignant lymphomas: results from a case-control study.**

Hellgren K, Iliadou A, Rosenquist R, Feltelius N, Backlin C, Enblad G, Askling J, Baecklund E.

**BACKGROUND:** Benefits and risks of corticosteroid treatment in rheumatoid arthritis (RA) are debated. Patients with RA are at increased risk of malignant lymphomas. In a large case-control study of risk factors for lymphoma in RA, it was recently reported that steroid treatment was associated with decreased lymphoma risk. **OBJECTIVE:** To further assess the nature of the association between steroid treatment in RA and the risk of lymphoma. **METHODS:** In a cohort of 74 651 patients with RA, 378 patients with lymphoma and 378 matched RA controls were identified, and information on inflammatory activity and different aspects of steroid treatment (duration, therapeutic strategy and mode of administration) abstracted from their medical records. Lymphomas were reclassified (WHO classification) and examined for Epstein-Barr virus. Relative risks were assessed as adjusted odds ratios (ORs) through conditional logistic regression. **RESULTS:** A total duration of oral steroid treatment of <2 years was not associated with lymphoma risk (OR=0.87; 95% CI 0.51 to 1.5), whereas total treatment >2 years was associated with a lower lymphoma risk (OR=0.43; 95% CI 0.26 to 0.72). RA duration at the initiation of oral steroids did not affect lymphoma risk. Intra-articular steroids were associated with a reduced lymphoma risk, but only when used as swift flare treatment (OR=0.22; 95% CI 0.13 to 0.37). Analyses by lymphoma subtype showed a reduced risk of diffuse large B-cell lymphoma (crude OR=0.59; 95% CI 0.37 to 0.94). **CONCLUSION:** In this RA population, use of steroids was associated with reduced lymphoma risk. Whether this association is a generic effect of steroids or specific to the studied population remains unknown.

Scand J Rheumatol. 2009;38(4):321-2.

**On the recurrence risk of arthritis among psoriatic patients.**

Pedersen OB, Junker P.

No abstract available

Ann Rheum Dis. 2010 Mar 16. [Epub ahead of print]

**Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study.**

Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, Dijkmans BA, Tak PP, Wolbink GJ.

**OBJECTIVE:** To investigate how antibodies against anti-tumour necrosis factor (anti-TNF) agents influence response after switching from infliximab to adalimumab in rheumatoid arthritis (RA). **METHODS:** This cohort study consisted of 235 patients with RA, all treated with adalimumab. At baseline 52 patients (22%) had been previously treated with infliximab ('switchers'), and 183 (78%) were anti-TNF naive. Disease activity (using the 28-joint count Disease Activity Score (DAS28)) and presence of antibodies against infliximab and adalimumab were assessed. Clinical response to adalimumab was compared between switchers and anti-TNF naive patients and their anti-infliximab and anti-adalimumab antibody status. **RESULTS:** After 28 weeks of adalimumab treatment the decrease in DAS28 (DeltaDAS28) for the 235 patients was 1.6+/-1.5 (mean+/-SD). Anti-adalimumab antibodies were detected in 46 patients (20%). DeltaDAS28 was 1.8+/-1.4 in patients without anti-adalimumab and 0.6+/-1.3 in patients with anti-adalimumab ( $p < 0.0001$ ). Thirty-three of the 52 switchers (63%) had anti-infliximab antibodies. Patients with anti-infliximab more often developed anti-adalimumab than anti-TNF naive patients (11 (33%) vs 32 (18%);  $p = 0.039$ ). DeltaDAS28 was greater for anti-TNF naive patients (1.7+/-1.5) than for switchers without anti-infliximab antibodies (DeltaDAS28=0.9+/-1.4) ( $p = 0.009$ ). DeltaDAS28 for switchers with anti-infliximab was 1.2+/-1.3 and did not differ significantly from anti-TNF naive patients ( $p = 0.262$ ). **CONCLUSION:** Switchers with anti-infliximab antibodies more often develop antibodies against adalimumab than anti-TNF naive patients. Response to adalimumab was limited in switchers without anti-infliximab antibodies, which raises the question whether a second anti-TNF treatment should be offered to patients with RA for whom an initial treatment with an anti-TNF blocker fails, in the absence of anti-biological antibodies.

Br J Dermatol. 2009 Oct 26. [Epub ahead of print]

**Antinuclear antibodies associate with loss of response to antitumour necrosis factor-alpha therapy in psoriasis: a retrospective, observational study.**

Pink AE, Fonia A, Allen MH, Smith CH, Barker JN.

