Literature Update Immunology

Period: 1-30 November 2010

IBD

- **Anti-CD3 antibody visilizumab** is not effective in patients with **intravenous corticosteroid-refractory ulcerative colitis**
- **Immortal time bias** in **estimates of mortality** among **infliximab-treated patients** with **Crohn's disease**
- **Infliximab** for **Crohn's disease** in the **Swiss IBD Cohort Study**: clinical management and appropriateness.
- **Tumor necrosis factor-α monoclonal antibodies** in the treatment of **inflammatory bowel disease**: clinical practice **pharmacology**.
- The **London position statement** of the **World Congress of Gastroenterology on Biological Therapy for IBD** with the **European Crohn's and Colitis Organization**: When to start, when to stop, which drug to choose, and how to predict response?
- **Infliximab** decreases **colectomy rates** in **moderate to severe ulcerative colitis**: Big news or big deal?
- **Adherence to adalimumab** therapy in **Crohn's disease**: A **French multicenter experience**.
- **Surgery** for **intestinal Crohn's disease recurrence**.
- **Selective depletion of peripheral granulocyte/monocyte** enhances the efficacy of **scheduled maintenance infliximab** in **Crohn's disease**.
- **Characterization** of **CCX282-B**, an orally **bioavailable antagonist of the CCR9 chemokine receptor**, for the treatment of **inflammatory bowel disease**.
- **Autologous bone marrow-derived mesenchymal stromal cell treatment** for **refractory luminal Crohn's disease**: results of a **phase I study**
- **Predictive value** of **epithelial gene expression profiles** for response to **infliximab** in **Crohn's disease**
- Lost in translation: **Helping patients understand the risks** of **inflammatory bowel disease therapy.**
- **New insights** into the **role of IL-17** in **inflammatory bowel disease**
- **Clinical scenarios in IBD**: **Optimizing** the use of **conventional and biologic agents**
- **Cut-off levels** and **diagnostic accuracy** of **infliximab trough levels** and **anti-infliximab antibodies** in **Crohn's disease**.
- **Long-term effects** and **colectomy rates** in **ulcerative colitis** patients treated with **infliximab**: A **Danish single center experience**
- Appropriateness of **early management** of **newly diagnosed Crohn's disease** in a European population-based cohort
- **Biologic agent use** varies inversely with **age at diagnosis in Crohn's disease**.
- **Prevention of recurrence** after **surgery** for **Crohn's disease**: **Efficacy** of **infliximab.**

Safety

- **Pharmacologic immunomodulation** and **cutaneous malignancy** in **rheumatoid arthritis**, **psoriasis**, and **psoriatic arthritis**
- **Primary varicella-zoster infection** in patients on **biologic therapies** for **psoriasis**
- **Serious infections** in patients with **inflammatory bowel disease** receiving **anti-tumor-necrosis-factor-alpha therapy**: An **Australian** and **New Zealand** experience
- A case of generalized **psoriasiform** and **pustular eruption** induced by **infliximab**: evidence for skin-homing Th17 in the pathogenesis
- **Onset** of **psoriasis** following treatment with **tocilizumab**

- **Benefit-risk analysis** of **adalimumab** versus **methotrexate** and **placebo** in the treatment of **moderate to severe psoriasis**: Comparison of **adverse event–free response days** in the **CHAMPION trial**
- **Safety** of **infliximab** in **Crohn's disease**: A large single-center experience
- **Necrotising fasciitis** of the shoulder in **association with rheumatoid arthritis** treated with **etanercept**: a case report.
- Generalisability of **clinical registers** used for **drug safety** and comparative **effectiveness research**: coverage of **the Swedish Biologics Register**.
- **Tolerability** and **safety** of **biological therapies** for **psoriasis** in daily **clinical practice**: a study of 103 **Italian patients**.

IBD

Gut. 2010 Nov;59(11):1485-92.
Anti-CD3 antibody visilizumab is not effective in patients with intravenous corticosteroid-refractory ulcerative colitis.
Sandborn WJ, Colombel JF, Frankel M, Hommes D, Lowder JN, Mayer L, Plevy S, Stokkers P, Travis S, Van Assche G, Baumgart DC, Targan SR.

BACKGROUND AND AIMS: Pilot studies with visilizumab, a humanised monoclonal antibody to CD3, suggest efficacy for corticosteroid-refractory ulcerative colitis (UC). A placebo-controlled trial was warranted.
METHODS: A randomised, double-blind, placebo-controlled study evaluated the efficacy of visilizumab induction treatment in 127 patients with severely active UC despite treatment with ≥5 days of intravenous corticosteroids. Patients received placebo or visilizumab 5μg/kg intravenously on days 1 and 2. Corticosteroids were tapered according to disease activity. Patients were followed up for 90 days. The primary end point was induction of response at day 45. Secondary end points included remission and mucosal healing at day 45, symptomatic response at day 15 and colectomy.
RESULTS: Response at day 45 occurred in 55% of patients receiving visilizumab compared with 47% of those who received placebo (p=0.475). Remission at day 45 occurred in 8% of patients receiving visilizumab compared with 9% of those who received placebo (p=0.704). Mucosal healing at day 45 occurred in 29% of patients receiving visilizumab compared with 26% of those who received placebo (p=0.799). Symptomatic response at day 15 occurred in 82% of patients receiving visilizumab compared with 74% of those who received placebo (p=0.244). Colectomy was performed in 18% of patients receiving visilizumab compared with 7% of those who received placebo (p=0.130). Cardiac disorders and vascular disorders occurred more frequently in the patients who received visilizumab.
CONCLUSION: Visilizumab at a dose of 5μg/kg for two consecutive days was not effective for severe, corticosteroid-refractory UC and was associated with increased cardiac and vascular adverse events. (Registered at http://www.clinicaltrials.govNCT00279422/).

