

# Literature Update Immunology

Period: 01-30 Sept 2010

## IBD

- **Infliximab and azathioprine** for Crohn's disease: **a super-sonic combination?**
- **Infliximab paediatric Crohn's disease educational plan:** a European, cross-sectional, multicentre evaluation.
- **Infliximab** dependency is related to **decreased surgical rates** in adult Crohn's disease patients.
- **Infliximab improves inflammation** and anthropometric measures in pediatric Crohn's disease.
- Lifestyle-related disease in Crohn's disease: relapse prevention by a semi-vegetarian diet.
- Maintenance of **clinical benefit in Crohn's disease patients after discontinuation of infliximab:** long-term follow-up of a single centre cohort.
- Infliximab, azathioprine, or combination therapy for Crohn's disease.
- Natural history of **Crohn's disease** in a **population-based cohort** from Cardiff (1986-2003): a study of **changes in medical treatment and surgical resection rates.**
- **Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis:** a prospective multicentre comparison of predicting outcomes and monitoring response.
- Letter: **Comment on 'Predicting the response to infliximab from trough serum levels'**
- **Appraisal of the pediatric Crohn's disease activity index** on four prospectively collected datasets: recommended cutoff values and clinimetric properties.
- **Usefulness of co-treatment with immunomodulators** in patients with **inflammatory bowel disease** treated with **scheduled infliximab maintenance therapy.**
- A **fulminant colitis index** greater or equal to 8 is not predictive of **colectomy risk** in **infliximab-treated moderate-to-severe ulcerative colitis** attacks.
- **Investigational agents for Crohn's disease.**
- **Infliximab dependency** is related to decreased **surgical rates** in adult **Crohn's disease** patients.
- **Local injection of adalimumab for perianal Crohn's disease:** Better than infliximab?
- **Healing of anastomotic enterocutaneous fistulae** due to **Crohn's disease** by anti-TNF-alpha antibodies.
- **Phase I, double-blind, randomized, placebo-controlled, dose-escalation study of NI-0401 (a fully human anti-CD3 monoclonal antibody)** in patients with **moderate to severe active Crohn's disease.**
- Can **fecal calprotectin** or **lactoferrin** identify postoperative **recurrence in Crohn's disease?**
- **Management of inflammatory bowel diseases:** A changing paradigm. Can we finally change the disease course?
- Review article: **stem cell therapies for inflammatory bowel disease** – efficacy and safety.
- Clinical trial: **colectomy after rescue therapy in ulcerative colitis** – 3-year follow-up of the **Swedish-Danish controlled infliximab study.**
- **Appropriateness of therapy for fistulizing Crohn's disease:** findings from a national inflammatory bowel disease cohort.
- The **CHOICE trial: adalimumab** demonstrates **safety, fistula healing, improved quality of life and increased work productivity** in patients with **Crohn's disease who failed prior infliximab therapy.**
- Trends in **surgery for Crohn's disease** in the era of infliximab.
- **Endoscopic monitoring of infliximab therapy in Crohn's disease.**
- **Infliximab, azathioprine, or combination therapy for Crohn's disease.**
- Treatment of **complex perianal fistulas in Crohn disease:** infliximab, surgery or combined approach.

## Safety

- **ELISPOT-IFN- $\gamma$  assay instead of tuberculin skin test** for detecting latent Mycobacterium tuberculosis infection in rheumatic patients candidate to anti-TNF- $\alpha$  Treatment.
- **Psoriatic skin lesions** induced by tumor necrosis factor antagonist therapy: **clinical features** and possible immunopathogenesis.
- **Risk factors for severe infections** in patients with rheumatoid arthritis treated with **rituximab** in the autoimmunity and rituximab.
- **Liver dysfunction related to hepatitis B and C** in patients with **inflammatory bowel disease** treated with **immunosuppressive therapy**.
- Liver dysfunction in patients with IBD under immunosuppressive treatment: do we need to fear? (Commentary)
- Mapping the **safety profile of biologicals**: a disproportionality analysis using the WHO adverse drug reaction database, Vigibase.
- **Cutaneous drug eruption** with an interface dermatitis pattern due to **anti-tumour necrosis factor-alpha agents**: a relevant class-effect.
- Occurrence of **pustular psoriasis** after treatment of **Crohn disease** with **infliximab**.
- **Natural killer cell lymphoma** in a pediatric patient with **inflammatory bowel disease**.
- **Inflammatory bowel disease** and **pregnancy**: report of two cases treated with **infliximab** and a review of the literature.
- **Psoriatic skin lesions** induced by **certolizumab pegol**.
- **Safety of adalimumab in Crohn's disease during pregnancy**: Case report and review of the literature.
- **Inadvertent conception** during **concomitant treatment with infliximab and** methotrexate in a patient with **Crohn's disease**: is the game worth the candle?
- Incidence and **risk of hospitalisation** due to **shingles and chickenpox** in patients with **rheumatic diseases** treated with **TNF antagonists**.
- A novel method for the **detection of antibodies to adalimumab** in the presence of **drug reveals "hidden" immunogenicity** in **rheumatoid arthritis** patients.
- **Infliximab-induced psoriaform rash**.

## **IBD**

Gastroenterology. 2010 Sep;139(3):1059-61. Epub 2010 Jul 24.

### **Infliximab and azathioprine for Crohn's disease: a super-sonic combination?**

Peyrin-Biroulet L, Danese S.

No abstract available

Drug Saf. 2010 Jun 1;33(6):489-501.

### **Infliximab paediatric Crohn's disease educational plan: a European, cross-sectional, multicentre evaluation.**

Arana A, Allen S, Burkowitz J, Fantoni V, Ghatnekar O, Rico MT, Vanhaverbeke N, Wentworth CE, Brosa M, Arellano FM.

**BACKGROUND:** The infliximab (Remicade; Schering-Plough, Kenilworth, NJ, USA) Risk Management Plan included the development, execution and tracking of an education programme directed towards prescribers of infliximab for patients with paediatric Crohn's disease (the Infliximab Paediatric Crohn's Disease Educational Plan). The programme content consisted of educational materials and communications aimed at educating prescribers on the risks associated with infliximab use.

**OBJECTIVE:** To evaluate the effectiveness of the risk minimization plan.

**METHODS:** Evaluation focused on two components: documentation of training of sponsors' personnel, and evaluation of awareness among prescribing physicians in European countries. Treating physicians, identified both independently of the sponsor (6 countries) and by the sponsor (24 countries), were surveyed using a structured questionnaire.

**RESULTS:** Training of internal staff on the educational programme was performed and completed by every person designated an appropriate candidate for the programme in all European countries. The independent survey conducted in Germany, France, Italy, Spain, Sweden and the UK indicated that around 90% of the physicians were either paediatric gastroenterologists (57%) or paediatricians (33%). The great majority (96%) of the interviewed physicians were currently treating paediatric Crohn's disease, and most were currently using infliximab in their treatment of the disease. More specifically, 82% of gastroenterologists treating paediatric Crohn's disease were using infliximab; among paediatricians, the proportion was lower (42%). Ninety-six percent of paediatric gastroenterologists or gastroenterologists declared themselves aware of the benefits and risks of using infliximab for the treatment of paediatric Crohn's disease; in comparison, fewer paediatricians (82%) declared themselves aware of these benefits and risks. The majority initially gained awareness through congresses and workshops, and at the time of the survey only 25% declared that they were made aware of the benefits and risks through the educational programme. However, the majority of physicians reported that they had been approached by the sponsor's personnel in France (98%), Italy (100%), Spain (83%) and Sweden (70%). In Germany and the UK this proportion was 42%. Almost all physicians were aware of the need to perform tuberculosis (TB) and cancer screening prior to initiating therapy with infliximab, and to screen for hypersensitivity reactions before, during and after treatment. Ninety percent of the physicians were aware of the need to update immunization therapy before initiating therapy and, except in Italy (92% aware), around 50% of the physicians were aware of the need to provide patients with the infliximab Patient Alert Card. In the other European countries where the survey took place among physicians identified by the sponsor, 99% of paediatric gastroenterologists and 90% of gastroenterologists or paediatricians declared themselves aware of the benefits and risks of using infliximab for the treatment of paediatric Crohn's disease, and all of them were aware of the risk of TB and opportunistic infections and the need to perform TB and cancer screening prior to initiating therapy with infliximab.

