

Literature Update Immunology

Period: 1-30 April 2011

IBD

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Safety

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- **Frequency of thrombocytopenia in psoriasis patients** treated with **tumor necrosis factor- α inhibitors**.
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- **Very severe psoriasis** is associated with increased **noncardiovascular mortality** but not with increased **cardiovascular risk**.
- **Infliximab** induces **clonal expansion of $\gamma\delta$ -T Cells in Crohn's disease**: A **predictor of lymphoma risk**?
- **TNF alpha antagonist-induced lupus-like syndrome**: **report** and **review** of the literature with implications for treatment with alternative TNF alpha antagonists.

IBD

Inflamm Bowel Dis. 2011 Apr 11. doi: 10.1002/ibd.21697. [Epub ahead of print]

Long-term infliximab maintenance therapy for ulcerative colitis: The ACT-1 and -2 extension studies.

Reinisch W, Sandborn WJ, Rutgeerts P, Feagan BG, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Blank M, Lang Y, Johanns J, Colombel JF, Present D, Sands BE.

BACKGROUND: The aim was to evaluate long-term efficacy, quality of life, and safety in ulcerative colitis patients who received infliximab during the ACT-1 and -2 extension studies.

METHODS: Adults with moderate-to-severely active ulcerative colitis in the 54-week ACT-1 and 30-week ACT-2 studies who achieved benefit from infliximab were eligible to participate in extension studies and receive up to 3 additional years of therapy. Patients received randomized study medication until all sites were unblinded; placebo-treated patients were discontinued. Patients receiving 5 or 10 mg/kg infliximab continued to receive open-label infliximab every 8 weeks. Patients receiving infliximab 10 mg/kg could decrease to 5 mg/kg; patients receiving infliximab 5 mg/kg could increase to 10 mg/kg if response was lost.

RESULTS: A total of 229 of 484 infliximab-treated patients from the ACT-1 and ACT-2 main studies entered the long-term extensions. Overall, 70 (30.6%) patients discontinued infliximab infusions for adverse events (24 [10.5%]), lack of efficacy (11 [4.8%]), required a colectomy (1 [0.4%]), or for other reasons (34 [14.8%]). Proportions of patients whose Physician's Global Assessment scores were indicative of no or mild disease (score = 0 or 1) were maintained during the extension studies; 76.5% at Extension week 0 and ranged between 90.0% and 94.3% through Extension week 152. Improvement in Inflammatory Bowel Disease Questionnaire scores observed in the main studies was maintained. During the long-term extension, the infliximab safety profile was consistent with that of the main studies; no new or unexpected safety signals were observed.

CONCLUSIONS: Long-term treatment with infliximab for up to 3 additional years was effective and well tolerated. (Inflamm Bowel Dis 2011;).

Aliment Pharmacol Ther. 2011 May;33(9):987-95.Epub 2011 Mar 2.

Review article: loss of response to anti-TNF treatments in Crohn's disease.

Ben-Horin S, Chowers Y.

Aliment Pharmacol Ther 2011; 33: 987-995 **SUMMARY:** Background Loss of response to anti-TNF agents in Crohn's disease is an emerging clinical problem. Aim To review the causes, incidence and management approach of loss of response. Methods A search of medical database (PubMed) and of meetings' proceedings for definitions, causes and incidence of loss of response was carried out. Personal correspondence with principal investigators was conducted to retrieve missing data. Results Various definitions of loss of response abound, hampering the ability to assess accurately the magnitude and management of this clinical problem. We propose to distinguish between a clinical worsening on anti-TNF treatment and a true loss of response to anti-TNFs. Accordingly, loss of response to anti-TNFs at 12 months of therapy occurs in 23-46% of patients when judged by dose intensification, or 5-13% when gauged by drug discontinuation rates. The management of loss of response should allow for a period of watchful waiting as quite often the patients' symptoms may resolve without alteration of therapy. If they do not, then identifying the correct mechanism responsible for clinical deterioration is prudent. Once symptoms are ascertained to arise from inflammatory IBD activity, drug level and antidrug antibody measurement can then help distinguish between non-adherence to therapy, immunogenicity and non-immune clearance of anti-TNF, or an un-chequered inflammation despite adequate anti-TNF levels. The latter finding may be best addressed by a switch to another class of immunomodulators, whereas a low drug level should probably be managed by dose intensification or a switch to another anti-TNF. Conclusion Studies defining how best to translate drug-level monitoring and other mechanistic considerations into clinical decisions are urgently needed.

Aliment Pharmacol Ther. 2011 May;33(9):1028-35.Epub 2011 Mar 8.

Randomised clinical trial: early assessment after 2 weeks of high-dose mesalazine for moderately active ulcerative colitis - new light on a familiar question.

Orchard TR, van der Geest SA, Travis SP

Aliment Pharmacol Ther 2011; 33: 1028-1035 SUMMARY: Background Rapid resolution of rectal bleeding and stool frequency are important goals for ulcerative colitis therapy and may help guide therapeutic decisions. Aim To explore patient diary data from ASCEND I and II for their relevance to clinical decision making. Methods Data from two randomised, double-blind, Phase III studies were combined. Patients received mesalazine (mesalamine) 4.8 g/day (Asacol 800 mg MR) or 2.4 g/day (Asacol 400 mg MR). Time to improvement or resolution of rectal bleeding and stool frequency was assessed and the proportion of patients experiencing symptom improvement or resolution at day 14 evaluated using survival analysis. Symptoms after 14 days were compared to week 6. A combination of prespecified and post hoc analyses were used. Results Median times to resolution and improvement of both rectal bleeding and stool frequency were shorter with 4.8 g/day than 2.4 g/day (resolution, 19 vs. 29 days, $P = 0.020$; improvement, 7 vs. 9 days, $P = 0.024$). In total, 73% of patients experienced improvement in both rectal bleeding and stool frequency by day 14 with 4.8 g/day, compared to 61% with 2.4 g/day. More patients achieved symptom resolution by day 14 with 4.8 g/day than 2.4 g/day (43% vs. 30%; $P = 0.035$). Symptom relief after 14 days was associated with a high rate of symptom relief after 6 weeks. Conclusions High-dose mesalazine 4.8 g/day provides rapid relief of the cardinal symptoms of moderately active ulcerative colitis. Symptom relief within 14 days was associated with symptom relief at 6 weeks in the majority of patients. Day 14 is a practical timepoint at which response to treatment may be assessed and decisions regarding therapy escalation made (Clinicaltrials.gov: NCT00577473, NCT00073021).

Am J Gastroenterol. 2011 Apr;106(4):771-7. Epub 2011 Mar 8.

Successive treatment with cyclosporine and infliximab in steroid-refractory ulcerative colitis.

Leblanc S, Allez M, Seksik P, Flourié B, Peeters H, Dupas JL, Bouguen G, Peyrin-Biroulet L, Duclos B, Bourreille A, Dewit O, Bouhnik Y, Michetti P, Chaussade S, Saussure P, Mary JY, Colombel JF, Lémann M.

OBJECTIVES: Rescue therapy with either cyclosporine (CYS) or infliximab (IFX) is an effective option in patients with intravenous steroid-refractory attacks of ulcerative colitis (UC). In patients who fail, colectomy is usually recommended, but a second-line rescue therapy with IFX or CYS is an alternative. The aims of this study were to investigate the efficacy and tolerance of IFX and CYS as a second-line rescue therapy in steroid-refractory UC or indeterminate colitis (IC) unsuccessfully treated with CYS or IFX.