Gut. 2010 Nov;59(11):1586-7. Epub 2010 Aug 23.
Immortal time bias in estimates of mortality among infliximab-treated patients with Crohn's disease.
Lewis JD.

No abstract available

Eur J Gastroenterol Hepatol. 2010 Nov;22(11):1352-7.
Infliximab for Crohn's disease in the Swiss IBD Cohort Study: clinical management and appropriateness.
Juillerat P, Pittet V, Vader JP, Burnand B, Gonvers JJ, de Saussure P, Mottet C, Seibold F, Rogler G, Sagmeister M, Felley C, Michetti P, Froehlich F; Swiss IBD Cohort Study Group.

OBJECTIVE: Antitumor necrosis factor a agents have significantly improved the management of Crohn's disease (CD), but not all patients benefit from this therapy. We used data from the Swiss Inflammatory Bowel Disease Cohort Study and predefined appropriateness criteria to examine the appropriateness of use of infliximab (IFX) in CD patients.
METHODS: EPACT II (European Panel on the Appropriateness of CD Therapy, 2007; www.epact.ch) appropriateness criteria have been developed using a formal explicit panel process combining evidence from the published literature and expert opinion. Questionnaires relating to EPACT II criteria were used at enrollment and follow-up of all Swiss Inflammatory Bowel Disease Cohort Study patients. A step-by-step analysis of all possible indications for IFX therapy in a given patient allowed identification of the most appropriate indication and final classification in a single appropriateness category (appropriate, uncertain, inappropriate).
RESULTS: Eight hundred and twenty-one CD patients were prospectively enrolled between November 2006 and March 2009. IFX was administered to 146 patients (18%) at enrollment and was most frequently used for complex fistulizing disease and for the maintenance of remission induced by biological

therapy. IFX therapy was considered appropriate in 44%, uncertain in 44%, and inappropriate in 10% of patients.
CONCLUSION: In this cohort, 9 out of 10 indications for IFX therapy were clinically generally acceptable (appropriate or uncertain) according to EPACT II criteria. Uncertain indications resulted mainly from the current more liberal use of IFX in clinical practice as compared with the EPACT II criteria.

Gastroenterol Clin North Am. 2010 Sep;39(3):543-57.
Tumor necrosis factor-α monoclonal antibodies in the treatment of inflammatory bowel disease: clinical practice pharmacology.
Lee TW, Fedorak RN.

In the last 10 years, anti-tumor necrosis factor (TNF)-α therapy has become a cornerstone in the management of autoimmune diseases. Clinical trial data have consistently found that infliximab, adalimumab, and recently certolizumab pegol offer therapeutic benefits to patients with inflammatory bowel diseases (Crohn's disease and ulcerative colitis). Recent understanding on how these monoclonal antibodies evoke changes at the physiological and molecular levels have provided insights into disease pathogenesis and helped to identify new targets for future drug therapy. With increased experience in the use of these anti-TNF-α antibodies the long-term safety data, use in pregnancy have become available. This article provides an overview of the current knowledge regarding anti-TNF-α therapies for clinicians caring for patients with Crohn's disease and ulcerative colitis.

Am J Gastroenterol. 2010 Nov 2. [Epub ahead of print]
The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organization: When to Start, When to Stop, Which Drug to Choose, and How to Predict Response?
D'Haens GR, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, Hanauer SB, Herfarth H, Hommes DW, Kamm M, Löfberg R, Quary A, Sands B, Sood A, Watermayer G, Lashner B, Lémann M, Plevy S, Reinisch W, Schreiber S, Siegel C, Targan S, Watanabe M, Feagan B, Sandborn WJ, Colombel JF, Travis S.

The advent of biological therapy has revolutionized inflammatory bowel disease (IBD) care. Nonetheless, not all patients require biological therapy. Selection of patients depends on clinical characteristics, previous response to other medical therapy, and comorbid conditions. Availability, reimbursement guidelines, and patient preferences guide the choice of first-line biological therapy for luminal Crohn's disease (CD). Infliximab (IFX) has the most extensive clinical trial data, but other biological agents (adalimumab (ADA), certolizumab pegol (CZP), and natalizumab (NAT)) appear to have similar benefits in CD. Steroid-refractory, steroid-dependent, or complex fistulizing CD are indications for starting biological therapy, after surgical drainage of any sepsis. For fistulizing CD, the efficacy of IFX for inducing fistula closure is best documented. Unique risks of NAT account for its labeling as a second-line biological agent in some countries. Patients who respond to induction therapy benefit from systematic re-treatment. The combination of IFX with azathioprine is better than monotherapy for induction of remission and mucosal healing up to 1 year in patients who are naïve to both agents. Whether this applies to other agents remains unknown. IFX is also effective for treatment-refractory, moderate, or severely active ulcerative colitis. Patients who have a diminished or loss of response to anti-tumor necrosis factor (TNF) therapy may respond to dose adjustment of the same agent or switching to another agent. Careful consideration should be given to the reasons for loss of response. There are insufficient data to make recommendations on when to stop anti-TNF therapy. Preliminary evidence suggests that a substantial proportion of patients in clinical remission for >1 year, without signs of active inflammation can remain in remission after stopping treatment.Am J Gastroenterol advance online publication, 2 November 2010; doi:10.1038/ajg.2010.392.

Inflamm Bowel Dis. 2010 Nov 4. [Epub ahead of print]
Infliximab decreases colectomy rates in moderate to severe ulcerative colitis: Big news or big deal?
Cheifetz AS, Rosenberg L.