**CONCLUSIONS:** Overall, the results of the evaluation of the Infliximab Paediatric Crohn's Disease Educational Plan were satisfactory. The objective of education of internal personnel of the pharmaceutical companies distributing infliximab was completely achieved; over 90% of physicians reported being aware of the benefits and risks of infliximab for the treatment of paediatric Crohn's disease. Further work should be carried out across all countries to educate physicians on providing patients with the infliximab Patient Alert Card. In Germany and the UK in particular, where <50% of physicians reported having been approached by the sponsor's personnel, further work is needed to raise awareness of the educational programme.

Eur J Gastroenterol Hepatol. 2010 Oct;22(10):1196-1203.

**Infliximab dependency is related to decreased surgical rates in adult Crohn's disease patients.**

Pedersen N, Duricova D, Lenicek M, Elkjaer M, Bortlik M, Andersen PS, Vitek L, Davidsen B, Wewer V, Lukas M, Munkholm P.

**BACKGROUND:** Infliximab dependency in children with Crohn's disease (CD) has recently been described and found to be associated with a decreased surgery rate.

**AIM:** To assess infliximab dependency of adult CD patients, evaluate the impact on surgery, and search for possible clinical and genetic predictors.

**METHODS:** Two hundred and forty-five CD patients treated with infliximab were included from Danish and Czech Crohn Colitis Database (1999-2006). Infliximab response was assessed as immediate outcome, 1 month after infliximab start: complete, partial, and no response. Three months outcome, after last intended infusion: prolonged response (maintenance of complete/partial response), infliximab dependency (relapse requiring repeated infusions to regain complete/partial response or need of infliximab >12 months to sustain response).

**RESULTS:** Forty-seven percent obtained prolonged response, 29% were infliximab dependent and 24% nonresponders. The cumulative probability of surgery 40 months after infliximab start was 20% in prolonged responders, 23% in infliximab-dependent patients and 76% in nonresponders ( $P < 0.001$ ). The cumulative probability of surgery at 40 months in patients on maintenance versus on demand regime was 33 and 31%, respectively ( $P = 0.63$ ). No relevant clinical or genetic predictors were identified.

**CONCLUSION:** The infliximab dependency response seems to be equivalent to the prolonged response in adult CD patients when comparing surgery rates.

J Gastroenterol Hepatol. 2010 Apr;25(4):810-6.

**Infliximab improves inflammation and anthropometric measures in pediatric Crohn's disease.**

Sinitsky DM, Lemberg DA, Leach ST, Bohane TD, Jackson R, Day AS.

**BACKGROUND AND AIM:** Infliximab (IFX) is a monoclonal antibody licensed to treat medically refractory Crohn's disease (CD). Our aim was to elucidate the effects of IFX therapy on clinical, growth and serum parameters in children with CD in a single pediatric center in Sydney, Australia.

**METHODS:** A retrospective case series review of children treated with IFX for CD at Sydney Children's Hospital, Australia was undertaken, with a review of outcomes after starting IFX. Main outcome measures were response and remission (as measured according to improvements in Pediatric Crohn's Disease Activity Index scores and Physician Global Assessment), laboratory markers (C-reactive protein, erythrocyte sedimentation rate, hemoglobin, white cell count, lymphocytes, neutrophils, platelets, albumin) and growth (Z scores).

**RESULTS:** The 16 patients included had a mean age at first infusion of 13.0 years (1.25-17.5 years). Six of 12 patients (with adequate data available) were in remission at 2 weeks following the first infusion. At 1 year, 10 of 12 patients (83%) were in remission. Mean C-reactive protein and erythrocyte sedimentation rate had fallen significantly ( $P < 0.05$ ) at 2 weeks (from 29 to 7 mg/L and 40 to 19 mm/h, respectively). Positive trends were observed for all other parameters, excluding lymphocytes and white cell count. At 1 year, mean Z score for body mass index improved significantly from -0.9 to -0.1 ( $P < 0.01$ ).

**CONCLUSIONS:** Disease activity subsides in most children treated with IFX for CD. IFX therapy also improves some growth parameters. The pattern of improvement requires further elucidation, as the results in the present study suggest differing dosing frequency of infusion may achieve better efficacy.

World J Gastroenterol. 2010 May 28;16(20):2484-95.

**Lifestyle-related disease in Crohn's disease: relapse prevention by a semi-vegetarian diet.**

Chiba M, Abe T, Tsuda H, Sugawara T, Tsuda S, Tozawa H, Fujiwara K, Imai H.

**AIM:** To investigate whether semi-vegetarian diet (SVD) has a preventive effect against relapse of Crohn's disease (CD) in patients who have achieved remission, who are a high-risk group for relapse.

**METHODS:** A prospective, single center, 2-year clinical trial was conducted. Twenty-two adult CD patients who achieved clinical remission either medically ( $n = 17$ ) or surgically ( $n = 5$ ) and consumed an SVD during hospitalization were advised to continue with an SVD and avoid known high-risk foods for inflammatory bowel disease. The primary endpoint was clinical relapse defined as the appearance of active symptoms of CD. Kaplan-Meier survival analysis was used to calculate the cumulative proportion of patients who had a relapse. A 2-year analysis of relapse rates of patients who followed an SVD and those who did not (an omnivorous diet group) was undertaken.

**RESULTS:** SVD was continued by 16 patients (compliance 73%). Remission was maintained in 15 of 16 patients (94%) in the SVD group vs two of six (33%) in the omnivorous group. Remission rate with SVD was 100% at 1 year and 92% at 2 years. SVD showed significant prevention in the time to relapse compared to that in the omnivorous group ( $P = 0.0003$ , log rank test). The concentration of C-reactive protein was normal at the final visit in more than half of the patients in remission who were taking an SVD, who maintained remission during the study (9/15; 60%), who terminated follow-up (8/12; 67%), and who completed 2 years follow-up (7/10; 70%). There was no untoward effect of SVD.  
**CONCLUSION:** SVD was highly effective in preventing relapse in CD.

Aliment Pharmacol Ther. 2010 Aug 30. doi: 10.1111/j.1365-2036.2010.04446.x. [Epub ahead of print]

**Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort.**

Waugh AW, Garg S, Matic K, Gramlich L, Wong C, Sadowski DC, Millan M, Bailey R, Todoruk D, Cherry R, Teshima CW, Dieleman L, Fedorak RN.