METHODS: This was a retrospective survey of patients seen during the period 2000-2008 in the GETAID centers. Inclusion criteria included a delay of <1 month between CYS withdrawal (when used first) and IFX, or a delay of <2 months between IFX (when used first) and CYS, and a follow-up of at least 3 months after inclusion. Time-to-colectomy, clinical response, and occurrence of serious adverse events were analyzed.

RESULTS: A total of 86 patients (median age 34 years; 49 males; 71 UC and 15 IC) were successively treated with CYS and IFX. The median (\pm s.e.) follow-up time was 22.6 (7.0) months. During the study period, 49 patients failed to respond to the second-line rescue therapy and underwent a colectomy. The probability of colectomy-free survival (\pm s.e.) was $61.3 \pm 5.3\%$ at 3 months and $41.3 \pm 5.6\%$ at 12 months. A case of fatal pulmonary embolism occurred at 1 day after surgery in a 45-year-old man. Also, nine infectious complications were observed during the second-line rescue therapy.

CONCLUSIONS: In patients with intravenous steroid-refractory UC and who fail to respond to CYS or IFX, a second-line rescue therapy may be effective in carefully selected patients, avoiding colectomy within 2 months in two-thirds of them. The risk/benefit ratio should still be considered individually.

J Crohns Colitis. 2011 Apr;5(2):91-4. Epub 2010 Nov 5.

The use of cyclosporin A in acute steroid-refractory ulcerative colitis: Long term outcomes.

Sharkey L, Bredin F, Nightingale A, Parkes M.

BACKGROUND AND AIMS: Approximately 15% of patients with ulcerative colitis will have a severe flare requiring hospitalisation at some stage. For those who fail to respond to intravenous steroids Cyclosporin A (CyA) therapy is one option. We have evaluated the management of such patients in our centre and present the long term colectomy avoidance rates.

METHODS: 38 consecutive patients receiving CyA for an acute, steroid-refractory flare of colitis were retrieved from our database. Records were unavailable for 2 patients and 2 received therapy twice, hence 38 episodes were analysed.

RESULTS: 24/36 patients were male; median age 37years. On admission 20 patients were taking oral steroids; 8 were taking a thiopurine and 7 patients were on no treatment. CyA was started a median of 8days after admission (range 1-28) and most patients (32/38) received this orally at doses of 4.5-8.3mg/kg. 15 patients have undergone colectomy, 11 of these during the same admission for lack of response to CyA. Of the patients who were discharged without surgery, 84% have still not required colectomy after a median follow-up of 3.8years. Adverse effects were mostly minor, though two patients developed neutropenia on dual immunosuppression.

CONCLUSIONS: CyA can be administered orally with good tolerability. We use it as a bridging therapy to Azathioprine. In our population, 84% of those who responded to CyA have not required surgery.

J Crohns Colitis. 2011 Apr;5(2):165-6. Epub 2010 Feb 12.

On the updated ECCO consensus guidelines for medical management of Crohn's disease.

Esser D, Cornillie F, Diamond RH, Spiegel RJ.

No abstract available.

Gut. 2011 Apr;60(4):449-55. Epub 2010 Oct 22.

Suppression of inflammation in ulcerative colitis by interferon- β -1a is accompanied by inhibition of IL-13 production.

Mannon PJ, Hornung RL, Yang Z, Yi C, Groden C, Friend J, Yao M, Strober W, Fuss IJ.

Objective Ulcerative colitis is associated with increased interleukin 13 (IL-13) production by natural killer T cells. Taking advantage of the inhibitory actions of interferon β on IL-13 expression, this proof-of-concept study aimed to show that decreasing IL-13 production is associated with clinical improvement of ulcerative colitis symptoms. Design Open-label interventional drug trial. Setting Outpatient clinical research hospital. Patients Adult patients with active ulcerative colitis (Short Clinical Colitis Activity Index (SCCAI) \geq 5). Interventions Treatment with 30 μ g IM interferon- β -1a (Avonex) weekly for 12 weeks with 6 month follow-up. Main outcome measures Clinical response was defined as \geq 3 point drop in the SCCAI for at least two consecutive monitoring visits, and cytokine production was measured in cultured peripheral blood and lamina propria mononuclear cells (LPMC) before and after treatment. Results 11 of 16 patients were clinical responders, and 4 were in remission (SCCAI \leq 2) at the end of treatment. Rectal bleeding subscores improved dramatically by week 4 (38% with frank bleeding vs 87% pretreatment). Increased IL-13 production by LPMC T cells fell significantly in clinical responders (690 \pm 99 vs 297 \pm 58 pg/ml p=0.015) but was unchanged in non-responders (542 \pm 83 vs 510 \pm 39 pg/ml). In addition, non-responders had significantly higher production of IL-17 and IL-6 pre-treatment compared to responders. Conclusions Interferon- β -1a induces clinical response and remission in a large subset of patients with ulcerative colitis that is associated with significant inhibition of IL-13 production. In addition, increased IL-17 and IL-6 production is associated with no response to interferon- β . These data provide a proof-of-concept that IL-13 is an effector cytokine in ulcerative colitis and should be a target for novel therapies.

World J Gastroenterol. 2011 Mar 7;17(9):1174-9.

Long-term efficacy of infliximab maintenance therapy for perianal Crohn's disease.

Uchino M, Ikeuchi H, Bando T, Matsuoka H, Takesue Y, Takahashi Y, Matsumoto T, Tomita N.

AIM: To assess the long-term efficacy of seton drainage with infliximab maintenance therapy in treatment of stricture for perianal Crohn's disease (CD).

METHODS: Sixty-two patients with perianal CD who required surgical treatment with or without infliximab between September 2000 and April 2010 were identified from our clinic's database. The activities of the perianal lesions were evaluated using the modified perianal CD activity index (mPDAI) score. The primary endpoint was a clinical response at 12-15 wk after surgery as a short-term efficacy. Secondary endpoints were recurrence as reflected in the mPDAI score, defined as increased points in every major element. The clinical responses were classified as completely healed (mPDAI = 0), partially improved (mPDAI score decreased more than 4 points), and failure or recurrence (mPDAI score increased or decreased less than 3 points).

RESULTS: There were 43 males and 19 females, of whom 26 were consecutively treated with infliximab after surgery as maintenance therapy. Complete healing was not seen. Failure was seen in 10/36 (27.8%) patients without infliximab and 4/26 (15.4%) patients with infliximab (P = 0.25). Partial improvement was seen in 26/36 (72.2%) patients without infliximab and 22/26 (88.5%) patients with

infliximab ($P = 0.25$). Short-term improvement was achieved in 48/62 (77.4%) patients. Although the mPDAI score improved significantly with surgery regardless of infliximab, it decreased more from baseline in patients with infliximab (50.0%) than in those without infliximab (28.6%), ($P = 0.003$). In the long-term, recurrence rates were low regardless of infliximab in patients without anorectal stricture. In patients with anorectal stricture, cumulative recurrence incidences increased gradually and exceeded 40% at 5 years regardless of infliximab. No efficacy of infliximab treatment was found ($P = 0.97$). Although the cumulative rate of ostomy creation was also low in patients without stricture and high in patients with stricture, no protective efficacy was found with infliximab treatment ($P = 0.6$ without stricture, $P = 0.22$ with stricture). **CONCLUSION:** Infliximab treatment was demonstrated to have short-term efficacy for perianal lesions. Long-term benefit with infliximab was not proven, at least in patients with anorectal stricture.

Gut Liver. 2011 Mar;5(1):37-45. Epub 2011 Mar 16.

Infliximab therapy impacts the peripheral immune system of immunomodulator and corticosteroid naïve patients with Crohn's disease.