No abstract available

Inflamm Bowel Dis. 2010 Nov 8. [Epub ahead of print]
Adherence to adalimumab therapy in Crohn's disease: A French multicenter experience.
Billioud V, Laharie D, Filippi J, Roblin X, Oussalah A, Chevaux JB, Hébuterne X, Bigard MA, Peyrin-Biroulet L.

BACKGROUND: We evaluated adherence to adalimumab therapy in Crohn's disease (CD).
METHODS: This was an observational multicenter study conducted in four French university hospitals between April 4, 2008 and January 1, 2010. Patients were systematically asked, at each clinical visit, whether or not they delayed or missed an injection of adalimumab over the past 3 months. Patients were also asked about the reasons for their nonadherence.
RESULTS: Of the 108 patients analyzed, 33 (30.6%) delayed the administration of at least one injection and 16 (14.8%) missed at least one injection over the past 3 months. The main reasons for overall nonadherence were: forgetfulness (24.6%), infection (24.6%), and travel (20%). Other reasons for nonadherence were intentional nonadherence (10.8%), pharmaceutical supply issues (9.2%), side effects (7.7%), pregnancy (1.5%), and CD-related hospitalization (1.5%). Adalimumab regimen of 40 mg every other week was a positive predictor for injection delays (P = 0.02, odds ratio [OR] = 3.76, 95% confidence interval [CI], 1.28-11.05), whereas having at least one relapse in the past 12 months was associated with fewer delays (P = 0.03, OR = 0.39, 95% CI, 0.17-0.92). Disease duration over 90 months negatively predicted failure to inject adalimumab (P = 0.009, OR = 0.17, 95% CI, 0.05-0.64).
CONCLUSIONS: The overall nonadherence rate for adalimumab use was 45.4%. Most of the reasons for nonadherent behaviors could be avoided. An adalimumab regimen of 40 mg every other week was negatively related to adalimumab adherence; both the occurrence of at least one relapse in the past 12 months and disease duration over 90 months were positively related to adherence. (Inflamm Bowel Dis 2010).

Surgery. 2010 Nov;148(5):936-46. Epub 2010 Apr 2.
Surgery for intestinal Crohn's disease recurrence.
Brouquet A, Blanc B, Bretagnol F, Valleur P, Bouhnik Y, Panis Y.

BACKGROUND: Operative therapy for Crohn's disease (CD) recurrence is supposed to be more complex and demanding than primary resection. The purpose of this study was to assess a postoperative course after reoperation for the recurrence of CD.
METHODS: From 1998 to 2008, 61 patients underwent reoperation for the recurrence of CD. First, risk factors for postoperative morbidity, with special reference to major postoperative complications, were analyzed. Second, a case-matched study was used to compare the postoperative morbidity of 54 ileocolonic resections for the recurrence of CD (reoperation group) with 57 identical primary ileocolonic resections (primary resection group) according to matching criteria (age, fistulizing or stenotic disease, pre-operative steroids therapy, pre-operative general status, and surgical approach).
RESULTS: Postoperative mortality was nil. Postoperative complications were observed in 23 cases (38%). Of these cases, 6 (10%) had major complications (2 anastomotic leakages and 6 intra-abdominal abscesses requiring radiological drainage). Univariate analysis did not identify risk for major complication. None of the 14 patients with temporary stoma developed a major complication (NS). A case-matched study showed a higher morbidity rate (21/54 vs 5/57; P = .0006) with a greater risk of postoperative intra-abdominal abscess (9/59 vs 1/59; P = .007) and a longer postoperative hospital stay in reoperation versus the primary resection group (9 vs 7 days; P < .001).
CONCLUSION: Reoperation for CD recurrence is demanding and complex with a frequent need for an associated surgical procedure (because of the severity of the disease and/or adherences). It also is associated with a higher morbidity rate and a longer hospital stay than primary resection. For these reasons, the indication of temporary defunctionning stoma should be discussed systematically in these patients.

J Clin Apher. 2010;25(4):226-8.
Selective depletion of peripheral granulocyte/monocyte enhances the efficacy of scheduled maintenance infliximab in Crohn's disease.
Fukunaga K, Yokoyama Y, Kamikozuru K, Yoshida K, Kikuyama R, Nagase K, Nakamura S, Takei Y, Miwa H, Matsumoto T.

BACKGROUND: This is the first report on a case of Crohn's disease (CD), who was successfully maintained with a combination of infliximab (IFX) and selective depletion of granulocytes/monocytes by adsorption (GMA).
CASE: A 33-year-old female with CD activity index (CDAI) 294.2 responded to iv IFX (5mg/kg) administered at weeks 0, 2, and 6 in combination with 3000 mg/day oral 5-aminosalicylic acid (5-ASA; CDAI = 118). Then IFX at 8 week intervals was given as maintenance therapy. Two weeks before the 5th scheduled IFX, the patient worsened with an increase in stool frequency and a rise in CDAI. GMA was administered at weeks 5, 6, and 7 after her 6th iv IFX. Her CDAI decreased from 166.2 to 126.3 and 111.9 before 2nd and 3rd GMA sessions. She received her 7th iv IFX while the CDAI was 83.6. GMA course was repeated before 8th and 9th IFX. The patient remained in stable clinical and endoscopic remission without experiencing any serious side effect. After achieving mucosal healing, the patient decided to cease IFX therapy while continuing with GMA.
CONCLUSIONS: IFX appears to induce and maintain remission of CD, but it may lose its efficacy after repeated administration. GMA is safe and by selectively depleting elevated/activated leukocytes may be a useful adjunct for IFX efficacy.

