# Literature Update Immunology

Period: 1-31 May 2010

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- **Adalimumab** sustains **clinical remission** and overall **clinical benefit** after **2 years of therapy** for Crohn's disease **(ADHERE)**
- **Emerging drugs** to treat Crohn's disease
- Scheduled **maintenance therapy with infliximab** improves the **prognosis of Crohn's disease**: a single center prospective cohort study in Japan.
- **Effectiveness of infliximab in Brazilian children** and adolescents with **Crohn disease and ulcerative colitis** according to clinical manifestations, activity indices of inflammatory bowel disease, and corticosteroid use
- **Anti-TNF therapy** in **inflammatory bowel diseases**: a huge **review.**
- An approach to the **management of re-fractory ulcerative colitis**.

**Safety**

- The challenges of quantifying the **risk of serious infection with tumor necrosis factor antagonist therapy**
- **Observational studies of infections in rheumatoid arthritis**: A metaanalysis of tumor necrosis factor antagonists
- **Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated** interstitial lung disease: results from the British Society for Rheumatology Biologics Register
- **Risk of elevated liver enzymes** associated with **TNF inhibitor** utilisation in patients with **rheumatoid arthritis.**
- **Paradoxical reactions** to targeted **biological treatments**: A way to treat and trigger?
- Practical guidelines for treating inflammatory bowel disease safely with anti-tumour necrosis factor therapy in Australia.
- **Necrotizing external otitis** on a Crohn's disease patient treated **with infliximab**
- The **safety profile** and sustained remission associated with response to multiple courses of **intramuscular alefacept** for treatment of **chronic plaque psoriasis**
- **Safety of etanercept** in **patients with psoriasis and hepatitis C** virus assessed by liver histopathology: Preliminary data
- **Infliximab** therapy in a patient with **refractory ileocolic Crohn's disease** and **Takayasu arteritis**
- Comment on: Complications and features after **joint surgery in rheumatoid arthritis patients** treated with **tumour necrosis factor-α blockers**: perioperative interruption of tumour necrosis factor- blockers decreases complications?
- **Disease activity and venous thromboembolism** in **inflammatory bowel disease**
- **Venous thromboembolism** during active disease and remission in **inflammatory bowel disease**: a cohort study
- **Safety of antitumour necrosis factor- therapy in psoriatic patients** with **hepatitis B virus infection**
- Nationwide linkage analysis in Scotland implicates **age** as the **critical overall determinant** of **mortality in ulcerative colitis**
- **Inflammatory bowel disease-patients** are **insufficiently educated** about the **basic characteristics of their disease** and the associated **risk of colorectal cancer**
- **Mycobacterium marinum infection** complicated by **anti-tumour necrosis factor therapy**.
- **Influence of anti-infliximab antibodies** and **residual infliximab concentrations** on the occurrence of **acquired drug resistance to infliximab** in rheumatoid arthritis patients.
- **Antibodies against cyclic citrullinated peptide** don't decrease after **6 months of infliximab treatment** in refractory rheumatoid arthritis.
- **Anti-TNFα therapy** did not increase **short- or medium-term risk for cancer** in patients with rheumatoid arthritis
- **Long-term safety** of **anti-TNF treatment** in **patients with rheumatic diseases** and chronic or resolved **hepatitis B virus infection**
- The effect of **infliximab** and **timing of vaccination** on the humoral **response to influenza vaccination** in patients with **rheumatoid arthritis and ankylosing spondylitis**
- **Adverse events** and factors associated with **toxicity** in patients with **early rheumatoid arthritis** treated with **methotrexate** tight control therapy: **the CAMERA study**
- Influence of **anti-TNF therapy** on **mortality** in patients with **rheumatoid arthritis-associated interstitial lung disease**: results from the British Society for Rheumatology Biologics Register
- How **tumour necrosis factor blockers** interfere with **tuberculosis immunity**.

## IBD

Nat Rev Gastroenterol Hepatol. 2010 Feb;7(2):79-85.
**The potential for disease modification in Crohn's disease**
Van Assche G, Vermeire S, Rutgeerts P.