Kato K, Fukunaga K, Kamikozuru K, Kashiwamura S, Hida N, Ohda Y, Takeda N, Yoshida K, Imuro M, Yokoyama Y, Kikuyama R, Miwa H, Matsumoto T.

BACKGROUND/AIMS: Infliximab (IFX), an antibody to tumor necrosis factor, (TNF)- α has efficacy in treating Crohn's disease (CD). However, knowledge of the potential effects of IFX on patients' immune profiles is lacking. The purpose of this study was to reveal the immunological effects of IFX.

METHODS: Twenty-two patients with a CD activity index (CDAI) of 194.2 ± 92.9 and an average duration of disease of 3.26 months and 21 healthy controls were included. Patients were to have their first IFX remission induction therapy with 3 infusions (5 mg/kg) at weeks 0, 2, and 6. Oral 5-aminosalicylic acid was the only ongoing medication in the patient population. Blood samples at baseline, 12 hours after the first infusion and at week 14 were labeled with anti-CD4/CD25 antibodies for immunohistochemical measurement of regulatory T-cells (Treg). Serum cytokines and chemokines were measured by suspension array and ELISA.

RESULTS: CDAI significantly decreased prior to the second IFX infusion ($p < 0.001$). Clinical remission rates were 77.3% and 91% by the second and third infusions, respectively. At baseline, interleukin (IL)-6 ($p < 0.03$), IL-8 ($p < 0.03$), IL-10 ($p = 0.050$), IL-13 ($p < 0.01$), transforming growth factor- $\beta 1$ ($p < 0.01$), and 'regulated on activation, normal T cell expressed and secreted' (RANTES) ($p < 0.01$) were elevated in patients. After the initial IFX infusion, TNF- α ($p < 0.04$), IL-6 ($p < 0.03$), interferon (IFN)- γ ($p < 0.04$), IFN- γ -inducible protein-10 ($p < 0.01$), monocyte chemoattractant protein-1 ($p < 0.01$), macrophage inflammatory protein-1 β ($p < 0.01$), and RANTES ($p < 0.01$) were decreased. IFX infusion was associated with an increase in Treg ($p < 0.01$) and a decrease in the Th1 (IFN- γ)/Th2 (IL-4) ratio ($p < 0.03$).

CONCLUSIONS: IFX use was associated with restoration of the Th1/Th2 balance after a single infusion and seemed to promote induction of naïve Th0 lymphocytes to Treg. This knowledge should have clinical relevance.

Eur Surg Res. 2011 Mar 31;46(4):163-168. [Epub ahead of print]

Infliximab in drug-naïve patients with failed ileorectal anastomosis for Crohn's disease: A new chance for sparing the rectum?

Sciaudone G, Pellino G, Riegler G, Selvaggi F.

The aim of this intervention study is to determine whether long-term infliximab therapy can decrease the proctectomy rate in patients with failed total colectomy and ileorectal anastomosis (IRA) for Crohn's disease (CD). Twelve patients (5 females) - with a median age of 36.6 years (range 18-56 years), previously treated with IRA (5 in our institution and 7 referred) for colorectal and perianal CD (median Crohn's Disease Activity Index 334.5, range 220-426), with rectal disease recurrence requiring proctectomy, no responders to conventional therapy but infliximab-naïve - were treated with infliximab infusions (Remicade™ 5 mg/kg at 0, 2, 6 weeks and then every 8 weeks) to avoid proctectomy. The main outcome measures consisted of IRA preservation and bowel function at study end. Mortality and major adverse reactions have not been observed. At the time of the median follow-up (57.4 months, range 36-92), the rectum was preserved in 10 patients (83.3%). One patient underwent proctectomy 6 weeks after the beginning of the treatment for unresponsiveness to drugs and another after 26 weeks for rectal stenosis. Anorectal function (maximum tolerated volume: 239 ± 43 vs. 294 ± 36 ml) and quality of life (Inflammatory Bowel Disease Questionnaire score 89.2 ± 20.6 vs. 173.8 ± 31.9) improved, and the Wexner Continence score (4.4 ± 2.4 vs. 1.7 ± 1.0) and daily defecations (5.2 ± 1.03 vs. 2.7 ± 1.05)

decreased in 10 patients. Our results, although preliminary, are encouraging and seem to justify a less aggressive approach in patients with rectal and perianal recurrence after IRA for CD.

Gut. 2011 May;60(5):571-607.

Guidelines for the management of inflammatory bowel disease in adults.

Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L,

The management of inflammatory bowel disease represents a key component of clinical practice for members of the British Society of Gastroenterology (BSG). There has been considerable progress in management strategies affecting all aspects of clinical care since the publication of previous BSG guidelines in 2004, necessitating the present revision. Key components of the present document worthy of attention as having been subject to re-assessment, and revision, and having direct impact on practice include: The data generated by the nationwide audits of inflammatory bowel disease (IBD) management in the UK in 2006, and 2008. The publication of 'Quality Care: service standards for the healthcare of people with IBD' in 2009. The introduction of the Montreal classification for Crohn's disease and ulcerative colitis. The revision of recommendations for the use of immunosuppressive therapy. The detailed analysis, guidelines and recommendations for the safe and appropriate use of biological therapies in Crohn's disease and ulcerative colitis. The reassessment of the role of surgery in disease management, with emphasis on the importance of multi-disciplinary decision-making in complex cases. The availability of new data on the role of reconstructive surgery in ulcerative colitis. The cross-referencing to revised guidelines for colonoscopic surveillance, for the management of metabolic bone disease, and for the care of children with inflammatory bowel disease. Use of the BSG discussion forum available on the BSG website to enable ongoing feedback on the published document <http://www.bsg.org.uk/forum> (accessed Oct 2010). The present document is intended primarily for the use of clinicians in the United Kingdom, and serves to replace the previous BSG guidelines in IBD, while complementing recent consensus statements published by the European Crohn's and Colitis Organisation (ECCO) <https://www.ecco-ibd.eu/index.php> (accessed Oct 2010).

Dig Liver Dis. 2011 Jan;43(1):1-20. Epub 2010 Sep 16.

The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: The use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease.

Orlando A, Armuzzi A, Papi C, Annese V, Ardizzone S, Biancone L, Bortoli A, Castiglione F, D'Inca R, Gionchetti P, Kohn A, Poggioli G, Rizzello F, Vecchi M, Cottone M; Italian Society of Gastroenterology; Italian Group for the study of Inflammatory Bowel Disease.

Biological therapies are an important step in the management of Inflammatory Bowel Diseases. In consideration of high cost and safety issues there is the need to have clear recommendations for their use. Despite the American Gastroenterological Association and the European Crohn's and Colitis Organisation have published exhaustive Inflammatory Bowel Disease guidelines, national guidelines may be necessary as cultural values, economical and legal issues may differ between countries. For these reasons the Italian Society of Gastroenterology and the Italian Group for the study of Inflammatory Bowel Disease have decided to elaborate the Italian guidelines on the use of biologics in Inflammatory Bowel Disease. The following items have been chosen: definitions of active, inactive, steroid dependent and resistant disease; measures of activity; anti-tumor necrosis factor alpha therapy use in active steroid dependent and refractory luminal Crohn's Disease, in fistulising Crohn's Disease, in steroid dependent and resistant active Ulcerative Colitis; risk of cancer; risk of infections during anti-tumor necrosis factor alpha therapy; special situations. These guidelines are based on evidence from relevant medical literature and clinical experience of a national working group.