J Pharmacol Exp Ther. 2010 Oct;335(1):61-9. Epub 2010 Jul 21.
Characterization of CCX282-B, an orally bioavailable antagonist of the CCR9 chemokine receptor, for treatment of inflammatory bowel disease.
Walters MJ, Wang Y, Lai N, Baumgart T, Zhao BN, Dairaghi DJ, Bekker P, Ertl LS, Penfold ME, Jaen JC, Keshav S, Wendt E, Pennell A, Ungashe S, Wei Z, Wright JJ, Schall TJ.

The chemokine system represents a diverse group of G protein-coupled receptors responsible for orchestrating cell recruitment under both homeostatic and inflammatory conditions. Chemokine receptor 9 (CCR9) is a chemokine receptor known to be central for migration of immune cells into the intestine. Its only ligand, CCL25, is expressed at the mucosal surface of the intestine and is known to be elevated in intestinal inflammation. To date, there are no reports of small-molecule antagonists targeting CCR9. We report, for the first time, the discovery of a small molecule, CCX282-B, which is an orally bioavailable, selective, and potent antagonist of human CCR9. CCX282-B inhibited CCR9-mediated Ca(2+) mobilization and chemotaxis on Molt-4 cells with IC(50) values of 5.4 and 3.4 nM, respectively. In the presence of 100% human serum, CCX282-B inhibited CCR9-mediated chemotaxis with an IC(50) of 33 nM, and the addition of α1-acid glycoprotein did not affect its potency. CCX282-B inhibited chemotaxis of primary CCR9-expressing cells to CCL25 with an IC(50) of 6.8 nM. CCX282-B was an equipotent inhibitor of CCL25-directed chemotaxis of both splice forms of CCR9 (CCR9A and CCR9B) with IC(50) values of 2.8 and 2.6 nM, respectively. CCX282-B also inhibited mouse and rat CCR9-mediated chemotaxis. Inhibition of CCR9 with CCX282-B results in normalization of Crohn's disease such as histopathology associated with the TNF(ΔARE) mice. Analysis of the plasma level of drug associated with this improvement provides an understanding of the pharmacokinetic/pharmacodynamic relationship for CCR9 antagonists in the treatment of intestinal inflammation.

Gut. 2010 Dec;59(12):1662-9. Epub 2010 Oct 4.
Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study.
Duijvestein M, Vos AC, Roelofs H, Wildenberg ME, Wendrich BB, Verspaget HW, Kooy-Winkelaar EM, Koning F, Zwaginga JJ, Fidder HH, Verhaar AP, Fibbe WE, van den Brink GR, Hommes DW.

BACKGROUND AND AIM: Mesenchymal stromal cells (MSCs) are pluripotent cells that have immunosuppressive effects both in vitro and in experimental colitis. Promising results of MSC therapy have been obtained in patients with severe graft versus host disease of the gut. Our objective was to determine the safety and feasibility of autologous bone marrow derived MSC therapy in patients with refractory Crohn's disease.
PATIENTS AND INTERVENTION: 10 adult patients with refractory Crohn's disease (eight females and two males) underwent bone marrow aspiration under local anaesthesia. Bone marrow MSCs were isolated and expanded ex vivo. MSCs were tested for phenotype and functionality in vitro. 9 patients received two doses of 1-2×10(6) cells/kg body weight, intravenously, 7 days apart. During follow-up, possible side effects and changes in patients' Crohn's disease activity index (CDAI) scores were monitored. Colonoscopies were performed at weeks 0 and 6, and mucosal inflammation was assessed by using the Crohn's disease endoscopic index of severity.

RESULTS: MSCs isolated from patients with Crohn's disease showed similar morphology, phenotype and growth potential compared to MSCs from healthy donors. Importantly, immunomodulatory capacity was intact, as Crohn's disease MSCs significantly reduced peripheral blood mononuclear cell proliferation in vitro. MSC infusion was without side effects, besides a mild allergic reaction probably due to the cryopreservant DMSO in one patient. Baseline median CDAI was 326 (224-378). Three patients showed clinical response (CDAI decrease ≥70 from baseline) 6 weeks post-treatment; conversely three patients required surgery due to disease worsening.
CONCLUSIONS: Administration of autologous bone marrow derived MSCs appears safe and feasible in the treatment of refractory Crohn's disease. No serious adverse events were detected during bone marrow harvesting and administration.

Inflamm Bowel Dis. 2010 Dec;16(12):2090-8. doi: 10.1002/ibd.21301.
Predictive value of epithelial gene expression profiles for response to infliximab in Crohn's disease.
Arijs I, Quintens R, Lommel LV, Van Steen K, De Hertogh G, Lemaire K, Schraenen A, Perrier C, Van Assche G, Vermeire S, Geboes K, Schuit F, Rutgeerts P.

BACKGROUND: Infliximab (IFX) has become the mainstay of therapy of refractory Crohn's disease (CD). However, a subset of patients shows incomplete or no response to this agent. In this study we investigated whether we could identify a mucosal gene panel to predict (non)response to IFX in CD.
METHODS: Mucosal biopsies were obtained during endoscopy from 37 patients with active CD (19 Crohn's colitis [CDc] and 18 Crohn's ileitis [CDi]) before and after first IFX treatment. Response was defined based on endoscopic and histologic findings. Total RNA was analyzed with Affymetrix Human Genome U133 Plus 2.0 Arrays. Quantitative real-time reverse-transcription polymerase chain reaction (RT-PCR) was used to confirm microarray data.
RESULTS: At baseline, significant gene expression differences were found between CDc and CDi. For predicting response in CDc, comparative analysis of CDc pretreatment expression profiles identified 697 significant probe sets between CDc responders (n = 12) and CDc nonresponders (n = 7). Class prediction analysis of CDc top 20 and top 5 significant genes allowed complete separation between CDc responders and CDc nonresponders. The CDc top 5 genes were TNFAIP6, S100A8, IL11, G0S2, and S100A9. Only one patient with CDi completely healed the ileal mucosa. Even using less stringent response criteria, we could not identify a predictive gene panel for IFX responsiveness in CDi.
CONCLUSIONS: This study identified a 100% accurate predictive gene signature for (non)response to IFX in CDc, whereas no such a predictive gene set could be identified for CDi.