The natural history of Crohn's disease is characterized by progression to complicated and disabling disease, often necessitating surgical interventions. There is either circumstantial or direct evidence to support the disease-modifying potential of several therapeutic agents. Healing of endoscopic lesions is an emerging surrogate marker of disease modification, as mucosal lesions are considered to reflect ongoing inflammation and tissue damage that lead to the formation of fistulas and fibrotic strictures, which are the main indications for surgery. In contrast to systemic steroids, both azathioprine and anti-tumor necrosis factor (TNF) agents have demonstrated the potential of mucosal healing. Prevention of hospitalization and surgery in the short and medium term has been demonstrated for the anti-TNF agents infliximab and adalimumab. The evidence supporting a role for medical therapy in the prevention of fibrotic wall thickening and in the obliteration of fistula tracks is limited and should be the focus of further prospective studies. These studies should validate predictors of complicated disease and randomized studies should be performed in high-risk groups to investigate whether early introduction of immunosuppressive agents or biologic therapies slows down disease progression and alters the natural history of the disease.

Journal of Gastroenterology and Hepatology 2010; 25(5): 886-891
**Efficacy and safety of infliximab as rescue therapy for ulcerative colitis refractory to tacrolimus**
Shuji Yamamoto, Hiroshi Nakase, Minoru Matsuura, Yusuke Honzawa, Satohiro Masuda, Ken-ichi Inui, Tsutomu Chiba

No abstract available

Aliment Pharmacol Ther. 2010 Mar 8. [Epub ahead of print]
**Infliximab for refractory ulcerative proctitis**
Peyrin-Biroulet L, Bouguen G, Roblin X, Bourreille A, Feier L, Filippi J, Nancey S, Bretagne JF, Flourié B, Hébuterne X, Bigard MA, Siproudhis L.

Summary Background: Efficacy of infliximab in treating ulcerative proctitis is unknown. Aim: To evaluate clinical, biological and endoscopic efficacy of infliximab therapy in refractory proctitis. Methods: The charts of 420 patients treated with infliximab for ulcerative colitis were reviewed. Thirteen patients were treated with infliximab for refractory ulcerative proctitis in six referral centers between 2005 and 2009. Results: Following infliximab therapy induction, 9/13 patients (69%) had a complete response (defined as absence of diarrhea and blood), 2/13 (15%) had a partial response and 2/13 (15%) were primary non-responders. The median follow-up was 17 months (range, 3-48). Among the 11 patients with clinical response after infliximab induction therapy, 9 (82%) patients maintained response at last news. Disappearance of rectal disorders was observed in all 9 patients who maintained clinical response at last news. Following infliximab induction therapy, the mean CRP level fell from 12.8 mg/L to 4.7 mg/L. Endoscopic evaluation was performed before and after infliximab in 7 patients, showing an improvement in mucosal lesions in 4 patients, persistent mild endoscopic activity in 2 patients, and no improvement in one patient. One patient underwent proctocolectomy. Conclusion: Infliximab therapy seems to be effective in inducing and maintaining clinical response in refractory ulcerative proctitis.

Int J Clin Pharmacol Ther. 2010 May;48(5):297-308.
**Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis.**
Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM.

Objectives: Infliximab, an IgG1 monoclonal antibody (mab), has large inter-individual serum concentration variability. The objective was to determine the extent of the association of baseline albumin concentration and infliximab disposition in patient with ulcerative colitis. Method: Data from 728 patients with ulcerative colitis from two clinical trials were analyzed to evaluate trends between infliximab pharmacokinetics and

serum albumin, or liver or kidney function. Response in the placebo and treated groups were compared by baseline serum albumin concentrations (SAC) groups. Results: Patients with higher SAC maintained higher infliximab concentrations, lower clearance, and longer half-life than patients with lower SAC. When analyzed by SAC quartiles, patients in the highest quartile had several-fold greater trough infliximab concentrations when compared with those in the lowest quartile. These observations were consistent in both studies and at different dose levels. Generally, clinical response in patients did not vary with SAC when the SAC was within the normal range, apparently because serum infliximab concentrations remained at therapeutic levels. However, patients with SAC lower than the normal laboratory reference range had much lower median serum infliximab concentrations and lower response rates compared with patients within normal SAC. Infliximab pharmacokinetics did not correlate with SGOT or creatinine clearance. Conclusions: It is hypothesized that the common rescue pathway for both albumin and IgG involving the neonatal Fc receptor may be responsible for the relationship between serum albumin and serum infliximab levels. Baseline albumin level may serve as a valuable and convenient measure of mab pharmacokinetic expectations in these patients.