Aliment Pharmacol Ther. 2011 May;33(10):1133-1142. doi: 10.1111/j.1365-2036.2011.04628.x. Epub 2011 Mar 16.

The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10- to 19-year-old age bracket (1988-2007).

Chouraki V, Savoye G, Dauchet L, Vernier-Massouille G, Dupas JL, Merle V, Laberrenne JE, Salomez JL, Lerebours E, Turck D, Cortot A, Gower-Rousseau C, Colombel JF.

Aliment Pharmacol Ther 2011; 33: 1133-1142 SUMMARY: Background Crohn's disease incidence rates have stabilised in industrialised countries since the 1980s. Conversely, a continuing increase in childhood-onset Crohn's disease incidence has been reported. Aim To confirm trends in inflammatory bowel disease (IBD) incidence in northern France over an extended time period (1988-2007) with a focus on childhood-onset Crohn's disease. Methods The IBD patients recorded in the EPIMAD registry between 1988 and 2007 were included. Standardised incidence rates were calculated for Crohn's disease and ulcerative colitis in the entire population, and separately according to age. Evolution of phenotypes at diagnosis was also studied. Results A total of 12 084 incident IBD cases (7428 Crohn's disease and 4656 ulcerative colitis) were recorded. Crohn's disease incidence rates increased from 5.2 cases/100 000 persons in 1988-1990 to 6.7 in 2006-2007 (+29%), stabilising after a peak at 7.1 in 1997-1999. Crohn's disease incidence rates in the 10-19-year age category increased by 71%, from 6.5 (1988-1990) to 11.1 (2006-2007). The frequency of initial ileo-colonic localisation increased from 52.9% in 1988-1990 to 68.6% in 2006-2007 ($P < 0.0001$). Ulcerative colitis incidence rates decreased during the same period. Conclusions From 1988 to 2007, Crohn's disease incidence increased by 29% in northern France and by 71% in the 10-19-year-old age group. Consequently, studies on Crohn's disease risk factors should focus on the population under 20 years of age.

Aliment Pharmacol Ther. 2011 May;33(10):1143-51. doi: 10.1111/j.1365-2036.2011.04636.x. Epub 2011 Mar 28.

Evaluation of a daily practice composite score for the assessment of Crohn's disease: the treatment impact of certolizumab pegol.

Feagan BG, Hanauer SB, Coteur G, Schreiber S.

Background: Successful treatment of systemic inflammatory symptoms is essential for improving health-related quality of life in patients with active Crohn's disease. Patient-reported outcomes provide unique perspectives on the impact of chronic disease. It is unknown whether a combination of different instruments might improve sensitivity to clinically relevant changes in health status. Aim: To develop a composite score based upon Crohn's Disease Activity Index (CDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ) items. Methods Patients from the PRECiSE 2 trial who responded at week 6 to certolizumab pegol (CZP) were randomised to receive treatment with CZP 400 mg or placebo for up to 26 weeks. IBDQ and CDAI scores were assessed at weeks 0, 6, 16 and 26. A 'daily practice' composite score (DP-6) containing two items from the CDAI and four items from IBDQ was constructed. Results Correlation coefficients between the CDAI score and IBDQ total score at baseline and at week 26 were -0.344 and -0.603, respectively ($P < 0.05$). All IBDQ items were improved following CZP treatment. The DP-6 had the highest responsiveness at assessing response to treatment, relative to CDAI total score, when compared with other scores. Conclusions: The DP-6 composite score could be used to optimise the use of existing instruments by serving as an index of symptoms due to systemic inflammation. Additional studies are needed to determine if the DP-6 composite score differentiates the impact of different treatments on patient-reported outcomes, and to determine if the use of the DP-6 improves the care of patients in clinical practice.

J Intern Med. 2011 Jan 17. doi: 10.1111/j.1365-2796.2011.02344.x. [Epub ahead of print]

Use of biological molecules in the treatment of inflammatory bowel disease.

Nielsen OH, Seidelin JB, Munck LK, Rogler G.

Abstract. Nielsen OH, Seidelin JB, Munck LK, Rogler G (Herlev Hospital, University of Copenhagen, Copenhagen; Køge Hospital, University of Copenhagen, Copenhagen, Denmark; and University Hospital of Zürich, Zürich, Switzerland) Use of biological molecules in the treatment of inflammatory bowel disease (Review). J Intern Med 2011; doi: 10.1111/j.1365-2796.2011.02344.x. The introduction of biological agents (i.e. antitumour necrosis factor- α and anti-integrin treatments) for the treatment of inflammatory bowel disease (IBD) [i.e. Crohn's disease (CD) and ulcerative colitis] has led to a substantial change in the treatment algorithms and guidelines, especially in CD. However, many questions still remain about the true efficacy and the best treatment regimens. Thus, a need for further treatment options still exists as up to 40% of IBD patients treated with the presently available biologicals do not have positive clinical responses. Better patient selection might maximize the clinical benefit for those in most need of an effective therapy to avoid disabling disease whilst also minimizing the complications associated with therapy. Further, the 'trough-level strategy' may help clinicians to optimize therapy and to avoid loss of response and/or immunogenicity. The idea behind this dosage regimen is that correct dosing must ensure that the patient's lowest level of drug concentration (i.e. the trough level) occurring just before the next

drug administration is high enough for the full effect to be seen. Controversy continues regarding the appropriate use of biologicals; therefore, in this review, we focus on considerations that might lead to a more rational strategy for antitumor necrosis factor- α agents in IBD, emphasizing the situations in which the risks may outweigh the benefits. Finally, the need for an appropriate strategy for stopping biological treatment is discussed.

Curr Gastroenterol Rep. 2011 Feb;13(1):95-100.

Prevention and treatment of postoperative Crohn's disease recurrence: an update for a new decade.

Schwartz M, Regueiro M.

Poorly controlled Crohn's disease (CD) often requires surgery for such complications as strictures, fistulas, and abscesses. The goal of postoperative treatment is to suppress or prevent inflammation and maintain mucosal healing. Probiotics, antibiotics, 5-aminosalicylates, immunomodulators, and antibodies to tumor necrosis factor are all used to prevent postoperative recurrence. In this article, recent studies are reviewed. Azathioprine/6-mercaptopurine are moderately effective at preventing and treating postoperative CD, whereas infliximab/adalimumab are highly effective and probiotics and 5-aminosalicylates minimally effective. We base the choice of postoperative medical therapy on the patient's risk profile for postoperative recurrence. Whatever postoperative therapy is used, the mucosa should be assessed within 12 months to determine if the approach is effective. If active inflammation is found, then treatment should be intensified. By treating CD aggressively after a first surgery, future surgeries can be delayed or averted.

Am J Gastroenterol. 2011 Apr;106(4):574-88. Epub 2011 Jan 11.

Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN.

Turner D, Travis SP, Griffiths AM, Ruemmele FM, Levine A, Benchimol EI, Dubinsky M, Alex G, Baldassano RN, Langer JC, Shamberger R, Hyams JS, Cucchiara S, Bousvaros A, Escher JC, Markowitz J, Wilson DC, van Assche G, Russell RK.

OBJECTIVES: Acute severe ulcerative colitis (ASC) is a potentially life-threatening disease. We aimed to formulate guidelines for managing ASC in children based on systematic review of the literature and robust consensus process. This manuscript is a product of a joint effort of the ECCO (European Crohn's and Colitis Organization), the Pediatric Porto Inflammatory Bowel Disease (IBD) Working group of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology, and Nutrition) and ESPGHAN.

METHODS: A group of 19 experts in pediatric IBD participated in an iterative consensus process including two face-to-face meetings. A total of 17 predefined questions were addressed by working subgroups based on a systematic review of the literature.