**Background** An increasing number of patients with severe psoriasis are failing to respond to antitumour necrosis factor (TNF)-alpha therapy (etanercept, infliximab and adalimumab). **Objectives** We observed that many of these patients developed antinuclear antibodies (ANA) and antidouble-stranded DNA (anti-dsDNA) antibodies while on treatment prompting us to investigate whether their development is associated with anti-TNF treatment failure. **Methods** All patients with psoriasis who had received anti-TNF therapies were identified and their blood results and treatment histories were obtained from electronic patient records and case notes. **Results** A total of 97 patients had been treated with anti-TNF agents (60 were on their first agent, 22 had been on and stopped one agent, nine had been on and stopped two agents and six had been on and stopped all three agents). ANA developed in 17% of patients on their first treatment, 54% of patients who had failed one treatment, 78% of patients who had failed two treatments and 83% of patients who had failed all three treatments. Anti-dsDNA antibodies developed in 2%, 27%, 33% and 83% of patients from the same respective groups. Significantly, the antibodies developed before treatment had failed with all three agents and their development was not related to the total time that patients had been on anti-TNF therapy. **Conclusions** This study suggests that the development of ANA and anti-dsDNA antibodies on anti-TNF treatment may act as a marker of forthcoming treatment failure. Large-scale prospective studies are required to assess the importance of this observation.

Arch Dermatol. 2010 Feb;146(2):127-32.

**Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis.**

Lecluse LL, Driessen RJ, Spuls PI, de Jong EM, Stapel SO, van Doorn MB, Bos JD, Wolbink GJ.

**OBJECTIVES:** To investigate the extent antibodies to adalimumab are formed in patients with plaque psoriasis and whether these antibodies have clinical consequences. Also, to examine the relationship between antibodies to adalimumab and adalimumab trough titers. **DESIGN:** Prospective observational cohort study. **SETTING:** Two Dutch dermatology departments in university hospitals. **PATIENTS:** All consecutive patients starting a regimen of adalimumab for chronic plaque psoriasis. Patients were screened and fulfilled the Dutch reimbursement criteria for adalimumab to treat psoriasis.

INTERVENTION: Adalimumab treatment (per label). MAIN OUTCOME MEASURES: The titer of antibodies to adalimumab, the adalimumab trough concentration, and the Psoriasis Area and Severity Index at weeks 12 and 24. RESULTS: Antibodies to adalimumab were detected in 13 of 29 patients (45%) during 24 weeks of treatment. Differences in response rates among patients with low, high, and no titers of antibodies to adalimumab were significant at weeks 12 and 24 ( $P = .04$  and  $P < .001$ , respectively). The median adalimumab trough concentrations varied significantly among patients with low, high, and no titers of antibodies to adalimumab (1.30 [range, 0.01-5.50], 0.0 [range, 0.0-0.0], and 9.6 [range, 0.0-22.6] mg/L, respectively;  $P < .001$ ). At week 24, the median adalimumab trough concentrations also differed significantly among good responders, moderate responders, and nonresponders (9.7 [range, 0.0-22.6], 8.9 [range, 3.2-12.6], and 0.0 [range, 0.0-13.3] mg/L, respectively;  $P = .01$ ). CONCLUSION: Antibodies to adalimumab are associated with lower serum adalimumab trough concentrations and with nonresponse or loss of response to adalimumab in patients with plaque psoriasis.

Arch Dermatol. 2010 Mar;146(3):283-7.

**Incidence estimate of nonmelanoma skin cancer in the United States, 2006.**

Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, Coldiron BM.

OBJECTIVES: To estimate the incidence of nonmelanoma skin cancer (NMSC) in the US population in 2006 and secondarily to indicate trends in numbers of procedures for skin cancer treatment. DESIGN: A descriptive analysis of population-based claims and US Census Bureau data combined with a population-based cross-sectional survey using multiple US government data sets, including the Centers for Medicare and Medicaid Services Fee-for-Service Physicians Claims databases, to calculate totals of skin cancer procedures performed for Medicare beneficiaries in 1992 and from 1996 to 2006 and related parameters. The National Ambulatory Medical Care Service database was used to estimate NMSC-related office visits. We combined these to estimate totals of new skin cancer diagnoses and affected individuals in the overall US population. RESULTS: The total number of procedures for skin cancer in the Medicare fee-for-service population increased by 76.9% from 1 158 298 in 1992 to 2 048 517 in 2006. The age-adjusted procedure rate per year per 100 000 beneficiaries increased from 3514 in 1992 to 6075 in 2006. From 2002 to 2006 (the years for which the databases allow procedure linkage to patient demographics and diagnoses), the number of procedures for NMSC in the Medicare population increased by 16.0%. In this period, the number of procedures per affected patient increased by 1.5%, and the number of persons with at least 1 procedure increased by 14.3%. We estimate the total number of NMSCs in the US population in 2006 at 3 507 693 and the total number of persons in the United States treated for NMSC at 2 152 500. CONCLUSIONS: The number of skin cancers in Medicare beneficiaries increased dramatically over the years 1992 to 2006, due mainly to an increase in the number of affected individuals. Using nationally representative databases, we provide evidence of much higher overall totals of skin cancer diagnoses and patients in the US population than previous estimates. These data give the most complete evaluation to date of the underrecognized epidemic of skin cancer in the United States.