Am J Gastroenterol. 2010 May;105(5):1133-9.
**Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease.**
Afif W, Loftus EV Jr, Faubion WA, Kane SV, Bruining DH, Hanson KA, Sandborn WJ.

OBJECTIVES: Human anti-chimeric antibodies (HACAs) and subtherapeutic infliximab concentrations are associated with decreased duration of response. We evaluated the clinical utility of measuring HACA and infliximab concentrations. METHODS: The medical records of patients with inflammatory bowel disease (IBD) who had HACA and infliximab concentrations measured were reviewed to determine whether the result affected clinical management. RESULTS: One hundred fifty-five patients had HACA and infliximab concentrations measured. The main indications for testing were loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune/delayed hypersensitivity reaction (10%). HACAs were identified in 35 patients (23%) and therapeutic infliximab concentrations in 51 patients (33%). Of 177 tests assessed, the results impacted treatment decisions in 73%. In HACA-positive patients, change to another anti-tumor necrosis factor (TNF) agent was associated with a complete or partial response in 92% of patients, whereas dose escalation had a response of 17%. In patients with subtherapeutic infliximab concentrations, dose escalation was associated with complete or partial clinical response in 86% of patients whereas changing to another anti-TNF agent had a response of 33%. Patients with clinical symptoms and therapeutic infliximab concentrations were continued at the same dose 76% of the time and had no evidence of active inflammation by endoscopic/radiographic assessment 62% of the time. CONCLUSIONS: Measurement of HACA and infliximab concentration impacts management and is clinically useful. Increasing the infliximab dose in patients who have HACAs is ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy may be a good alternative to changing to another anti-TNF agent.

Am J Gastroenterol. 2010 May;105(5):1140-1
**Anti-TNF treatment in Crohn's disease: toward tailored therapy?**
D'Haens G.

Infliximab is a potent therapy for induction and maintenance of remission in Crohn's disease. Unfortunately, many patients lose response and/or develop allergic reactions caused by the chimeric antibody. By means of measuring the presence of antibodies against infliximab and the trough levels of the drug, it seems easier to predict whether patients will respond to intensified dose regimens or will rather benefit from a switch to alternative agents.

Am J Gastroenterol. 2010 May;105(5):1142-9. Epub 2010 Apr 13.
**Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy**
Oussalah A, Chevaux JB, Fay R, Sandborn WJ, Bigard MA, Peyrin-Biroulet L.

OBJECTIVES: Whether all Crohn's disease (CD) patients should maintain long-term azathioprine treatment in combination with infliximab remains controversial. We analyzed the predictive factors of infliximab failure after azathioprine withdrawal. METHODS: This was an observational study from a single

referral center. All patients with luminal CD in remission who stopped azathioprine after receiving infliximab in combination with azathioprine for at least 6 months were studied. Cumulative probabilities of infliximab failure-free survival were estimated by the Kaplan-Meier method from the date of azathioprine withdrawal to the date of infliximab failure or last known follow-up. Infliximab failure was defined by: (i) disease flare requiring shortening of the dosing interval or increasing the infliximab dose to 10 mg/kg, or switching to adalimumab; (ii) acute or delayed hypersensitivity reactions leading to infliximab discontinuation; or (iii) CD-related surgery. RESULTS: At last known follow-up, 35 out of 48 (73%) patients were infliximab failure free. The survival probabilities were 85% (+/-5%) at 12 months and 41% (+/-18%) at both 24 and 32 months. Cox proportional-hazards regression identified three predictors of infliximab failure: infliximab-azathioprine exposure duration of < or = 811 days (hazard ratio (HR)=7.46, P=0.01), C-reactive protein > 5 mg/l (HR=4.79, P=0.008), and platelet count > 298 10(9)/l (HR=4.75, P=0.02). CONCLUSIONS: In CD in clinical remission under azathioprine-infliximab combination therapy, azathioprine withdrawal is associated with a high risk of relapse in patients with a duration of combination therapy of < 27 months and/or the presence of biological inflammation.

Am J Gastroenterol. 2010 May;105(5):1150-7. Epub 2009 Dec 8.