**Background** Tumour necrosis factor-blockade with infliximab has advanced the treatment of Crohn's disease. While infliximab is efficacious, it remains to be determined whether patients who enter clinical remission with an anti-tumour necrosis factor therapy can have their treatment stopped and retain the state of remission. **Aim** to assess in patients with Crohn's disease who obtained infliximab-induced remission, the proportion who relapsed after infliximab discontinuation. **Methods** This longitudinal cohort study examined patients from a University-based IBD referral centre. Forty eight patients with Crohn's disease in full clinical remission and who then discontinued infliximab were followed up for up to 7 years. Crohn's disease relapse was defined as an intervention with Crohn's disease medication or surgery. **Results** Kaplan-Meier analysis of the proportion of patients with sustained clinical benefit demonstrated that 50% relapsed within 477 days after infliximab discontinuance. In contrast, 35% of patients remained well, and without clinical relapse, up to the end of the nearly 7-year follow-up. **Conclusion** In patients with Crohn's disease with an infliximab-induced remission, stopping infliximab results in a predictable relapse in a majority of patients. Nevertheless, a small percentage of patients sustain a long-term remission.

N Engl J Med. 2010 Sep 9;363(11):1086-8.

**Infliximab, azathioprine, or combination therapy for Crohn's disease.**

Letter to the Editor

No abstract available

Gut. 2010 Sep;59(9):1200-6. Epub 2010 Jul 21.

**Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates.**

Ramadas AV, Gunesh S, Thomas GA, Williams GT, Hawthorne AB.

**INTRODUCTION:** Benefits of immunosuppressive therapy in Crohn's disease have been demonstrated in controlled trials; however, it is unclear whether these drugs alter the longer-term natural history of this condition.

**AIMS AND METHODS:** To assess changes in disease outcomes in a population-based cohort of patients diagnosed in Cardiff from 1986 to 2003. Case notes from Crohn's disease incidence studies in Cardiff were reviewed retrospectively for disease characteristics and follow-up information on drug therapy, and the need for surgery for Crohn's disease. The study population was divided into three groups by year of diagnosis (Group A=1986-1991, Group B=1992-1997 and Group C=1998-2003).

**RESULTS:** 341 patients were included. Kaplan-Meier (KM) analysis showed increasing use of immunosuppressants over time. At 5 years after diagnosis this was 11% in Group A, 28% in Group B, and 45% in Group C ( $p=0.001$ ) and the median time to start of thiopurines was 77, 21 and 11 months in Group A, B and C respectively. There was a significant reduction in long-term steroid use at 5 years post diagnosis: 45 (44%), 31 (31%) and 24 (19%) patients in Group A, B and C respectively ( $p=0.001$ ). KM analysis showed a significant reduction in the cumulative probability of intestinal surgery: At 5 years this was 59% (Group A), 37% (Group B) and 25% (Group C) ( $p=0.001$ ). In a multivariate Cox analysis, year of diagnosis, disease location, oral corticosteroids within 3 months of diagnosis and early thiopurine use (within the first year of diagnosis) were all independent factors affecting likelihood of intestinal surgery.

CONCLUSION: This population-based cohort shows marked changes in rates of surgery, and the reduction is independently associated with year of diagnosis, and associated temporally with increased and earlier thiopurine use.

Gut. 2010 Sep;59(9):1207-12.

**Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicentre comparison of predicting outcomes and monitoring response.**

Turner D, Leach ST, Mack D, Uusoue K, McLernon R, Hyams J, Leleiko N, Walters TD, Crandall W, Markowitz J, Otley AR, Griffiths AM, Day AS.

OBJECTIVE: To compare four faecal markers for their ability to predict steroid refractoriness in severe paediatric ulcerative colitis (UC). Construct validity and responsiveness to change were also assessed. METHODS: This was a prospective multicentre cohort study. Stool samples from 101 children (13.3 + or - 3.6 years; Pediatric UC Activity Index (PUCAI) at admission 72 + or - 12 points) were obtained at the third day of intravenous steroid therapy. Repeated samples at discharge were obtained from 24 children. Predictive validity was assessed using diagnostic utility statistics to predict steroid failure (ie, the need for salvage treatment). Concurrent validity was assessed using correlational analysis with the following constructs: PUCAI, Lindgren and Seo scores, physician's global assessment, albumin, erythrocyte sedimentation rate and C-reactive protein (CRP). Responsiveness was assessed using test utility and correlational strategies.

RESULTS: Median values (IQR) were very high at baseline for all four markers (calprotectin 4215 microg/g (2297-8808); lactoferrin 212 microg/g (114-328); M2-pyruvate kinase (M2-PK) 363 U/g (119-3104); and S100A12 469 microg/g (193-1112)). M2-PK was numerically superior to the other three markers and CRP in predicting response to corticosteroid treatment (area under the receiver operating characteristic (ROC) curve 0.75 (95% CI 0.64 to 0.85;  $p < 0.001$ ) vs  $< 0.65$  for the others). However, it did not add to the predictive ability of the PUCAI (area under the ROC 0.81 (95% CI 0.73 to 0.89)). M2-PK also had the highest construct validity but with a modest mean correlation with all constructs ( $r = 0.3$ ;  $p < 0.05$ ). None of the markers was responsive to change (Spearman's rho correlation with change in the PUCAI  $< 0.1$ ;  $p > 0.05$ , area under the ROC curve  $< 0.65$ ;  $p > 0.05$ ).

CONCLUSIONS: The four markers were greatly elevated in severe paediatric UC. Only M2-PK had good construct and predictive validity, and none was responsive to change. The PUCAI, a simple clinical index, performed better than the faecal markers in predicting outcome following a course of intravenous corticosteroids in severe UC.

Gut. 2010 Sep;59(9):1298-9; and author reply 1299-300.

**Comment on 'Predicting the response to infliximab from trough serum levels'.**

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

No abstract available

Am J Gastroenterol. 2010 Sep;105(9):2085-92. Epub 2010 Apr 6.

**Appraisal of the pediatric Crohn's disease activity index on four prospectively collected datasets: recommended cutoff values and clinimetric properties.**

Turner D, Griffiths AM, Walters TD, Seah T, Markowitz J, Pfefferkorn M, Keljo D, Otley A, Leleiko NS, Mack D, Hyams J, Levine A.

OBJECTIVES: The Pediatric Crohn's Disease Activity Index (PCDAI) is the outcome measure of choice in clinical trials of pediatric Crohn's disease. The aim of this study was to provide knowledge on its performance and accuracy of different cutoff scores.

METHODS: Longitudinal data prospectively generated from four sources were used, including the REACH and budesonide trials, a North-American inflammatory bowel diseases (IBD) registry, and a cohort aimed at evaluating growth. Cutoff values of disease activity were determined by physician global assessment from the pooled cohort using serial receiver operator characteristic curves and area under the curve (AUC) as well as comparing the overall accuracy. Test-retest reliability and responsiveness were ascertained by comparing the baseline and follow-up scores, using an external anchor.

RESULTS: A total of 437 children were included (268 (61%) males, mean age 12.9 +/- 2.6 years). To define remission, a composite definition of  $< 10$  points or  $< 7.5$  points without the height item had the highest accuracy; this addressed the limitation that height is not a responsive item. The best cutoff of 10-

27.5 was determined for mild disease, 30-37.5 for moderate disease, 40-100 for severe disease, and a change of >12.5 points for response (AUC 0.8-0.9; P<0.001). Ninety children whose disease remained unchanged showed fair test-retest reliability (intraclass correlation coefficient=0.74-0.8; P<0.001). The PCDAI showed good responsiveness, as reflected from the correlational (r=0.7; P<0.001), distributional (Guyatt's responsiveness statistics=0.9), and diagnostic utility analysis (AUC 0.85 (95% confidence interval 0.81-0.88).

**CONCLUSIONS:** The clinimetric properties of the PCDAI are sufficient to support its use in clinical research. Cutoff values suggested by this study differ slightly from those previously published on much smaller cohorts.

Gut. 2010 Oct;59(10):1363-8. Epub 2010 Jun 29.

**Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy.**

Sokol H, Seksik P, Carrat F, Nion-Larmurier I, Vienne A, Beaugerie L, Cosnes J.

**BACKGROUND AND AIMS:** Concomitant use of immunosuppressants (IS) with scheduled infliximab (IFX) maintenance therapy for Crohn's disease (CD) or ulcerative colitis (UC) is debated. The aim of this study was to assess whether IS co-treatment is useful in patients with inflammatory bowel disease (IBD) on scheduled IFX infusions.

**METHODS:** 121 consecutive patients with IBD (23 UC, 98 CD) treated by IFX and who received at least 6 months of IS co-treatment (azathioprine (AZA) or methotrexate (MTX)) were studied. In each patient, the IFX treatment duration was divided into semesters which were independently analysed regarding IBD activity.

**RESULTS:** Semesters with IS (n=265) and without IS (n=319) were analysed. IBD flares, perianal complications and switch to adalimumab were less frequently observed in semesters with IS than in those without IS (respectively: 19.3% vs 32.0%, p=0.003; 4.1% vs 11.8%, p=0.03; 1.1% vs 5.3%, p=0.006).

Maximal C-reactive protein (CRP) level and IFX dose/kg observed during the semesters were lower in semesters with IS. Within semesters with IS, IBD flares and perianal complications were less frequently observed in semesters with AZA than in those with MTX. In multivariate analysis, IS co-treatment was associated with a decreased risk of IBD flare (OR 0.52; 95% CI 0.35 to 0.79).

**CONCLUSION:** In patients with IBD receiving IFX maintenance therapy, IS co-treatment is associated with reduced IBD activity, IFX dose and switch to adalimumab. In this setting, co-treatment with AZA seems to be more effective than co-treatment with MTX. Benefit of such a combination treatment has to be balanced with potential risks, notably infections and cancers.

Gastroenterol Clin Biol. 2010 Sep 8. [Epub ahead of print]

**A fulminant colitis index greater or equal to 8 is not predictive of colectomy risk in infliximab-treated moderate-to-severe ulcerative colitis attacks.**

Baudet A, Colombel JF, Cortot A, Dupas JL, Brazier F, Savoye G, Lerebours E, Justum AM, Reimund JM.

**INTRODUCTION:** In severe attacks of ulcerative colitis (UC) treated with intravenous corticosteroids, a fulminant colitis index (FCI) greater or equal to 8 has been associated with a greater likelihood of colectomy (72 vs 16% with an FCI<8). This retrospective study aimed to assess the accuracy of such an association in infliximab-treated patients with moderate-to-severe bouts of UC.

**PATIENTS AND METHODS:** The study was based on the medical files of 43 patients who had received at least one infusion of infliximab to treat moderate-to-severe UC (partial Mayo Clinic score). Remission and clinical response were also assessed using the partial Mayo score. The accuracy of an FCI greater or equal to 8 to predict the likelihood of colectomy was assessed by calculating the sensitivity, specificity, positive and negative predictive values, Yule's Q coefficient, Youden's index and statistical significance (Chi(2) test).

**RESULTS:** After treatment with infliximab, 10 patients were in remission (23.3%), 21 (48.8%) had a clinical response, four (9.3%) had treatment failure (without, however, requiring colectomy) and eight (18.6%) had a colectomy. Calculation of the above-mentioned indicators revealed that an FCI greater or equal to 8 was not an indicator of the risk of colectomy in this patient population, and found that only an FCI greater or equal to 16 was statistically significant. However, low values for sensitivity, positive predictive value and Youden's index preclude the clinical application of this latter result.

**CONCLUSION:** In patients treated with infliximab for moderate-to-severe UC attacks, the FCI is not a predictor of colectomy. In such patients, the factors predictive of a response to treatment or likelihood of

colectomy, currently acknowledged with corticosteroid treatment, need to be further assessed for infliximab treatment.

Expert Opin Investig Drugs. 2010 Oct;19(10):1147-59.

**Investigational agents for Crohn's disease.**

Cottone M, Orlando A, Renna S.

**IMPORTANCE OF THE FIELD:** Increased understanding of the biological mechanisms of Crohn's disease has opened the door to a large number of new molecules; some of these are approved for clinical use, while others remain under evaluation. In this review, we examine the clinical efficacy of all the new drugs that have been evaluated in controlled trials in the last 12 years.

**AREAS COVERED IN THIS REVIEW:** Anti-TNF therapy has been reviewed briefly, given the many comprehensive reviews on this topic; attention is focused mainly on the other biological therapies. In assessing the clinical efficacy of these molecules, we consider only the remission rate, as this is considered the most meaningful end point in clinical practice.

**WHAT THE READER WILL GAIN:** We analyzed the main biological mechanisms of Crohn's disease and the new drugs whose use is based on insights into these mechanisms. We reviewed the following new drugs: probiotics, GM-CSF, IL-10, IL-11, anti-IL-6, anti-IL-12/-23, everolimus, anti-IFN- $\gamma$ , IFN- $\beta$ -I, co-stimulators, anti-integrins, anti-intercellular adhesion molecule 1, small molecules and mitogen-activated protein kinase inhibitors.

**TAKE HOME MESSAGE:** Anti-TNF therapies remain the best options, followed by anti-integrin drugs. The most promising new therapies are anti-IL-23, but further data are necessary. The disappointing results with other molecules may depend on the quality of trials and possibly on inadequate dosage of the drug.

Eur J Gastroenterol Hepatol. 2010 Oct;22(10):1196-203.

**Infliximab dependency is related to decreased surgical rates in adult Crohn's disease patients.**

Pedersen N, Duricova D, Lenicek M, Elkjaer M, Bortlik M, Andersen PS, Vitek L, Davidsen B, Wewer V, Lukas M, Munkholm P.

**BACKGROUND:** Infliximab dependency in children with Crohn's disease (CD) has recently been described and found to be associated with a decreased surgery rate.

**AIM:** To assess infliximab dependency of adult CD patients, evaluate the impact on surgery, and search for possible clinical and genetic predictors.

**METHODS:** Two hundred and forty-five CD patients treated with infliximab were included from Danish and Czech Crohn Colitis Database (1999-2006). Infliximab response was assessed as immediate outcome, 1 month after infliximab start: complete, partial, and no response. Three months outcome, after last intended infusion: prolonged response (maintenance of complete/partial response), infliximab dependency (relapse requiring repeated infusions to regain complete/partial response or need of infliximab >12 months to sustain response).

**RESULTS:** Forty-seven percent obtained prolonged response, 29% were infliximab dependent and 24% nonresponders. The cumulative probability of surgery 40 months after infliximab start was 20% in prolonged responders, 23% in infliximab-dependent patients and 76% in nonresponders ( $P < 0.001$ ). The cumulative probability of surgery at 40 months in patients on maintenance versus on demand regime was 33 and 31%, respectively ( $P = 0.63$ ). No relevant clinical or genetic predictors were identified.

**CONCLUSION:** The infliximab dependency response seems to be equivalent to the prolonged response in adult CD patients when comparing surgery rates.

Inflamm Bowel Dis. 2010; 16(10): 1631

**Local injection of adalimumab for perianal Crohn's disease: Better than infliximab?**

Poggioli G, Laureti S, Pierangeli F, Bazzi P, Coscia M, Gentilini L, Gionchetti P, Rizzello F.

No abstract available

Inflamm Bowel Dis. 2010; 16(10): 1632-33

**Healing of anastomotic enterocutaneous fistulae due to Crohn's disease by anti-tNF-alpha antibodies.**

Cougard PA, Desjeux A, Berdah S, Ezzedine S, Barthet M, Grimaud JC.