Eur Heart J. 2010 Mar 9. [Epub ahead of print]

**Psoriasis, inflammation, and vascular risk: a problem more than skin deep?**

Ridker PM.

No abstract available

Best Pract Res Clin Gastroenterol. 2010 Apr;24(2):167-82.

**Adverse effects of biologics used for treating IBD.**

Stallmach A, Hagel S, Bruns T.

In the last decade, biologic agents, in particular anti-TNF agents such as infliximab, adalimumab, and certolizumab have substantially extended the therapeutic armamentarium of inflammatory bowel disease (IBD). Additional approaches include biologicals, such as natalizumab, that block leucocyte adhesion; those that target cytokines, such as interleukin-12/23 antibodies; or those that inhibit T-cell signaling, such as interleukin-6 receptor antibodies. However, these drugs have a number of contraindications and side effects, especially when used in combination with classical immunosuppressive agents or corticosteroids. Areas of concern include opportunistic infections, malignancies, and miscellaneous complications such as injection/infusion reactions and autoimmunity and contraindications, such as heart failure and acute infectious diseases. In this review, the indications of biologicals in IBD treatment are

briefly reported, and the potential disadvantages of a more active therapeutic approach in IBD are discussed. We have learned in the last decade that anti-TNF-alpha therapy is an effective and relatively safe treatment option for selected patients that changes the natural course of severe IBD. However, despite these changed therapeutic paradigms and goals in IBD, clinicians should be aware that the powerful immunosuppressive capacity of biologicals necessitates a rigorous long-term safety follow-up.

Scand J Gastroenterol. 2010 Apr;45(4):509-10.

**Cytomegalovirus colitis complicating ulcerative colitis treated with adalimumab.**

Charles P, Ackermann F, Burdy G, Blétry O, Lepout J, Kahn JE.

No abstract available

Semin Arthritis Rheum. 2010 Apr;39(5):327-46. Epub 2008 Dec 31.

**The risk of infections with biologic therapies for rheumatoid arthritis.**

Furst DE.

**OBJECTIVES:** To assess the risk of serious and nonserious bacterial and viral infections associated with the use of biologic therapy (abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab) in patients with rheumatoid arthritis (RA). **METHODS:** Information was derived from PubMed, EMBASE, and the Cochrane clinical trials register and database of systematic reviews and relevant congress abstracts up to and including February 2008. **RESULTS:** Compared with the general population, patients with RA have a heightened risk of infection, including tuberculosis. Long-term clinical trials and postmarketing studies indicate that anakinra and the tumor necrosis factor (TNF) inhibitors are associated with an increased risk of infections versus conventional disease-modifying antirheumatic drugs (DMARDs), especially early in the course of treatment. The most common sites of infection are the respiratory tract (including pneumonia), skin and soft tissue, and the urinary tract. The risk of tuberculosis also appears higher with TNF inhibitors (in particular, infliximab) versus DMARDs, although this can be reduced by screening and prophylaxis. TNF inhibitors do not appear to significantly increase the risk of reactivating chronic viral infections. Influenza and pneumococcal vaccinations are generally effective in the face of TNF inhibitors or abatacept. Available data suggest that the risk of infections and serious infections with abatacept and rituximab may be similar to that of the TNF inhibitors. To date, there have been no reports from clinical trials of increased tuberculosis or opportunistic infections with abatacept or rituximab. **CONCLUSIONS:** All marketed TNF inhibitors for compared to control RA appear to increase the risk of serious and nonserious infections compared with DMARDs. Although suggestive, data for abatacept and rituximab are less definitive and longer periods of patient exposure to these agents are needed before an assessment of their risks can be made.

Mod Rheumatol. 2010 Mar 11. [Epub ahead of print]

**Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions.**

Nishimoto N, Ito K, Takagi N.

We present safety and efficacy data from Japanese clinical studies on monotherapy with tocilizumab (TCZ), a humanized anti-interleukin 6 receptor monoclonal antibody, in which 601 patients with moderate to severe rheumatoid arthritis, with a total of 2188 patient-years (pt-yr) exposure, were enrolled. The median treatment duration was 3.8 years. The incidence of adverse events (AEs), including abnormal laboratory test results, was calculated as 465.1 per 100 pt-yr. The most common serious adverse events (SAEs) were infections (6.22 per 100 pt-yr). There was no increase in the frequency of AEs or SAEs with long-term treatment. Abnormalities in the laboratory test results, such as increases in lipid parameters or abnormal liver function parameters, were common, but most were mild and there were no SAEs related to them. At baseline, 546 patients (90.8%) were taking corticosteroids; of these, 77.8% were able to decrease their corticosteroid dose during the study period, while 35.2% discontinued corticosteroids altogether. In the patients treated longer than 5 years, 91.3, 73.0, and 51.3% met the ACR20, ACR50, and ACR70 response criteria, respectively, and 59.7% met the DAS remission criterion (DAS28 <2.6) at 5 years. In conclusion, based on these results, TCZ has shown good tolerability and high efficacy during long-term treatment.