**Are colonoscopy and bowel ultrasound useful for assessing response to short-term therapy and predicting disease outcome of moderate-to-severe forms of ulcerative colitis?: a prospective study.**

Parente F, Molteni M, Marino B, Colli A, Ardizzone S, Greco S, Sampietro G, Foschi D, Gallus S.

OBJECTIVES: Mucosal healing has been proposed as an important sign of the efficacy of medical treatment of inflammatory bowel disease; however, direct evidence in ulcerative colitis (UC) is scarce. We evaluated the usefulness of colonoscopy and bowel ultrasound (US) as indexes of response to short-term therapy and as predictors of subsequent outcome in UC. METHODS: A total of 83 patients with moderate-to-severe UC were recruited; endoscopic and US severity was graded 0-3 at entry according to validated scores. Of the recruited patients, 74, who were clinically responsive to steroids, were followed up with repeated colonoscopy and bowel US at 3, 9, and 15 months from recruitment. Concordance between clinical, endoscopic, and US scores at various visits was determined by kappa statistics. Multiple unconditional logistic regression models were used to assess the predictivity of clinical, endoscopic, and US scores measured at 3 and 9 months on the development of endoscopic UC relapse within 15 months. RESULTS: A variable concordance was found over time between endoscopic and clinical score (weighted kappa between 0.38 and 0.95), with high and consistent concordance between endoscopic and US scores (weighted kappa between 0.76 and 0.90). On logistic regression analysis, moderate-to-severe endoscopic and US scores at 3 months were associated with a high risk of endoscopic activity at 15 months (odds ratio (OR): 5.2; 95% confidence interval (CI): 1.6-17.6 and OR: 9.1; 95% CI: 2.5-33.5, respectively). CONCLUSIONS: Bowel US may be used as a surrogate of colonoscopy in assessing the short-term response of severe forms of UC to therapy. Both US score and endoscopic score after 3 months of steroid therapy predict outcome of disease at 15 months.

Am J Gastroenterol. 2010 May;105(5):1158-64. Epub 2009 Dec 15.

**The impact of thiopurines on the risk of surgical recurrence in patients with Crohn's disease after first intestinal surgery.**

Papay P, Reinisch W, Ho E, Gratzer C, Lissner D, Herkner H, Riss S, Dejaco C, Miehsler W, Vogelsang H, Novacek G.

OBJECTIVES: Smoking and a lack of immunosuppressive (IS) therapy are considered risk factors for intestinal surgery in Crohn's disease (CD). Good evidence for the latter is lacking. The objective of this study was to evaluate the impact of thiopurine treatment on surgical recurrence in patients after first intestinal resection for CD and its possible interaction with smoking. METHODS: Data on 326 patients after first intestinal resection were retrieved retrospectively, and subjects were grouped according to their postoperative exposure to thiopurines. Treatment with either azathioprine (AZA) or 6-mercaptopurine (6-MP) was recorded on 161 patients (49%). Smoking status was assessed by directly contacting the patients. RESULTS: Surgical recurrence occurred in 151/326 (46.3%) patients after a median time of 71 (range 3-265) months. Cox regression revealed a significant reduction of re-operation rate in patients treated with AZA/6-MP for > or = 36 months as compared with patients treated for 3-35 months, for less than 3 months, and to those without postoperative treatment with AZA/6-MP (P=0.004). Cox regression analysis revealed treatment with thiopurines for > or = 36 months (hazard ratio (HR) 0.41; 95% confidence interval (CI) 0.23-0.76, P=0.004) and smoking (HR 1.6; 95% CI 1.14-2.4, P=0.008) as

independent predictors for surgical recurrence. Furthermore, longer duration of disease tended to be protective (HR 0.99; 95% CI 0.99-1.0, P=0.067). CONCLUSIONS: Long-term maintenance treatment with AZA/6-MP reduces the risk of surgical recurrence in patients with CD. We also identified smoking as a risk factor for surgical recurrence.

Inflamm Bowel Dis 2010; 16(6): 933-938
**Efficacy and safety of certolizumab pegol induction therapy in an unselected Crohn's disease population: Results of the FACTS survey.**
Schoepfer AM, Vavricka SR, Binek J, Felley C, Geyer M, Manz M, Rogler G, de Saussure P, Sauter B, Seibold F, Straumann A, Michetti P.