No abstract available

Inflamm Bowel Dis. 2010 Oct;16(10):1708-16.

**Phase I, double-blind, randomized, placebo-controlled, dose-escalation study of NI-0401 (a fully human anti-CD3 monoclonal antibody) in patients with moderate to severe active Crohn's disease.**

van der Woude CJ, Stokkers P, van Bodegraven AA, Van Assche G, Hebzda Z, Paradowski L, D'Haens G, Ghosh S, Feagan B, Rutgeerts P, Dijkstra G, de Jong DJ, Oldenburg B, Farhan M, Richard T, Dean Y, Hommes DW; Initiative on Crohn's and Colitis, The Netherlands.

**BACKGROUND:** NI-0401 is a fully human monoclonal antibody, which binds to the CD3 subunit of the T-cell receptor, causing modulation of T-cell activity. We investigated the safety and the ability to modulate the TCR-CD3 complex of NI-0401 in patients with active Crohn's disease (CD).

**METHODS:** A double-blind, placebo-controlled, randomized, multicenter, dose-escalating trial was conducted in CD patients age 18-70 years, a Crohn's Disease Activity Index (CDAI) of 220-450, and detectable levels of C-reactive protein. The primary outcome was safety and the ability of NI-0401 to modulate the TCR-CD3 complex on T cells. Efficacy parameters included the proportion of patients achieving remission (CDAI <150), clinical response (CDAI fall  $\geq$ 100), and change from baseline in the CD Endoscopy Index of Severity (CDEIS).

**RESULTS:** Forty patients received placebo (n = 7) or NI-0401 (n = 33) 0.05-10 mg daily for 5 days. NI-0401 doses  $\leq$ 1 mg were well tolerated. Infusion reactions occurred at doses  $\geq$ 2 mg. The extent and duration of TCR-CD3 modulation increased with dose. No differences between groups were observed in the proportions of patients achieving clinical remission or response. The mean CDEIS at week 6 differed significantly between the 1-mg and placebo group.

**CONCLUSIONS:** NI-0401 was tolerated at doses  $\leq$ 1 mg with manageable side effects. NI-0401 induced a dose-dependent modulation of the TCR-CD3 complex. No significant improvement of CDAI was observed but 1 mg NI-0401 demonstrated an improvement in CDEIS.

Inflamm Bowel Dis. 2010 Oct;16(10):1814-5.

**Can fecal calprotectin or lactoferrin identify postoperative recurrence in Crohn's disease?**

Seibold F, Schoepfer AM.

No abstract available

Inflamm Bowel Dis. 2010 Oct;16(10):1816-7.

**Management of inflammatory bowel diseases: a changing paradigm. Can we finally change the disease course?**

Lakatos PL.

No abstract available

Aliment Pharmacol Ther. 2010 Oct;32(8):939-52.

**Review article: stem cell therapies for inflammatory bowel disease - efficacy and safety.**

García-Bosch O, Ricart E, Panés J.

**Background** Drugs available for the treatment of inflammatory bowel disease fail to induce and maintain remission in a significant number of patients. **Aim** To assess the value of stem cell therapies for treatment of inflammatory bowel disease based on published studies. **Methods** Publications were identified through a MEDLINE search using the Medical Subject Heading terms: inflammatory bowel diseases, or Crohn's disease, or ulcerative colitis, and stem cell, or stromal cell or transplant. **Results** Haematopoietic stem cell therapy as a primary treatment for inflammatory bowel disease was originally supported by animal experiments, and by remissions in patients undergoing transplant for haematological disorders. Later, transplantation specifically performed for patients with refractory Crohn's disease showed long-lasting clinical remission and healing of inflammatory intestinal lesions. Use of autologous nonmyeloablative regimens and concentration of the procedures in centres with large experience are key in reducing treatment-related mortality. Initial trials of mesenchymal stem cell therapy with local injection

in Crohn's perianal fistulas had positive results. Conclusions Autologous haematopoietic stem cell transplant changes the natural course of Crohn's disease, and may be a therapeutic option in patients with refractory disease if surgery is not feasible due to disease location or extension.

Aliment Pharmacol Ther. 2010 Oct;32(8):984-989

**Clinical trial: colectomy after rescue therapy in ulcerative colitis – 3-year follow-up of the Swedish-Danish controlled infliximab study**

A. Gustavsson, G. J rnerot, E. Hertervig, I. Friis-Liby, L. Blomquist, P. Karlén, C. Gr nnö, M. Vilien, M. Ström, H. Verbaan, P. M. Hellström, A. Magnuson, J. Halfvarson and C. Tysk

No abstract available

Aliment Pharmacol Ther. 2010 Oct;32(8):1007-1016

**Appropriateness of therapy for fistulizing Crohn's disease: findings from a national inflammatory bowel disease cohort**

V. Pittet, P. Juillerat, P. Michetti, J.-P. Vader, B. Burnand, G. Rogler, C. Beglinger, F. Seibold, C. Mottet, C. Felley, J.-J. Gonvers, F. Froehlich

No abstract available

Aliment Pharmacol Ther published online: 28 sep 2010

**The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy**

S. Lichtiger, D. G. Binion, D. C. Wolf, D. H. Present, A. G. Bensimon, E. Wu, A. P. Yu, A. T. Cardoso, J. Chao, P. M. Mulani, K. G. Lomax and J. D. Kent

No abstract available

Ann Surg. 2010 Aug;252(2):307-12.

**Trends in surgery for Crohn's disease in the era of infliximab.**

Jones DW, Finlayson SR.

**OBJECTIVE:** To examine the use of surgical procedures for Crohn's disease since the introduction of infliximab.

**SUMMARY BACKGROUND DATA:** Prior studies have shown that the overall rate of surgery for Crohn's disease has not changed significantly since the introduction of infliximab, an immunomodulator considered particularly effective in treating Crohn's fistulas. How infliximab has affected individual rates of specific types of procedures, particularly surgery for intestinal fistulas, is unknown.

**METHODS:** We used the Nationwide Inpatient Sample to identify all hospital admissions for Crohn's disease for each year from 1993 through 2004. Cases of Crohn's disease and relevant surgical interventions were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Using US Census data to establish population denominators, trends in population-based rates of use of these procedures were examined over time. Trends were tested for significance with Spearman rank correlation tests.

**RESULTS:** From 1993 to 2004, there was no statistically significant change in population-based rates of small bowel and right colon resection, while rates of left colon resection, other colon resection, and rectal resection declined moderately. However, rates of surgical repair of fistulas of the small intestine, the most commonly performed fistula operation, increased by 60%, from 1.5 per 1,000,000 in 1993 to 2.4 per 1,000,000 in 2004 (P = 0.04).

**CONCLUSIONS:** During the period of adoption of infliximab as a novel treatment for Crohn's disease, overall rates of bowel resections have either remained relatively stable or decreased moderately, while rates of small bowel fistula repair have increased significantly. These findings call into question the effectiveness of infliximab in preventing the need for surgery for Crohn's disease at the population level.

Inflamm Bowel Dis. 2010 Sep 21. [Epub ahead of print]

**Endoscopic monitoring of infliximab therapy in Crohn's disease.**

Björkesten CG, Nieminen U, Turunen U, Arkkila PE, Sipponen T, Färkkilä MA.

**BACKGROUND:** So far, infliximab (IFX) therapy for the treatment of Crohn's disease (CD) has generally been guided by clinical symptoms. Data on treatment response as ascertained by endoscopy in IFX therapy are scarce. The aims of this study were to measure the endoscopic response rate during IFX induction and maintenance therapy in luminal CD, and also evaluate the role of endoscopy in monitoring IFX therapy.