Inflamm Bowel Dis. 2010 Dec;16(12):2168-72. doi: 10.1002/ibd.21305.
Lost in translation: Helping patients understand the risks of inflammatory bowel disease therapy.
Siegel CA.

Patients with inflammatory bowel disease are commonly treated with immunomodulators and biologic therapy. These treatments can be very effective, but are associated with risks of adverse events that need to be discussed with patients. Effectively communicating risks of therapy can be challenging based on time constraints, misinformation available on the Internet and from others, and the lack of tools to efficiently share accurate data with patients and their families. Providers need to acknowledge the emotional aspect involved in the perception of risk, and be aware of mistakes that can easily be made in communicating with patients. Tools are available to make medical data easier to understand, and these techniques have been adapted for patients with inflammatory bowel disease. By more clearly communicating with patients, we can ensure that they are making informed medical decisions that fit with their personal preferences for treatment.

Inflamm Bowel Dis. 2010 Dec;16(12):2180-1.
New insights into the role of IL-17 in inflammatory bowel disease.
Noronha AM.

No abstract available

Inflamm Bowel Dis. 2010 Dec;16 Suppl 1:S1-11.
Clinical scenarios in IBD: optimizing the use of conventional and biologic agents.
Hanauer SB, Kornbluth AA, Messick J, Rubin DT, Sandborn WJ, Sands BE.

No abstract available

Scand J Gastroenterol. 2010 Nov 18. [Epub ahead of print]
Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease.
Steenholdt C, Bendtzen K, Brynskov J, Thomsen OO, Ainsworth MA.

Introduction. Reasons for infliximab failure in Crohn's disease and ulcerative colitis are debated. Serum levels of infliximab and anti-infliximab antibodies have been associated with loss of response. We aimed at determining cut-off levels for infliximab and anti-infliximab antibody concentrations associated with clinical response to infliximab maintenance therapy. Methods. Patients with inflammatory bowel disease (n = 106) were retrospectively classified as having maintained response or loss of response to infliximab maintenance therapy. Trough concentrations were measured by fluid-phase radioimmunoassays. Results. Infliximab levels were significantly lower, and anti-infliximab antibody levels significantly higher, in Crohn's disease patients with loss of response (median infliximab 0 μg/ml, median anti-infliximab antibodies 35 U/ml) compared to patients with maintained response (median infliximab 2.8 μg/ml, median anti-infliximab antibodies 0 U/ml; $p < 0.0001$). Receiver operating characteristic (ROC) analysis identified optimal cut-off values: infliximab <0.5 μg/ml, which was associated with loss of response with sensitivity 86% [64-97] and specificity 85% [72-94]; and anti-infliximab antibodies ≥10 U/ml yielding a sensitivity of 81% [61-93] and specificity 90% [79-96]. Combined measurements of infliximab and anti-infliximab antibodies using these cut-off values had higher accuracy yielding a sensitivity of 81% [57-94] and specificity 94% [82-98]. Similar pattern was observed in a smaller cohort of patients with ulcerative colitis. Conclusions. Combined measurements of infliximab and anti-infliximab antibodies using cut-off levels provided high accuracy for discriminating between clinical response types to infliximab maintenance therapy. Cut-off levels are considered a prerequisite to further investigations of clinical usefulness of measurements of infliximab and anti-infliximab antibodies in patients failing infliximab therapy.

Scand J Gastroenterol. 2010 Dec;45(12):1457-63. Epub 2010 Aug 11.
Long-term effects and colectomy rates in ulcerative colitis patients treated with infliximab: A Danish single center experience.
Teisner AS, Ainsworth MA, Brynskov J.

Abstract Objective. Infliximab (IFX) is a well-established treatment for both acute, severe ulcerative colitis (UC) and chronic, refractory UC. However, data on the long-term clinical outcome and colectomy rates after IFX treatment in a routine clinical setting are sparse. The aim of this study was to provide further data on the long-term effect of IFX for acute, severe and chronic, refractory UC in unselected patients treated at a single center. Material and Methods. A retrospective analysis of all patients (n = 52) treated with IFX for UC before February 2009 was performed. The material comprised 19 patients (37%) with acute, severe UC and 33 patients (63%) with chronic, refractory UC. The primary outcome was colectomy rate; the secondary outcome clinical response. Results. The overall colectomy rate was 27% (14/52 patients) after a median follow-up of 22 months (range 4-57 months). The colectomy rate was 37% (7/19 patients) in the group with acute, severe UC and 21% (7/33 patients) among those with chronic, refractory UC. In all, 77% of the patients had clinical response to IFX treatment with no difference between the two subgroups. Among those with an initial clinical response, 50% (20/40 patients) had sustained clinical response. Conclusion. IFX is of long-term benefit as rescue treatment in selected patients with acute, severe UC with about two-thirds of the patients avoiding colectomy. The beneficial effect on colectomy rate in chronic, refractory UC seems less convincing although these patients may still achieve a sustained clinical response.

Scand J Gastroenterol. 2010 Dec;45(12):1449-1456. Epub 2010 Jul 26.
Appropriateness of early management of newly diagnosed Crohn's disease in a European population-based cohort*
Juillerat P, Pittet V, Mottet C, Felley C, Gonvers JJ, Vader JP, Burnand B, Froehlich F, Wolters FL, Stockbrügger RW, Michetti P; the EC-IBD Group.