BACKGROUND: Switzerland was the first country to approve certolizumab pegol (Cimzia, CZP) for the treatment of patients with moderate to severe Crohn's disease (CD) in September 2007. This phase IV study aimed to evaluate the efficacy and safety of CZP in a Swiss multicenter cohort of practice-based patients. METHODS:: Baseline and Week 6 evaluation questionnaires were sent to all Swiss gastroenterologists in hospitals and private practices. Disease activity was assessed with the Harvey-Bradshaw Index (HBI) and adverse events were evaluated according to WHO guidelines. RESULTS:: Fifty patients (31 women, 19 men) were included; 56% had complicated disease (stricture or fistula) and 52% had undergone prior CD-related surgery. All patients had prior exposure to systemic steroids, 96% to immunomodulators, 78% to infliximab, and 50% to adalimumab. A significant decrease in HBI was observed at Week 6 (versus Week 0) following induction therapy with CZP 400 mg subcutaneously at Weeks 0, 2, and 4 (12.6 +/- 4.7 Week 0 versus 6.2 +/- 4.4 Week 6, P < 0.001). Response and remission rates at Week 6 were 54% and 40%, respectively. We identified 8/11 CD patients undergoing a 50% fistula response (P = 0.021). The frequency of adverse drug reactions attributed to CZP was 6%. CZP was continued in 80% of patients beyond Week 6. CONCLUSIONS:: In a population of CD patients with complicated disease behavior, CZP induced a response and remission in 54% and 40% of patients, respectively. This series provides the first evidence of the effectiveness of CZP in perianal fistulizing CD.

Inflamm Bowel Dis 2010; 16 (6): 953-961
**Natural history of Crohn's disease: Comparison between childhood- and adult-onset disease.**
Pigneur B, Seksik P, Viola S, Viala J, Beaugerie L, Girardet JP, Ruemmele FM, Cosnes J.

BACKGROUND:: Childhood-onset Crohn's disease (CD) might reflect a more severe form of disease. To test this hypothesis we analyzed the long-term natural history of CD in an adult cohort of patients with childhood-onset compared to adult-onset CD. METHODS:: We selected 206 childhood-onset CD patients among 2992 adult patients with a diagnosis of CD established before December 31, 2000. Disease characteristics were prospectively assessed during follow-up until December 2007 and compared to adult-onset CD patients matched 2 to 1 on gender, year of CD diagnosis, and disease location. RESULTS:: Compared to adult-onset CD, patients with childhood-onset CD were more likely to have a severe disease, with an increased year-by-year disease activity index (37% of patient-years in childhood-onset group versus 31% in the adult-onset group, P < 0.001). Immunosuppressant requirement was also increased with a 10-year cumulative risk of 54 +/- 3% in childhood-onset CD group versus 45 +/- 2%, in the adult-onset CD group (P < 0.001). Cumulative risks of stricturing and penetrating complications and surgical resections were not statistically different between groups. Accordingly, these events occurred at a younger age in the childhood-onset CD group. At the age of 30 years the actuarial risk of having undergone an extensive intestinal resection was 48 +/- 5% in the childhood-onset group versus 14 +/- 2% in the adult-onset group (P < 0.001). CONCLUSIONS:: Patients with childhood-onset CD exhibit a more active disease and require more immunosuppressive therapy. This feature is observed irrespective of the disease location, suggesting an intrinsic more severe phenotype.

Inflamm Bowel Dis 2010; 16(6): 962-973
**Teduglutide, a novel mucosally active analog of glucagon-like peptide-2 (GLP-2) for the treatment of moderate to severe Crohn's disease**
Buchman AL, Katz S, Fang JC, Bernstein CN, Abou-Assi SG et al.

BACKGROUND:: Teduglutide, an analog of glucagon-like peptide-2 (GLP-2), is associated with trophic effects on gut mucosa. Its role in the treatment of active Crohn's disease (CD) was assessed in a pilot, randomized, placebo-controlled, double-blinded, dose-ranging study. METHODS:: Subjects with