RESULTS: The recommendations and practice points were eventually endorsed with a consensus rate of at least 95% regarding: definitions, initial evaluation, standard therapy, timing of second-line therapy, the role of endoscopic evaluation and heparin prophylaxis, how to administer second-line medical therapy, how to assess response, surgical considerations, and discharge recommendations. A management flowchart is presented based on daily scoring of the Pediatric Ulcerative Colitis Activity Index (PUCAI), along with 28 formal recommendations and 34 practice points.

CONCLUSIONS: These guidelines provide clinically useful points to guide the management of ASC in children. Taken together, the recommendations offer a standardized protocol that allows effective monitoring of disease progress and timely treatment escalation when needed.

Am J Gastroenterol. 2011 Apr;106(4):644-59. Epub 2011 Mar 15.

Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis.

Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P.

OBJECTIVES: Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory disorders of the gastrointestinal tract of unknown etiology. Evidence for treatment of the condition with biological therapies exists, but no systematic review and meta-analysis has examined this issue in its entirety.

METHODS: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through to December 2010). Trials recruiting adults with active or quiescent CD or UC and comparing

biological therapies (anti-tumor necrosis factor- α (TNF α) antibodies or natalizumab) with placebo were eligible. Dichotomous symptom data were pooled to obtain relative risk (RR) of failure to achieve remission in active disease and RR of relapse of activity in quiescent disease once remission had occurred, with a 95% confidence interval (CI).

RESULTS: The search strategy identified 3,061 citations, 27 of which were eligible. Anti-TNF α antibodies and natalizumab were both superior to placebo in inducing remission of luminal CD (RR of no remission=0.87; 95% CI 0.80-0.94 and RR=0.88; 95% CI 0.83-0.94, respectively). Anti-TNF α antibodies were also superior to placebo in preventing relapse of luminal CD (RR of relapse=0.71; 95% CI 0.65-0.76). Infliximab was superior to placebo in inducing remission of moderate to severely active UC (RR=0.72; 95% CI 0.57-0.91).

CONCLUSIONS: Biological therapies were superior to placebo in inducing remission of active CD and UC, and in preventing relapse of quiescent CD.

Am J Gastroenterol. 2011 Apr;106(4):674-84. Epub 2011 Mar 15.

Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review.

Billioud V, Sandborn WJ, Peyrin-Biroulet L.

The objective of this study was to review loss of response and need for adalimumab dose intensification in adult and pediatric patients with Crohn's disease. Studies were identified through the electronic databases of MEDLINE and the annual meetings of Digestive Disease Week, of the United European Gastroenterology Week, and of the American College of Gastroenterology and the European Crohn's and Colitis Organization meetings. Studies evaluating loss of efficacy and/or need for dose intensification were included. Thirty-nine studies were included. The mean percentage of loss of response to adalimumab among primary responders was 18.2% and the annual risk was 20.3% per patient-year. The mean percentage of patients who required dose intensification among primary responders to adalimumab was 37% and the annual risk was 24.8% per patient-year. When considering initial responders and patients with primary non-response, the mean percentage of patients who needed an adalimumab dose escalation was 21.4% and the annual risk was 24.4% per patient-year. Pooled analysis showed that dose escalation permitted response to be regained in 71.4% and remission in 39.9% of patients. Predictors for loss of response or dose escalation were male gender, current/former smoker status, family history of inflammatory bowel disease, isolated colonic disease, extra-intestinal manifestations, 80/40 mg induction therapy, longer disease duration, greater baseline Crohn's Disease Activity Index, concomitant corticosteroid use, no deep remission at week 12, low serum trough concentrations of adalimumab, previous infliximab non-response and being previously treated with an anti-tumor necrosis factor agent. Overall, around one fifth of adult patients require dose intensification and experience a loss of response after initiation of adalimumab therapy. Adalimumab dose escalation permits response to be regained in the majority of patients.

Am J Gastroenterol. 2011 Apr;106(4):685-98. Epub 2011 Mar 22.

Assessing response and loss of response to biological therapies in IBD.

Yanai H, Hanauer SB.

OBJECTIVES: The advent of biological therapies for inflammatory bowel disease (IBD) began in 1998 with the approval of infliximab for the treatment of refractory (to conventional agents) Crohn's disease (CD). Since then, the indications for anti-tumor necrosis factor- α (anti-TNF α) therapy have increased to include induction and maintenance of clinical responses and remissions for luminal and fistulizing CD, the treatment of children with CD, and the treatment of adults with ulcerative colitis. Additional utilities of biological therapies have included demonstrable mucosal healing, improvement in quality of life, reduction in surgeries and hospitalizations, and the treatment of extraintestinal manifestations of IBD including central and peripheral arthritis and pyoderma gangrenosum. Natalizumab has also been approved for the treatment of refractory Crohn's in patients who have failed conventional agents and anti-TNF α therapies. Unfortunately, despite the overall effectiveness of biological agents in a spectrum of indications for IBD, a significant proportion of patients do not respond or lose response over time. In this review, we intend to appraise the latest evolution in treatment strategies in IBD and to suggest an evidence-based approach and risk stratification while coping with cases of non-responders or loss of response to biological therapies.

METHODS: We conducted a literature search of English publications listed in the electronic databases of MEDLINE (source PUBMED) and constructed an analytical review based on definitions of response and

loss of response, considering potential responsible mechanisms, clinical assessment tools, and finally recommending a practical approach for its prevention and management.

RESULTS: Favorable clinical outcome appears to be the consequence of sustained therapeutic drug levels, and the current literature supports a practice of dose adjustments. When immunogenicity develops to a single biological agent, response can be regained by introduction of an alternative biological agent of the same or different class. Efficacy is reduced with second-line agents either within or across classes compared with naive patients. In the absence of direct measurement of drug levels and anti-drug antibodies, clinical judgment is necessary to assess the mechanisms of loss of response, and more empiric decision making may be necessary to determine the choice of second-line biological agents. Optimal treatment strategies are still controversial.

CONCLUSIONS: It is essential to recognize the spectrum of mechanisms affecting response and loss of response to form a logical and efficient management algorithm, and, perhaps, it is time to incorporate the measurement of trough levels and anti-drug antibodies in the strategy of such an assessment.

Prospective controlled trials are direly needed to investigate the optimal tailored management in individual patients who lose response.

Am J Gastroenterol. 2011 Apr;106(4):748-61. Epub 2011 Feb 15.

Mucosal gene expression of cell adhesion molecules, chemokines, and chemokine receptors in patients with inflammatory bowel disease before and after infliximab treatment.

Arijs I, De Hertogh G, Machiels K, Van Steen K, Lemaire K, Schraenen A, Van Lommel L, Quintens R, Van Assche G, Vermeire S, Schuit F, Rutgeerts P.

OBJECTIVES: Inflammatory bowel disease (IBD) is characterized by a continuous influx of leukocytes into the gut wall. This migration is regulated by cell adhesion molecules (CAMs), and selective antimigration therapies have been developed. This study investigated the effect of infliximab therapy on the mucosal gene expression of CAMs in IBD.

METHODS: Mucosal gene expression of 69 leukocyte/endothelial CAMs and E-cadherin was investigated in 61 IBD patients before and after first infliximab infusion and in 12 normal controls, using Affymetrix gene expression microarrays. Quantitative reverse transcriptase-PCR (qRT-PCR), immunohistochemistry, and western blotting were used to confirm the microarray data.