Abstract Objective. The European Panel on the Appropriateness of Crohn's disease Therapy (EPACT) has developed appropriateness criteria. We have applied these criteria retrospectively to the population-based inception cohort of Crohn's disease (CD) patients of the European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD). Material and methods. A total of 426 diagnosed CD patients from 13 European centers were enrolled at the time of diagnosis (first flare, naive patients). We used the EPACT definitions to identify 247 patients with active luminal CD. We then assessed the appropriateness of the initial drug prescription according to the EPACT criteria. Results. Among the cohort patients 163 suffered from mild-to-moderate CD and 84 from severe CD. Among the mild-to-moderate disease group, 96 patients (59%) received an appropriate treatment, whereas for 66 patients (40%) the treatment was uncertain and in one case (1%) inappropriate. Among the severe disease group, 86% were treated medically and 14% required surgery. 59 (70%) were appropriately treated, whereas for one patient (1%) the procedure was considered uncertain and for 24 patients (29%) inappropriate. Conclusion. Initial treatment was appropriate in the majority of cases for non-complicated luminal CD. Inappropriate or uncertain treatment was given in a significant minority of patients, with an increased potential risk of adverse events.

Dig Dis Sci. 2010 Nov;55(11):3164-70. Epub 2010 Sep 16.
Biologic agent use varies inversely with age at diagnosis in Crohn's disease.
Feagins LA, Spechler SJ.

BACKGROUND: For patients with Crohn's disease, age at onset is known to influence the clinical course of the illness.
AIMS: The aim of this study is to seek an association between age at onset of Crohn's disease and use of biologic agents for its treatment.
METHODS: We reviewed the medical records of 127 veteran patients with Crohn's disease treated at our hospital, and compared differences in age at disease onset between patients who had received biologics and those who had not.
RESULTS: The mean age of our patients was 54.9 ± 15.4 years, and 34% were currently receiving or had previously received treatment with a biologic agent. For those with biologic use, average age at time of diagnosis of Crohn's disease was 32.3 ± 12.2 years, compared with 43.7 ± 16.3 years for those who had not received biologics (P = 0.005). This relationship remained significant even after controlling for disease severity. The frequency of use of biologic agents varied inversely with age at diagnosis. For patients diagnosed before age 21 years, 55.5% had used biologics, whereas no patient >70 years of age at time of diagnosis had used biologics. We found no significant correlation between biologic use and duration of disease, smoking or ethnicity. Perianal disease and concomitant arthritis were both significantly associated with use of biologics.
CONCLUSIONS: In our veteran patients with Crohn's disease, frequency of treatment with a biologic agent varied inversely with age at disease onset.

World J Gastroenterol. 2010 Nov 21;16(43):5405-10.
Prevention of recurrence after surgery for Crohn's disease: Efficacy of infliximab.
Yamamoto T.

After surgery for Crohn's disease (CD), early endoscopic lesions are frequently observed despite no symptomatic recurrence. The severity of lesions found at postoperative endoscopy is reported to be a strong predictive factor for future clinical recurrence. If endoscopic lesions in the early postoperative period can be reduced with medications, symptomatic recurrence will likely be delayed and decreased. Before the introduction of biologic therapies, various medications were used for the maintenance of clinical remission after surgery; however, few demonstrated consistent efficacy. Infliximab is a recombinant anti-tumor necrosis factor-α antibody. Although infliximab is one of the most effective medications in the management of CD, its efficacy for early endoscopic lesions after surgery has not yet been assessed. The author and colleagues recently conducted a prospective study in order to investigate the impact of infliximab on early endoscopic lesions after resection for CD. We found that infliximab therapy showed clear suppressive effects on clinical and endoscopic disease activity in patients with early endoscopic lesions after resection.

Safety

J Rheumatol. 2010 Nov;37(11):2205-15. Epub 2010 Sep 1.
Pharmacologic immunomodulation and cutaneous malignancy in rheumatoid arthritis, psoriasis, and psoriatic arthritis.
Krathen MS, Gottlieb AB, Mease PJ.

OBJECTIVE: It is unclear if skin cancer risk is affected by the use of immunomodulatory medications in rheumatoid arthritis (RA), psoriasis, and psoriatic arthritis (PsA). The purpose of this study is to evaluate and summarize the available data pertinent to this question.
METHODS: The English language literature on PubMed was searched with a combination of phrases, including "malignancy," "skin cancer," "squamous cell carcinoma," "basal cell carcinoma," "melanoma," "psoriasis," "psoriatic arthritis," and "rheumatoid arthritis" in addition to the generic names of a variety of common immunomodulatory drugs. Relevant articles were identified and data were extracted.
RESULTS: In total, 2218 potentially relevant articles were identified through the search process. After further screening, 20 articles relevant to RA were included. An additional 19 articles relevant to either psoriasis or PsA were included as well. RA may be a risk factor for the development of cutaneous malignancy. Treatment with tumor necrosis factor inhibitors increases the rates of non-melanoma skin cancer (NMSC) in RA and psoriasis. This risk doubles when combination methotrexate therapy is used in RA. Methotrexate may increase the risk of malignant melanoma in patients with RA and the risk of NMSC in psoriasis. Cyclosporine and prior phototherapy significantly increase the risk of NMSC.
CONCLUSION: RA may potentiate the risk of cutaneous malignancy and therefore dermatologic screening in this population should be considered. The use of immunomodulatory therapy in RA, psoriasis, and PsA may further increase the risk of cutaneous malignancy and therefore dermatologic screening examinations are warranted in these groups. More careful recording of skin cancer development during clinical trials and cohort studies is necessary to further delineate the risks of immunomodulatory therapy.