**METHODS:** Data obtained from 71 patients with active luminal CD and treated with IFX were analyzed retrospectively. The endoscopy findings were scored according to mucosal activity as: 0 (remission), 1-2 (mild), 3-4 (moderate), and 5-6 (severe). A positive endoscopic response was determined by a decrease in score of at least two points and mucosal healing was assigned a score of between 0-2.

**RESULTS:** At baseline all patients presented with moderate or severe luminal inflammation. A positive endoscopic response occurred in 73% of patients at 3 months and when IFX was continued, the endoscopic response was maintained in 77% of these patients at 12 months. Mucosal healing at first follow-up endoscopy was documented in 45% of patients and was highly predictive for its persistence at 12 months, maintained in 90% of patients, when IFX was continued.

**CONCLUSIONS:** Endoscopy at 3 months from the start of IFX therapy helps to predict responders to IFX for maintenance therapy in active luminal CD.

N Engl J Med. 2010 Sep 9;363(11):1086-7; author reply 1087-8.

**Infliximab, azathioprine, or combination therapy for Crohn's disease.**

Ruffolo C, Scarpa M, Bassi N.

No abstract available

Can J Surg. 2010 Oct;53(5):299-304.

**Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach.**

Sciaudone G, Di Stazio C, Limongelli P, Guadagni I, Pellino G, Riegler G, Coscione P, Selvaggi F.

**BACKGROUND:** The aim of this study was to compare the outcomes of the management of perianal fistulas in Crohn disease between infliximab, surgery or a combination of surgery and infliximab.

**METHODS:** We prospectively subdivided 35 consecutive patients with Crohn disease with complex perianal fistulas into 3 groups: 11 patients received infliximab (5 mg/kg intravenously at 0, 2 and 6 wk; group A), 10 underwent surgery (group B) and 14 received a combination of surgery and postoperative infliximab (group C). We evaluated the rate and time of healing of perianal fistulas, the rate of recurrences and time to relapse at a median follow-up of 18.8 (standard deviation [SD] 10.8, range 8-38) months.

**RESULTS:** The time to healing of fistulas was significantly shorter among patients who received surgery and infliximab than among those who received surgery alone ( $p < 0.05$ ) and was close to statistically shorter among those who received both treatments than among those who received infliximab alone ( $p = 0.06$ ). Patients who received surgery and infliximab had a significantly longer mean time to relapse ( $p < 0.05$ ) than those who received infliximab (mean 2.6 [SD 0.7] mo) or surgery alone (mean 3.6 [SD 0.5] mo).

**CONCLUSION:** We found better outcomes among patients who received a combination of surgery and infliximab therapy. These patients experienced a short time to healing of fistulas and significantly longer mean time to relapse of complex fistulas.

## **Safety**

Clin Rheumatol. 2010 Oct;29(10):1135-41. Epub 2010 Jul 20.

### **ELISPOT-IFN-gamma assay instead of tuberculin skin test for detecting latent Mycobacterium tuberculosis infection in rheumatic patients candidate to anti-TNF-alpha treatment.**

Girlanda S, Mantegani P, Baldissera E, Aiello P, Ratti M, Sabbadini MG, Fortis C.

In rheumatic patients candidate to anti-TNF-alpha treatment, there is an increased risk of developing tuberculosis (TB). The tuberculin skin test (TST), the standard diagnostic test for latent tuberculosis infection (LTBI), suffers low specificity and sensitivity. Here, we compared the performance characteristics of an in-house ELISPOT-IFN-gamma assay (using a restricted pool of Mycobacterium tuberculosis-specific peptides or MTP) to TST for the diagnosis of LTBI in 69 rheumatic patients candidate to anti-TNF-alpha treatment and in 60 healthy LTBI individuals. Among the 69 patients enrolled, 17 (25%) had a positive TST response and 15 (22%) a positive ELISPOT-MTP response. Among the patients with a positive TST result, eight had a positive and nine a negative ELISPOT-MTP response, whereas among the 49 patients with a negative TST result, 42 were ELISPOT-MTP negative, but seven (14%) were ELISPOT-MTP positive, with three indeterminate results. The agreement between the two tests was poor ( $k = 0.341$ , 95% CI = 0.060 to 0.622) and the test of symmetry was not significant ( $P = 0.8$ ). Considering the ELISPOT assay, rheumatic patients had a reduced number of spot-forming cells after stimulation of lymphocytes with PHA or PPD when compared with healthy LTBI individuals. Thus, the ELISPOT-IFN-gamma assay performs better than the TST in recognizing patients with LTBI, on one hand reducing the number of patients submitted to isoniazid prophylaxis, and on the other hand, since the assay is less biased by immunosuppressive regimens than TST, recognizing LTBI patients among those with a negative TST response.

Semin Arthritis Rheum. 2010 Jun 25. [Epub ahead of print]

### **Psoriatic Skin Lesions Induced by Tumor Necrosis Factor Antagonist Therapy: Clinical Features and Possible Immunopathogenesis.**

Collamer AN, Battafarano DF.

**OBJECTIVE:** The induction or exacerbation of psoriasis in patients treated with tumor necrosis factor (TNF) antagonists is a well-established phenomenon. The goals of this comprehensive literature analysis were to update currently available data regarding this adverse event, to identify any clinical patterns in the cohort of reported patients, and to review the possible immunopathogenesis.

**METHODS:** A systematic literature review was performed utilizing PubMed and Medline databases (1996 to August 2009) searching the index terms "tumor necrosis factor alpha inhibitor," "TNF," "infliximab," "etanercept," "adalimumab," combined with the terms "psoriasis," "pustular," "skin," "rash," "palmoplantar," and "paradoxical." All relevant articles were reviewed. Patients who did not appear to meet accepted classification criteria for their treated disease, who had a more probable explanation or other likely diagnosis for their skin findings or known possible triggering factor for the skin eruption, including infection, were excluded from this analysis.

**RESULTS:** Two hundred seven cases met inclusion criteria for review. Of these, 43% were diagnosed with rheumatoid arthritis, 26% with seronegative spondyloarthritis, and 20% with inflammatory bowel disease. Mean patient age was 45 years and 65% were female. Fifty-nine percent were being treated with infliximab, 22% with adalimumab, and 19% with etanercept. Lesion morphology included pustular psoriasis in 56%, plaque psoriasis in 50%, and guttate lesions in 12%; 15% experienced lesions of more than 1 type. No statistically significant predisposing factors for the development of new-onset psoriasis were found. Sixty-six percent of patients were able to continue TNF antagonist therapy with psoriasis treatments. The pathogenesis appears to involve disruption of the cytokine milieu with production of unopposed interferon-alpha production by plasmacytoid dendritic cells in genetically predisposed individuals. Genetic polymorphisms may play a role in this paradoxical reaction to TNF blockade.

**CONCLUSIONS:** TNF antagonist induced psoriasis is a well-described adverse event without any known predisposing risk factors. Most patients can be managed conservatively without drug withdrawal. Registry data reporting is necessary to define the true incidence and prevalence of this condition. Genomic studies of affected patients may assist with identification of predisposed patients and elucidation of the molecular trigger of this perplexing response.

Arthritis Rheum. 2010; 62(9): 2625-32

**Risk factors of severe infections in patients with rheumatoid arthritis treated with rituximab in the Autoimmunity and Rituximab (AIR) registry.**

Gottenberg J, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, Dougados M, Flipo R, Godeau B, Guillevin L, Le Loët X, Hachulla E, Schaeferbeke T, Sibilia J, Baron G, Mariette X; on behalf of all the investigators of the AIR registry the French Society of Rheumatology..