RESULTS: When compared with control colons, the colonic mucosal gene expression of most leukocyte/endothelial adhesion molecules was upregulated and E-cadherin gene expression was downregulated in active colonic IBD (IBDc) before therapy, with no significant colonic gene expression differences between ulcerative colitis and colonic Crohn's disease. Infliximab therapy restored the upregulations of leukocyte CAMs in IBDc responders to infliximab that paralleled the disappearance of the inflammatory cells from the colonic lamina propria. Also, the colonic gene expression of endothelial CAMs and of most chemokines/chemokine receptors returned to normal after therapy in IBDc responders, and only CCL20 and CXCL1-2 expression remained increased after therapy in IBDc responders vs. control colons. When compared with control ileums, the ileal gene expression of MADCAM1, THY1, PECAM1, CCL28, CXCL1, -2, -5, -6, and -11, and IL8 was increased and CD58 expression was decreased in active ileal Crohn's disease (CDi) before therapy, and none of the genes remained dysregulated after therapy in CDi responders vs. control ileums. This microarray study identified a number of interesting targets for antiadhesion therapy including PECAM1, IL8, and CCL20, besides the currently studied $\alpha 4\beta 7$ integrin-MADCAM1 axis.

CONCLUSIONS: Our data demonstrate that many leukocyte/endothelial CAMs and chemokines/chemokine receptors are upregulated in inflamed IBD mucosa. Controlling the inflammation with infliximab restores most of these dysregulations in IBD. These results show that at least part of the mechanism of anti-tumor necrosis factor- α therapy goes through downregulation of certain adhesion molecules.

Safety

Am J Gastroenterol. 2011 Apr;106(4):778-85. Epub 2011 Mar 15.

Tolerability of shortened infliximab infusion times in patients with inflammatory bowel diseases: a single-center cohort study.

Breyngaert C, Ferrante M, Fidder H, Van Steen K, Noman M, Ballet V, Vermeire S, Rutgeerts P, Van Assche G.

OBJECTIVES: Scheduled maintenance therapy with infliximab decreases the risk of infusion reactions. Many centers have accelerated infusion times to 1 h in selected patients who tolerate 5 mg/kg infliximab infusions. The aim of this study was to compare the tolerability of 1-h and 2-h infliximab infusions in patients with inflammatory bowel disease (IBD) in a large single-center cohort. The primary end point was the incidence of infusion reactions in both groups.

METHODS: A retrospective chart analysis of all IBD patients treated with infliximab was performed. Infusions in scheduled maintenance for at least 6 months from December 1994 until March 2009 were included. All patients were treated at the infusion unit or during hospitalization under standard operating procedures. Infusion parameters were prospectively recorded. From 2004, in patients tolerating at least four 2-h infusions, infusions were given over 1 h.

RESULTS: As of March 2009, 953 patients with IBD (77.6% Crohn's disease, 22.4% ulcerative colitis) had been treated with infliximab. A total of 474 patients met the criteria of scheduled maintenance therapy. In total, 9,155 maintenance infusions were administered (4,307 over 1 h). No severe infusion reactions were documented. Mild acute reactions occurred in 0.6% (27/4,307) of the 1-h-infusion group and in 1.7% (80/4848) of the 2-h infusion group ($P=0.0034$). Delayed infusion reactions occurred in 0.2% of 1-h and 0.5% of 2-h infusion group patients ($P=0.277$). Loss of tolerability due to infusion reactions (1-h group 2.9% versus 2-h group 4.1%) was evenly distributed ($P=0.34$). None of the prespecified variables were predictive of infusion reactions in a multivariate analysis.

CONCLUSIONS: In patients with IBD tolerating 2-h infusions of infliximab scheduled maintenance therapy, the infusion time can be shortened to 1 h with good tolerability. No severe reactions were observed and no predictors of infusion reactions were identified.

Aliment Pharmacol Ther. 2011 May;33(9):1053-8. Epub 2011 Mar 1.

High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy.

Zelinkova Z, de Haar C, de Ridder L, Pierik MJ, Kuipers EJ, Peppelenbosch MP, van der Woude CJ.

SUMMARY: Background Typically, inflammatory bowel disease (IBD) patients are in their reproductive years, raising questions about safely using antitumour necrosis factor antibodies like infliximab (IFX) during pregnancy. IgG antibodies naturally cross the placenta, especially during the last trimester. To prevent foetal intra-uterine exposure, stopping IFX treatment at gestational week 30 is recommended. However, whether this limits intra-uterine and early postnatal IFX exposure is unestablished. Aim To determine the intra-uterine exposure to IFX following maternal treatment with IFX. Methods Four pregnant IBD patients intentionally continued IFX during pregnancy. IFX levels were assessed in newborns' cord blood and the mothers' peripheral blood at delivery. The children's development during the first 3-6 months, infections, vaccine reactions and antibody responses to vaccinations against Haemophilus influenzae type b and Pneumococcus were assessed. Results The patients stopped IFX therapy at gestational week 21, 26, 26 and 30, respectively. In three infants, therapeutic IFX levels were present in cord blood at levels of 5.5-13.7 $\mu\text{g/mL}$ and were two- to three-fold higher than in the peripheral blood of their mothers. During the 3- to 6-month follow-up, the children developed normally without signs of infections or allergic reactions, and had normal antibody titres after routine childhood vaccinations. Conclusion The use of IFX until gestational week 30 leads to foetal intra-uterine exposure to IFX at levels that exceed those in the mothers' peripheral blood. Although no short-term complications were detected, the high IFX levels observed in newborns raise concerns about unknown effects of IFX on the developing immune system.

J Crohns Colitis. 2011 Apr;5(2):157-61. Epub 2010 Dec 7.

Infliximab and adalimumab-induced psoriasis in Crohn's disease: A paradoxical side effect.

Iborra M, Beltrán B, Bastida G, Aguas M, Nos P.

Treatment with antitumor necrosis factor-alpha (anti-TNF- α) offers a significant improvement in several immune-based diseases, including Crohn's disease (CD) and psoriasis. Different cutaneous side effects have been described for anti-TNF- α therapy such as psoriasis. Previous reports showed that inhibition of TNF- α can induce over expression of cutaneous IFN- α , which in turn caused a predisposition to psoriasis. We report a 31-year-old woman with extensive CD and perianal lesions, without response to conventional treatment. She paradoxically developed a cutaneous eruption with psoriasiform morphology and distribution during treatment with both anti-TNF- α approved in Europe for CD, infliximab and adalimumab. These lesions cleared after topical application of corticosteroids and cessation of the anti-TNF- α treatment. Due to uneffectiveness of pharmacological treatment on disease, the patient had to undergo

surgery. TNF-induced psoriasis in patients with CD is rare and has been previously documented with infliximab or adalimumab. The reason for this apparently paradoxical effect of the therapy is still unclear. This is the first case of psoriasis induced first by infliximab and later by adalimumab in the same CD patient. We would like to review and to draw attention about psoriasis as a cutaneous side effect with anti-TNF- α treatments.

Ann Rheum Dis. 2011 May;70(5):823-6. Epub 2011 Feb 28.

Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register.

Verstappen SM, King Y, Watson KD, Symmons DP, Hyrich KL; BSRBR Control Centre Consortium, BSR Biologics Register.

OBJECTIVE: The British Society for Rheumatology Biologics Register (BSRBR) has collected data on adverse events including pregnancies in patients with rheumatoid arthritis treated with anti-tumour necrosis factor (anti-TNF) therapy. The purpose of this report is to summarise the pregnancy outcomes in women treated with anti-TNF in the BSRBR.