Br J Dermatol. 2010 Nov;163(5):1122. doi: 10.1111/j.1365-2133.2010.09938.x.
Primary varicella-zoster infection in patients on biologic therapies for psoriasis.
Hackett CB, Kirby B.

No abstract available

J Gastroenterol Hepatol. 2010 Nov;25(11):1732-8. doi: 10.1111/j.1440-1746.2010.06407.x.
Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience.
Lawrance IC, Radford-Smith GL, Bampton PA, Andrews JM, Tan PK, Croft A, Gearry RB, Florin TH.

BACKGROUND AND AIM: Anti-tumor-necrosis-factor-alpha (anti-TNF-α) medications are effective in inflammatory bowel disease (IBD), but have an increased risk of tuberculosis (TB) and serious infections. The aim of this study was to examine the Australian/New Zealand experience of serious infections and TB in IBD patients receiving anti-TNF-α therapy from 1999-2009.
METHODS: Serious infections, defined as 'requiring hospital admission' and TB cases in patients receiving, or within 3 months following, anti-TNF-α therapy were analyzed across Australia and New Zealand. Patient demographics, IBD medications, duration of anti-TNF-α therapy, and infection details were collected.
RESULTS: A total of 5562 IBD patients were managed across the centers. Of these, 489 (16.8%) Crohn's disease and 137 (5.2%) ulcerative colitis patients received anti-TNF-α therapy. There were three cases of latent TB that received prophylaxis prior to anti-TNF-α therapy. No cases of active TB were reported. Fourteen (2.2%) serious infections occurred. Seven occurred in patients receiving anti-TNF-α therapy for less than 6 months, including two cases of primary Varicella zoster (VZV), two cases of Pneumocystis jiroveci pneumonia, two cases of Staphylococcus aureus bacteremia, and one severe flu-like illness. Six patients were taking additional immunosuppressive medications. The other seven infections occurred after 6 months (mean 32.6 ± 24.3 months) and included one case of primary VZV, one flu-like illness, and five bacterial infections. All infections resolved with treatment.

CONCLUSION: TB is a very rare complication of anti-TNF-α therapy in Australia and New Zealand. Serious infections are uncommon but early opportunistic infections with Pneumocystis jiroveci pneumonia suggest a need for vigilance in patients on multiple immunosuppressive medications. VZV vaccination prior to immunosuppressive therapy should be considered in VZV-naïve patients.

Br J Dermatol. 2010 Dec;163(6):1347-51. doi: 10.1111/j.1365-2133.2010.10002.x. Epub 2010 Nov 4.
A case of generalized psoriasiform and pustular eruption induced by infliximab: evidence for skin-homing Th17 in the pathogenesis.
Teraki Y, Tanaka S, Hitomi K, Izaki S.

No abstract available

Br J Dermatol. 2010 Dec;163(6):1364-5. doi: 10.1111/j.1365-2133.2010.10005.x. Epub 2010 Nov 4.
Onset of psoriasis following treatment with tocilizumab.
Laurent S, Le Parc JM, Clérici T, Bréban M, Mahé E.

No abstract available

J Am Acad Dermatol. 2010 Dec;63(6):1011-8. Epub 2010 Oct 8.
Benefit-risk analysis of adalimumab versus methotrexate and placebo in the treatment of moderate to severe psoriasis: Comparison of adverse event-free response days in the CHAMPION trial.
Reich K, Signorovitch J, Ramakrishnan K, Yu AP, Wu EQ, Gupta SR, Bao Y, Mulani PM.

BACKGROUND: The Comparative Study of Humira versus Methotrexate (MTX) versus Placebo in Psoriasis Patients (CHAMPION) demonstrated superior efficacy of biologic over conventional systemic immunosuppressant therapy in psoriasis.
OBJECTIVE: We sought to compare the risk-benefit profile of adalimumab (ADA), MTX, and placebo using data from CHAMPION.
METHODS: Patients randomized to ADA (n = 107), MTX (n = 110), or placebo (n = 53) were followed up for 16 weeks. Response (≥75% improvement in Psoriasis Area and Severity Index), days free of adverse events (AEs), moderate to severe AEs, infection-related AEs, and study drug-related AEs were analyzed.
RESULTS: ADA treatment was associated with substantially more days (SD) of AE-free response compared with MTX or placebo treatment, respectively: 36.9 (31.1) versus 8.3 (15.9) or 6.7 (18.1) days of response free of any AEs, 43.8 (31.9) versus 11.1 (19.9) or 7.9 (19.9) days of response free of moderate to severe AEs, 48.5 (29.2) versus 12.4 (21.7) or 9.2 (21.8) days of response free of infection-related AEs, and 44.6 (31.4) versus 11.8 (21.1) or 10.0 (24.0) days free of study drug-related AEs (all $P < .0001$ for ADA vs MTX or placebo).
LIMITATIONS: This clinical trial-based analysis may not have captured the full spectrum of AEs in the actual clinical setting. The short (16-week) duration of the trial limited the ability to capture some important but uncommon AEs associated with long-term ADA or MTX use.
CONCLUSION: With 4 times as many AE-free response days, ADA demonstrated a superior benefit-risk profile.

Inflamm Bowel Dis. 2010 Dec;16(12):2109-16. doi: 10.1002/ibd.21290.
Safety of infliximab in Crohn's disease: A large single-center experience.
Hamzaoglu H, Cooper J, Alsahli M, Falchuk KR, Peppercorn MA, Farrell RJ.