**OBJECTIVE.:** The risk of a severe infection is a crucial factor in the assessment of the short-term risk/benefit ratio of biologic drugs in rheumatoid arthritis (RA). There is no increase in severe infections in RA patients treated with rituximab (RTX) in controlled trials, but this has not yet been assessed in daily practice. We investigated the occurrence and risk factors of severe infections in off-trial patients using data from the AIR (AutoImmunity and Rituximab) registry. **PATIENTS AND METHODS.:** The AIR registry was set up by the French Society of Rheumatology. The charts of patients with severe infections were reviewed. **RESULTS.:** 1303 of the included patients had at least 1 follow-up visit at 3 months or later, with a mean follow-up of 1.2 +/- 0.8 years (1690 patient-years). Eighty-two severe infections occurred in 78 patients (5.0 severe infections/100 patient-years), half of them in the 3 months following last RTX infusion. Multivariate analysis showed that chronic lung disease and/or cardiac insufficiency (OR 3.0, 95%CI [1.3-7.3], P= 0.01), extra-articular involvement (OR 2.9 [1.3-6.7], P= 0.009), and hypo IgG (below 6g/l) before initiation of RTX (OR 4.9 [1.6-15.2], P= 0.005) were significantly associated with increased risk of a severe infection. **CONCLUSION.:** The rate of severe infections in current practice is similar to that reported in clinical trials. The risk factors of severe infections include chronic lung and/or cardiac disease, extra-articular involvement, and hypo IgG before RTX. This suggests that serum IgG should be checked and the benefice/risk balance of RTX discussed for each patient having hypo IgG.

Gut. 2010 Oct;59(10):1340-6. Epub 2010 Jun 24.

**Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy.**

Loras C, Gisbert JP, Mínguez M, Merino O, Bujanda L, Saro C, Domenech E, Barrio J, Andreu M, Ordás I, Vida L, Bastida G, González-Huix F, Piqueras M, Ginard D, Calvet X, Gutiérrez A, Abad A, Torres M, Panés J, Chaparro M, Pascual I, Rodríguez-Carballeira M, Fernández-Bañares F, Viver JM, Esteve M; REPENTINA study; GETECCU (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa) Group.

**BACKGROUND:** There is no information about the frequency of liver dysfunction in patients with inflammatory bowel disease (IBD) treated with immunosuppressants and infected with hepatitis B (HBV) and/or C virus (HCV).

**AIM:** To assess the influence of immunosuppressants on the course of HBV and HCV infection in IBD.

**METHODS:** Patients with IBD with HBV and/or HCV infection from 19 Spanish hospitals were included. Clinical records were reviewed for the type of immunosuppressant used, treatment duration, liver function tests and viral markers before, during and after each immunosuppressant. Logistic and Cox regression analysis were used to identify predictors of outcome.

**RESULTS:** 162 patients were included; 104 had HBV markers (25 HBsAg positive) and 74 had HCV markers (51 HCV-RNA positive), and 16 patients had markers of both infections. Liver dysfunction was observed in 9 of 25 HBsAg positive patients (36%), 6 of whom developed hepatic failure. Liver dysfunction in HCV was observed in 8 of 51 HCV-RNA positive patients (15.7%), and only one developed hepatic failure. The frequency and severity of liver dysfunction was significantly higher in HBV-infected patients than in HCV-infected patients (p=0.045 and p=0.049, respectively). Treatment with ≥2 immunosuppressants was an independent predictor of HBV reactivation (OR 8.75; 95% CI 1.16 to 65.66). The majority of patients without reactivation received only one immunosuppressant for a short period and/or prophylactic antiviral treatment. No definite HBV reactivations were found in anti-HBc positive patients lacking HBsAg.

**CONCLUSION:** Liver dysfunction in patients with IBD treated with immunosuppressants is more frequent and severe in those with HBV than in HCV carriers and is associated with combined immunosuppression.

Gut. 2010 Oct;59(10):1310-1.

**Liver dysfunction in patients with IBD under immunosuppressive treatment: do we need to fear?**

Beaugerie L, Gerbes AL.

No abstract available

Drug Saf. 2010 Oct 1;33(10):865-78. doi: 10.2165/11538330-000000000-00000.

**Mapping the safety profile of biologicals: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase.**

Giezen TJ, Mantel-Teeuwisse AK, Meyboom RH, Straus SM, Leufkens HG, Egberts TC.

**BACKGROUND:** Biologicals have specific characteristics, as compared with the small molecule drugs, and carry specific risks. Safety problems, for example infliximab and the risk for tuberculosis, have been identified via spontaneous reports of suspected adverse drug reactions (ADRs). However, in general there is limited data on the nature of spontaneously reported suspected ADRs for biologicals.

**OBJECTIVE:** To map the safety profile of biologicals as compared with all other drugs. In addition, mechanistic classes of biologicals will be compared.

**METHODS:** Data was obtained from the ADR database (VigiBase) maintained by the WHO Collaborating Centre for International Drug Monitoring. A disproportionality analysis was performed in which case reports for biologicals and all other drugs (the reference group), reported between January 1995 and December 2008, were selected. Vaccines were not included in the analysis. Suspected ADRs were classified according to Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 at the System Organ Class (SOC) level. Biologicals were classified into mechanistic classes: antibodies, cytokines, enzymes, growth factors, hormones (reference group), interferons, receptors and others/various. The safety profile of the biologicals versus all other drugs in the database and of the various mechanistic classes of biologicals was compared using the proportional reporting ratio (PRR).

**RESULTS:** 191,004 case reports containing 546,474 suspected ADRs were reported for 62 different biologicals, and 2,556,209 case reports containing 8,761,522 suspected ADRs were reported for all other drugs (the reference group). It was found that two-thirds of all suspected ADRs reported for biologicals were reported for five active substances: etanercept (20.3%), interferon-beta-1a (15.6%), infliximab (11.6%), teriparatide (10.7%) and adalimumab (9.0%). Comparison of the safety profile of biologicals and the reference group showed that suspected ADRs for biologicals were more frequently reported in the SOCs 'Infections and infestations' (PRR 4.5), 'Surgical and medical procedures' (PRR 2.4) and 'Neoplasms benign, malignant and unspecified' (PRR 2.1), and less frequently reported in the SOCs 'Psychiatric disorders' (PRR 0.4), 'Vascular disorders' (PRR 0.4) and 'Pregnancy, puerperium and perinatal conditions' (PRR 0.4). Regarding the differences in safety profile between various mechanistic classes of biologicals, compared with hormones (reference group), 'Infections and infestations' were more frequently reported for receptors and antibodies. 'Neoplasms benign, malignant and unspecified' were more frequently reported for antibodies, cytokines, interferons and receptors, and less frequently for enzymes as compared with the reference group.

**CONCLUSIONS:** In VigiBase, five biologicals comprise two-thirds of the suspected ADRs reported for biologicals, which might distort the relation found between a specific biological and a specific adverse event in case of quantitative signal detection. Therefore the choice of reference group to be used in case of quantitative signal detection should be considered very carefully. This study confirmed that biologicals have a different safety profile compared with all other drugs in the database and, within the group of biologicals, differences exist between mechanistic classes. Infections are, for example, frequently reported for receptors and antibodies, which often have an immune compromising effect. Such predictable safety issues should be specifically studied by preregistration clinical trials and/or targeted pharmacovigilance. In addition, since not all adverse reactions can be predicted or detected during development, spontaneous reporting remains an important tool for the early detection of signals.

Acta Derm Venereol. 2010 May;90(3):311-2.