METHODS: Patients were categorised according to anti-TNF exposure as follows: (1) exposure to anti-TNF and to methotrexate (MTX) and/or leflunomide (LEF) at conception (n=21 pregnancies); (2) exposure to anti-TNF at conception (n=50); (3) exposure to anti-TNF prior to conception (n=59); (4) no exposure to anti-TNF (control group; n=10).

RESULTS: Eighty-eight live births in a total of 130 pregnancies were reported in patients who received anti-TNF before or during pregnancy. The rate of spontaneous abortion was highest among patients exposed to anti-TNF at the time of conception (with MTX/LEF 33% and without MTX/LEF 24%). This compared with 17% spontaneous abortions in those with prior exposure to anti-TNF and 10% spontaneous abortions in the control group. Ten terminations were performed.

CONCLUSION: Although the results to date have been promising, no firm conclusions can be drawn about the safety of anti-TNF during pregnancy and, without further evidence, guidelines which suggest these drugs should be avoided at the time of conception cannot yet be changed.

Br J Dermatol. 2011 Apr;164(4):862-72.

Cardiovascular safety of ustekinumab in patients with moderate to severe psoriasis: results of integrated analyses of data from phase II and III clinical studies.

Reich K, Langley RG, Lebwohl M, Szapary P, Guzzo C, Yeilding N, Li S, Hsu MC, Griffiths CE.

Background Patients with psoriasis are believed to be at an increased risk of cardiovascular (CV) morbidity, and the effect of biological agents on CV safety is not fully understood. **Objectives** To evaluate the effect of ustekinumab on CV events using detailed analyses of pooled data from the phase II/III clinical studies of its use in moderate to severe psoriasis. **Methods** The incidence of major adverse CV events [MACE: myocardial infarction (MI), stroke or CV death] is reported. Meta-analyses using risk difference and odds ratio estimates are presented based on data collected during the placebo-controlled period of ustekinumab trials. The cumulative numbers of events and rates of MIs and strokes over time were compared with those expected in the psoriasis and/or general populations. **Results** During the placebo-controlled period (12/20 weeks), five MACE were reported in 1582 ustekinumab-treated patients [0.3%; 95% confidence interval (CI) 0.1-0.7%] compared with no events in 732 placebo-treated patients (0.0%; 95% CI 0.0-0.5%). MACE rates were stable over time during both the controlled and uncontrolled study periods, with 19 of 3117 ustekinumab-treated patients (0.6%) experiencing 21 events for a combined event rate per 100 patient-years of follow-up of 0.44 (95% CI 0.27-0.67) through up to 3 years. Standardized incidence ratios for comparison of ustekinumab clinical data with external data sources ranged from 0.34 to 0.52, suggesting no increased risk of MI or stroke in ustekinumab-treated patients compared with the general U.S. and psoriasis populations. **Conclusions** The totality of available clinical data suggests neither a detrimental nor a beneficial effect of ustekinumab on serious CV events. Additional data are needed to define the net effect of ustekinumab on CV events.

J Drugs Dermatol. 2011 Mar;10(3):280-4.

Frequency of thrombocytopenia in psoriasis patients treated with tumor necrosis factor- α inhibitors.

Chen M, Holland MJ, Mir MR, Wong MG, Kelley BP, Grim KD, Bhuchar SS, Hsu S.

Tumor necrosis factor- α (TNF- α) inhibitors are biologic agents that are currently in wide use for the treatment of psoriasis as well as other inflammatory diseases. Following reports of thrombocytopenia as a potential adverse effect of anti-TNF- α therapy, we performed a retrospective study to determine the frequency of thrombocytopenia, defined as a platelet count $<50 \times 10^9$ cells/L, in a cohort of 187 psoriatic patients treated with anti-TNF- α agents over a nine-year period. Although none of our patients met serologic criteria for thrombocytopenia or displayed clinical manifestations of thrombocytopenia, two patients developed platelet counts below 100×10^9 cells/L. Thrombocytopenia induced by anti-TNF- α agents is a potential adverse effect, it is a rare occurrence that will require further investigation in large, placebo-controlled, double-blind, prospective studies.

J Drugs Dermatol. 2011 Mar;10(3):289-300.

Clinical trial safety and mortality analyses in patients receiving etanercept across approved indications.

Gottlieb AB, Gordon K, Giannini EH, Mease P, Li J, Chon Y, Maddox J, Weng HH, Wajdula J, Lin SL, Baumgartner SW.

OBJECTIVES: Assessment of associations between etanercept treatment and rare adverse events has been limited by the size of clinical trial populations. The authors examined the collective safety of etanercept in clinical trials across approved indications.

PATIENTS AND METHODS: Forty-nine U.S. and non-U.S. trials of etanercept, involving up to 13,977 patients for approved indications, with final trial reports as of May 2006, were selected from the Amgen Inc. clinical trials database. Exposure-adjusted rates of serious infections, opportunistic infections, malignancies, and deaths were reported by trial, indication, and dosage.

RESULTS: Rates of serious infections were generally similar between etanercept and controls. Overall rates of opportunistic infections and tuberculosis were low. The standardized incidence ratio (SIR) (95% CI) for malignancy was 1.00 (0.83-1.19) for all etanercept patients across all indications. The SIR for lymphoma for patients with rheumatoid arthritis was 3.45 (1.83-5.89); all other indications reported SIRs similar to those observed in the general population. The SIRs for cutaneous squamous cell carcinoma in patients with psoriasis relative to the general population with high or low sun exposure were 2.09 (1.27-3.22) and 4.96 (3.03-7.66), respectively. SIRs were less than 1.0 for all other indications regardless of sun exposure. Rates of melanoma and basal cell carcinoma were not significantly different from those in the general population. There was no increase in mortality associated with etanercept use relative to control populations.

CONCLUSION: These data support the overall tolerability of etanercept across approved indications.

JAMA. 2011 Apr 13;305(14):1460-8.

Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up.

Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, Dijkmans BA, Aarden L, Wolbink GJ.

CONTEXT: Short-term data on the immunogenicity of monoclonal antibodies showed associations between the development of antidrug antibodies and diminished serum drug levels, and a diminished treatment response. Little is known about the clinical relevance of antidrug antibodies against these drugs during long-term follow-up.

OBJECTIVE: To examine the course of antidrug antibody formation against fully human monoclonal antibody adalimumab and its clinical relevance during long-term (3-year) follow-up of patients with rheumatoid arthritis (RA).

DESIGN, SETTING, AND PATIENTS: Prospective cohort study February 2004-September 2008; end of follow-up was September 2010. All 272 patients were diagnosed with RA and started treatment with adalimumab in an outpatient clinic.

MAIN OUTCOME MEASURES: Disease activity was monitored and trough serum samples were obtained at baseline and 8 time points to 156 weeks. Serum adalimumab concentrations and antiadalimumab antibody titers were determined after follow-up. Treatment discontinuation, minimal disease activity, and clinical remission were compared for patients with and without antiadalimumab antibodies.