BACKGROUND: The aim of this study was to evaluate the short- and long-term safety experience of infliximab treatment in patients with Crohn's disease (CD) in clinical practice.
METHODS: The medical records of 297 consecutive patients with CD treated with infliximab at the Beth Israel Deaconess Medical Center were reviewed for demographic features and adverse events.
RESULTS: The 297 patients received a total of 1794 infusions. Patients received a median of four infusions and had a median follow-up of 14.3 months. Forty-four patients (15%) experienced a serious adverse event, requiring the infusion to be stopped in 33 patients (11%). Acute infusion reactions occurred in 18 patients (6%) including respiratory problems in 10 patients (3%) and an anaphylactoid reaction in 1 patient (0.3%). Serum sickness-like disease occurred in one patient (0.3%) and three

patients (1%) developed drug-induced lupus. One patient developed a probable new demyelination disorder. Eight patients (2.7%), all of whom were on concurrent immunosuppressants, developed a serious infection, one resulting in fatal sepsis. Six patients (2%) developed malignancies including two lymphomas and two skin cancers. A total of four (1.3%) deaths were observed (median age 72.5 years); two due to gastrointestinal bleeding, one due to sepsis, and one due to malignancy.
CONCLUSIONS: While short- and long-term infliximab therapy was generally well tolerated, serious adverse events occurred in 15% of patients including drug-induced lupus, fatal sepsis, and malignancy. Concomitant immunosuppressants were significantly associated with infections and deaths, particularly among elderly patients.

J Med Case Reports. 2010 Nov 17;4(1):367. [Epub ahead of print]
Necrotising fasciitis of the shoulder in association with rheumatoid arthritis treated with etanercept: a case report.
Smyth A, Houlihan DD, Tuite H, Fleming C, O'Gorman TA.

INTRODUCTION: Necrotising fasciitis is a severe infection characterised by the fulminant destruction of tissue with associated systemic signs of sepsis and toxicity. Etanercept is a fully human fusion protein that inhibits tumor necrosis factor and the inflammatory cascade, it is effective in the treatment of many disorders but concerns regarding severe life threatening infections have been raised in multiple reports.
CASE PRESENTATION: We present the case of a 39-year-old Caucasian man, who presented with sudden onset of severe and progressive neck and left shoulder pain with a two-year history of seronegative rheumatoid arthritis treated with azathoprine and etanercept. On examination his left neck and shoulder were oedematous, tender with an erythematous rash and his active range of movement was limited. Magnetic resonance imaging of his shoulder showed extensive oedema of the subcutaneous and intramuscular fat of the left lower neck consistent with fasciitis. He was treated medically and made a good recovery.
CONCLUSION: Our patient, while having a pre-existing increased mortality risk, had a serious infection which responded well to optimum medical treatment without the need for surgery. Although anti tumor necrosis factor agents are more frequently associated with infection, including tuberculous infection, this case highlights the need for a high index of suspicion for other severe bacterial infections in patients on immunosuppressants.

Ann Rheum Dis. 2010 Nov 15. [Epub ahead of print]
Generalisability of clinical registers used for drug safety and comparative effectiveness research: coverage of the Swedish Biologics Register.
Neovius M, Simard J, Sundström A, Jacobsson L, Geborek P, Saxne T, Feltelius N, Klareskog L, Askling J; for the ARTIS Study Group.

OBJECTIVE: /st> To determine coverage and generalisability of data in the Swedish Biologics Register ARTIS.
METHODS: /st> Patients with adult onset rheumatoid arthritis (RA) were identified in the National Patient Register and the Swedish Rheumatology Quality Register, including the ARTIS cohort of patients exposed to biological agents. Exposure to etanercept and adalimumab between 2006 and 2008 was determined by register linkage to the Prescribed Drug Register which contains patient-level data on >99% of all etanercept and adalimumab use in Sweden.
RESULTS: /st> Of 62 897 patients with RA, 6510 had received treatment with etanercept or adalimumab according to the Prescribed Drug Register. Of these, 5673 were also registered in ARTIS, resulting in a national coverage of 87%. The regional variation was small with >85% coverage in 18 of 21 counties. In multivariable analysis, ARTIS-registered and non-registered patients did not differ by age (p=0.62), sex (p=0.84) or education level (p=0.24).
CONCLUSION: /st> Nationwide drug dispensing and demographic data may function as quality metrics for coverage and generalisability assessments. Using such data, the coverage of ARTIS was estimated at 87% with no indications of compromised external generalisability regarding demography.

Acta Derm Venereol. 2010 Nov 19. doi: 10.2340/00015555-0959. [Epub ahead of print]
Tolerability and Safety of Biological Therapies for Psoriasis in Daily Clinical Practice: A Study of 103 Italian Patients.
Brunasso AM, Puntoni M, Salvini C, Delfino C, Curcic P, Gulia A, Massone C.

Studies comparing the safety and tolerability of biological therapies for psoriasis in the long-term and in daily clinical practice are lacking. Most published studies are of selected patients with short-term (3-6 months) follow-up. We performed a retrospective cohort study of 103 patients in order to describe the frequency and the clinical features of adverse events, and to evaluate and compare the tolerability and safety of efalizumab, etanercept, infliximab, and adalimumab in clinical practice. A total of 136 courses of biological therapies were administered, with a mean duration of 16 months/patient; 55 patients received efalizumab, 45 etanercept, 33 infliximab, and 3 adalimumab. Infliximab had an incidence rate ratio of suspension due to severe adverse events 5.9 times (95% confidence interval (95% CI) 1.9-18, $p < 0.001$) higher than etanercept and 9.8 times (95% CI 3.2-30.1, $p < 0.001$) higher than efalizumab. Safety profiles for efalizumab and etanercept were more favourable than for infliximab. Concerning tolerability, we found that more patients responded to infliximab, but long-term tolerability was higher for both efalizumab and etanercept due to the better safety profile and a higher compliance to therapy.