**Cutaneous drug eruption with an interface dermatitis pattern due to anti-tumour necrosis factor-alpha agents: a relevant class-effect.**

Garcovich S, Burlando M, Rongioletti F, Garcovich A, Parodi A, Amerio P.

No abstract available

Pediatr Dermatol. 2010 Aug 26. [Epub ahead of print]

**Occurrence of Pustular Psoriasis after Treatment of Crohn Disease with Infliximab.**

Pourciau C, Shwyder T.

We report a case of pustular psoriasis induced by anti-TNF-alpha therapy in a 12-year-old boy with inflammatory bowel disease. This is a well-documented phenomenon but remains a clinical challenge, especially when presenting in the pediatric setting.

Pediatrics. 2010 Sep 13. [Epub ahead of print]

**Natural killer cell lymphoma in a pediatric patient with inflammatory bowel disease.**

Deneau M, Wallentine J, Guthery S, O'Gorman M, Bohnsack J, Fluchel M, Bezzant J, Pohl JF.

Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) antibody agents are an effective therapy for the treatment of inflammatory bowel disease (IBD); however, because of the potential for immune suppression with these drugs, TNF- $\alpha$  antibody agents can increase the risk of malignancy. We report here the case of an 11-year-old boy who presented with bowel obstruction. He also had a history of periodic fever, aphthous stomatitis, and cervical adenitis (PFAPA). Intestinal inflammation continued and impaired his quality of life; he was diagnosed with IBD of an undetermined type (IBD-U). Symptoms improved with infliximab, but he developed elevated transaminase levels with hepatosplenomegaly 1 year after scheduled infusions. Skin biopsy revealed an atypical lymphoid infiltrate consistent with an Epstein-Barr virus (EBV)-positive natural killer (NK)/T-cell lymphoma with associated hemophagocytic lymphohistiocytosis. Bone marrow biopsy revealed a similar EBV-positive lymphoid infiltrate consistent with an NK/T-cell lymphoma. EBV-positive tissue was present in gastrointestinal biopsies. Flow-cytometric analysis revealed an atypical, clonal NK-cell population, and biopsy specimens from several tissue sites tested positive for CD3, CD56, and CD30. The patient died soon after the diagnosis was made. This patient developed an EBV-driven malignancy while receiving infliximab. All patients with IBD who receive infliximab should be monitored for malignancy, especially young patients. This case underscores the need for future studies to better understand the biology of lymphoproliferative disorders.

Eur J Gastroenterol Hepatol. 2010 Oct;22(10):1260-4.

**Inflammatory bowel disease and pregnancy: report of two cases treated with infliximab and a review of the literature.**

Correia LM, Bonilha DQ, Ramos JD, Ambrogini O, Miszputen SJ.

Inflammatory bowel disease is relatively frequent in women of childbearing age. Disease management requires greater attention during this clinical condition because of potential risk of maternal-fetal complications. Infliximab has been shown to be safe during pregnancy and lactation, but reports in the literature are scarce. We report two cases of refractory Crohn's disease treated with infliximab with good results, in women. Both patients became pregnant during maintenance regimen and treatment was continued. The literature regarding pregnant patients with inflammatory bowel disease was reviewed.

Arch Dermatol. 2010 Sep;146(9):1055-6.

**Psoriatic skin lesions induced by certolizumab pegol**

Klein RQ, Spivack J, Choate KA.

No abstract available

Inflamm Bowel Dis. 2010 Oct;16(10):1634-6.

**Safety of adalimumab in Crohn's disease during pregnancy: case report and review of the literature.**

Jürgens M, Brand S, Filik L, Hübener C, Hasbargen U, Beigel F, Tillack C, Göke B, Ochsenkühn T, Seiderer J.

No abstract available

Inflamm Bowel Dis. 2010 Oct;16(10):1641-2.

**Inadvertent conception during concomitant treatment with infliximab and methotrexate in a patient with Crohn's disease: is the game worth the candle?**

Angelucci E, Cesarini M, Vernia P.

No abstract available.

Ann Rheum Dis. 2010 Oct;69(10):1751-5. Epub 2010 Jun 15.

**Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists.**

García-Doval I, Pérez-Zafrilla B, Descalzo MA, Roselló R, Hernández MV, Gómez-Reino JJ, Carmona L; BIOBADASER 2.0 Study Group.

**OBJECTIVE:** To estimate the incidence of hospitalisation due to varicella zoster virus (VZV) infection in patients treated with tumour necrosis factor (TNF) antagonists for inflammatory rheumatic conditions and to compare it with the expected rate in the general population.

**METHODS:** Secondary data analysis was performed of two large databases: (1) the national registry of rheumatic diseases patients treated with biological agents (BIOBADASER); and (2) the national hospital discharge database Conjunto Mínimo Básico de Datos al Alta Hospitalaria. Hospitalisations due to shingles or chickenpox were analysed. For each condition the incidence rate (IR) and the age and gender standardised IR per 100,000 person-years plus the standardised incidence ratio (SIR) and the standardised incidence difference (SID) were estimated.

**RESULTS:** In patients exposed to TNF antagonists, the estimated IR of hospitalisation due to shingles was 32 cases per 100,000 patient-years (95% CI 14 to 78), the expected rate in the general population was 3.4 (95% CI 3.2 to 3.5), the SIR was 9 (95% CI 3 to 20) and the SID was 26 (95% CI 14 to 37). The estimated IR of hospitalisation due to chickenpox was 26 cases per 100,000 (95% CI 10 to 69), the expected rate was 1.9 (95% CI 1.8 to 2.0), the SIR was 19 (95% CI 5 to 47) and the SID 33 (95% CI 21 to 45).

**CONCLUSIONS:** Patients suffering rheumatic diseases exposed to TNF antagonists are hospitalised due to VZV infections significantly more frequently than expected in the general population. Since the absolute IR of hospitalisations due to chickenpox and shingles is low in these patients, the implementation of risky preventive measures may not be justified at present.

J Immunol Methods. 2010 Sep 9. [Epub ahead of print]

**A novel method for the detection of antibodies to adalimumab in the presence of drug reveals "hidden" immunogenicity in rheumatoid arthritis patients.**

van Schouwenburg PA, Bartelds GM, Hart MH, Aarden L, Wolbink GJ, Wouters D.

Production of anti drug antibodies (ADA) in adalimumab treated RA patients is associated with reduced serum adalimumab levels and less clinical response. However, most current assays to measure ADA are unable to detect ADA in complex with adalimumab. Thus, ADA is only measured if antibody production exceeds drug levels in the serum, meaning that ADA formation is underestimated. The aim of this study is to develop a method to detect ADA in the presence of drug. A pH-shift-anti-idiotypic Antigen binding test (PIA) was used to enable ADA measurement in the presence of adalimumab. ADA-adalimumab complexes were dissociated by acid treatment and addition of excess rabbit anti-idiotypic-F(ab) before neutralization. Rabbit anti-idiotypic-F(ab) blocks reformation of ADA-drug complexes by competing with patient ADA for adalimumab binding. Released ADA are measured by an antigen binding test (ABT). The PIA enabled detection of ADA in the presence of large excess of adalimumab and was used to measure ADA in 30 adalimumab treated rheumatoid arthritis (RA) patients during the first 28 weeks of treatment. It revealed ADA in 21 out of 30 tested patients, while the ABT detected ADA in only 5 patients. Indicating that an immunogenic reaction towards adalimumab is present in the majority of adalimumab treated patients.

Clin Gastroenterol Hepatol. 2010 Oct;8(10):A24. Epub 2010 May 22.

**Infliximab-Induced Psoriaform Rash.**

Goldstein J, Levine J.

No abstract available