RESULTS: After 3 years, 76 of 272 patients (28%) developed antiadalimumab antibodies--51 of these (67%) during the first 28 weeks of treatment. Patients without antiadalimumab antibodies had much higher adalimumab concentrations (median, 12 mg/L; IQR, 9-16 mg/L) compared with patients with antibody titers from 13 to 100 AU/mL (median, 5 mg/L; IQR, 3-9 mg/L; regression coefficient, -4.5; 95%

CI, -6.0 to -2.9; $P < .001$) and also those greater than 100 AU/mL (median, 0 mg/L; IQR, 0-3 mg/L; regression coefficient, -7.1; 95% CI, -8.4 to -5.8; $P < .001$). Patients with antiadalimumab antibodies more often discontinued participation due to treatment failure ($n = 29$ [38%]; hazard ratio [HR], 3.0; 95% CI, 1.6-5.5; $P < .001$) compared with antiadalimumab antibody-negative ones ($n = 28$ [14%]). Ninety-five of 196 patients (48%) without antiadalimumab antibodies had minimal disease activity vs 10 of 76 patients (13%) with antiadalimumab antibodies; patients with antiadalimumab antibodies less often had sustained minimal disease activity score in 28 joints (DAS28) (< 3.2 ; HR, 3.6; 95% CI, 1.8-7.2; $P < .001$) compared with antiadalimumab antibody-negative ones. Three of 76 patients (4%) with antiadalimumab antibodies achieved sustained remission compared with 67 of 196 (34%) antiadalimumab antibody-negative ones; patients with antiadalimumab antibodies less often achieved remission (DAS28 < 2.6 ; HR, 7.1; 95% CI, 2.1-23.4; $P < .001$) compared with antiadalimumab antibody-negative ones.

CONCLUSION: Among outpatients with RA in whom adalimumab was started over 3 years, the development of antidrug antibodies was associated with lower adalimumab concentration and lower likelihood of minimal disease activity or clinical remission.

J Invest Dermatol. 2011 May;131(5):1159-66. Epub 2011 Jan 20.

Very severe psoriasis is associated with increased noncardiovascular mortality but not with increased cardiovascular risk.

Stern RS, Huibregtse A.

It has been hypothesized that severe psoriasis is an independent risk factor for cardiovascular disease (CVD). We prospectively studied patients with severe psoriasis treated with psoralens and ultraviolet-A therapy (PUVA) who enrolled in a cohort study in 1975-1976. From 1977 to 2005, 617 of the 1,376 patients (45%) died. Compared with the general population, cohort death rates were significantly higher than expected (standard mortality ratio (SMR)=1.1, 95% confidence interval (CI)=1.02-1.20). The number of deaths due to CVD (SMR=1.02, 95% CI=0.9-1.6) was nearly identical to the expected number. Deaths due to liver disease were significantly elevated (SMR=4.04, 95% CI=2.76-5.70). Patients with exceptionally severe psoriasis at entry ($>42\%$ body surface area (BSA)) had a significantly increased risk of death compared with less severely affected cohort members (all-cause hazard ratio (HR)=1.42, 95% CI=1.18-1.69) as well as for deaths because of causes other than cancer or CVD (multivariate HR 1.56, 95% CI=1.14-2.13). Only patients with exceptionally severe psoriasis had an increased mortality risk compared with both the general population and other cohort members with less extensive but still severe psoriasis. These increases were not significant for CVD. Our data do not support the hypothesis that severe psoriasis is an independent risk factor for CVD. However, exceptionally severe psoriasis is associated with increased all-cause mortality.

PLoS One. 2011 Mar 31;6(3):e17890.

Infliximab induces clonal expansion of $\gamma\delta$ -T Cells in Crohn's disease: A predictor of lymphoma risk?

Kelsen J, Dige A, Schwindt H, D'Amore F, Pedersen FS, Agnholt J, Christensen LA, Dahlerup JF, Hvas CL

BACKGROUND: Concomitant with the widespread use of combined immunotherapy in the management of Crohn's disease (CD), the incidence of hepato-splenic gamma-delta ($\gamma\delta$)-T cell lymphoma has increased sharply in CD patients. Malignant transformation of lymphocytes is believed to be a multistep process resulting in the selection of malignant $\gamma\delta$ -T cell clones. We hypothesized that repeated infusion of anti-TNF- α agents may induce clonal selection and that concurrent treatment with immunomodulators further predisposes patients to $\gamma\delta$ -T cell expansion.

METHODOLOGY/PRINCIPAL FINDINGS: We investigated dynamic changes in the $\gamma\delta$ -T cells of patient with CD following treatment with infliximab (Remicade®; $n = 20$) or adalimumab (Humira®; $n = 26$) using flow cytometry. In patients with a high $\gamma\delta$ -T cell level, the $\gamma\delta$ -T cells were assessed for clonality. Of these 46 CD patients, 35 had a $\gamma\delta$ -T cells level (mean 1.6%) comparable to healthy individuals (mean 2.2%), and 11 CD patients (24%) exhibited an increased level of $\gamma\delta$ -T cells (5-15%). In the 18 patients also receiving thiopurines or methotrexate, the average baseline $\gamma\delta$ -T cell level was 4.4%. In three male CD patients with a high baseline value, the $\gamma\delta$ -T cell population increased dramatically following infliximab therapy. A fourth male patient also on infliximab monotherapy presented with 20% $\gamma\delta$ -T cells, which increased to 25% shortly after treatment and was 36% between infusions. Clonality studies revealed an oligoclonal $\gamma\delta$ -T cell pattern with dominant $\gamma\delta$ -T cell clones. In support of our clinical findings, in vitro experiments showed a dose-dependent proliferative effect of anti-TNF- α agents on $\gamma\delta$ -T cells.

CONCLUSION/SIGNIFICANCE: CD patients treated with immunomodulators had constitutively high levels of $\gamma\delta$ -T cells. Infliximab exacerbated clonal $\gamma\delta$ -T cell expansion in vivo and induced $\gamma\delta$ -T cell proliferation in vitro. Overall, young, male CD patients with high baseline $\gamma\delta$ -T cell levels may be at an increased risk of developing malignant $\gamma\delta$ -T cell lymphomas following treatment with anti-TNF- α agents.

Int J Dermatol. 2011 May;50(5):619-25. doi: 10.1111/j.1365-4632.2011.04871.x.

TNF alpha antagonist-induced lupus-like syndrome: report and review of the literature with implications for treatment with alternative TNF alpha antagonists.

Williams VL, Cohen PR.

Background In patients with various autoimmune and rheumatic diseases, a drug-induced lupus-like syndrome (DILS) has been reported with the use of adalimumab, cerrolizumab pegol, etanercept, and infliximab. **Objective** To review clinical characteristics of patients who develop tumor necrosis factor (TNF) alpha antagonist-induced lupus-like syndrome (TAILS) and review implications for further TNF alpha antagonist therapy. **Materials and methods** We describe a 62-year-old woman with rheumatoid arthritis who developed a pruritic photo-distributed rash two months after the initiation of etanercept therapy. Her skin biopsy showed lupus erythematosus, and she had positive serum ANA, anti-Sjogren's syndrome A (SSA)/Ro, and anti-Sjogren's syndrome B (SSB)/La antibodies. Her symptoms resolved after discontinuation of the drug, topical and systemic corticosteroids, and hydroxychloroquine sulfate. Subsequently, her rheumatoid arthritis was treated with golimumab for six months without recurrence of skin lesions. Published reports of individuals who have developed TAILS and those who have continued treatment with alternative TNF alpha antagonists are reviewed. **Results** TAILS is most commonly associated with the use of etanercept and infliximab. It occurs most often in women in the fifth decade of life. Onset of symptoms ranges from less than one month to more than four years. Syndrome-associated cutaneous lesions and induction of autoantibodies are common. There is no definitively established mechanism of pathogenesis. Treatment can include discontinuation of the drug, corticosteroids, immunosuppressives, and hydroxychloroquine sulfate. To date, 10 patients with TAILS have continued therapy with an alternative TNF alpha antagonist without recurrence of lupus symptoms. **Conclusions** Development of a DILS after one TNF alpha antagonist does not preclude continued treatment with an alternative TNF alpha antagonist.