moderate-to-severe CD were randomized 1:1:1:1 to placebo or 1 of 3 doses of teduglutide (0.05, 0.10, or 0.20 mg/kg daily) delivered as a daily subcutaneous injection for 8 weeks. The primary outcome measure was the percentage of subjects in each group that responded to treatment, defined as a decrease in Crohn's Disease Activity Index (CDAI) score to <150 or a decrease of > 100 points. At week 8 there was an optional 12-week open-label period of treatment with teduglutide 0.10 mg/kg/d. RESULTS:: One hundred subjects were enrolled and 71 completed the study. The mean baseline CDAI score was 290.8 +/- 57.6 and was similar across groups. There were numerically higher response and remission rates in all teduglutide-treated groups as compared with placebo, although the percentage of subjects who achieved a clinical response or remission was more substantial, and seen as early as week 2 of treatment in the highest dose (0.2 mg/kg/d) group (44% response and 32% remission versus 32% response and 20% remission in the placebo group). Of subjects who had not achieved remission during the 8-week placebo-controlled phase in the higher-dose group, 50% achieved remission during the more prolonged, open-label treatment phase. Plasma citrulline was similar across groups at baseline, but increased substantially over time in all teduglutide groups when compared with placebo at week 8. Adverse events were not different between placebo and active treatment groups. CONCLUSIONS:: Teduglutide is a novel and potentially effective therapy for inducing remission and mucosal healing in patients with active moderate-to-severe CD. Further clinical investigation of this growth factor is warranted.

Tech Coloproctol. 2009 Dec;13(4):295-300. Epub 2009 Sep 23.
**Immunomodulation does not alter histology in resected Crohn's disease.**
Frizelle FA, Ing A, Gearry RB, Whitehead M, Faragher IG, Dobbs B.

BACKGROUND: The use of immunomodulators (Azathioprine, 6-Mercaptopurine and Methotrexate) and biological agents (Infliximab and adalimumab) for the treatment of Crohn's disease (CD) has increased in the recent years with the aim of treating the inflammatory component of the disease and hoping to change the natural history of the disease. The aim of this study was to determine if the use of immunomodulators or biological agents in the 2 years prior to resection affects the histopathological characteristics of the patient's disease. METHODS: A retrospective review was conducted over a 10-year period (1996-2005) of patients who underwent resection for CD. Clinical case notes and histology specimens were reviewed. Patients treated with Azathioprine, 6-Mercaptopurine, Methotrexate or Infliximab for more than 3 months within the 2 years preceding surgery were deemed to have been immunomodulated. The results were also analysed by Montreal phenotype. RESULTS: A total of 165 patients were identified. 52 patients had been treated with either immunomodulator or biological agent. Of 20 histological features examined, only muscular hypertrophy approached significance (P = 0.05), Montreal A and Montreal L phenotypes were the same regardless on immunomodulators, however, there was a significant difference (P = 0.03) with regard to Montreal B in patients with stricturing disease being more likely to have received an immunomodulator. CONCLUSIONS: In this cohort of patients requiring resection for CD, those with stricturing disease were more likely to receive immunomodulators or biologics than those without stricturing disease. However, there were no significant histological differences in the resected specimens between those who did and those who did not receive these drugs.

Dig Liver Dis. 2010 Jun;42(6):432-5. Epub 2009 Oct 14.
**Sustained remission after steroids and leukocytapheresis induced response in steroid-dependent ulcerative colitis: results at 1 year.**
Cabriada JL, Ibargoyen N, Hernández A, Bernal A, Castiella A.

BACKGROUND: Leukocytapheresis (LAP) could be an alternative treatment for steroid-dependent ulcerative colitis (UC). AIMS: To assess the duration of response at 1 year after this treatment. PATIENTS AND METHODS: A prospective study in 18 patients with steroid-dependent UC treated with LAP plus steroids after failure or intolerance to immunomodulators. Clinical and endoscopic (Mayo Clinic index) examinations were performed at 1 month after the last apheresis and at 12 months. The clinical, endoscopic remission and the relapse during the 1-year follow-up were evaluated based on standard parameters. RESULTS: Induction of remission: clinical remission: 10/18 (55%). Partial response: 4. Endoscopic remission: 9 (50%), always accompanied by clinical remission. A significant correlation was observed between clinical remission and endoscopic remission (r(s)=0.894; p< or =0.001). At 1 year: sustained steroid-free clinical remission in 9 (50%), all of whom presented initial endoscopic remission. Remission and relapse before 1 year in 17%. A tendency for sustained remission at 1 year was observed when initial endoscopic remission was achieved. CONCLUSIONS: Initial remission can be maintained at

1 year in half of the patients without the need for additional steroids. Complete remission and endoscopic mucosal healing is proposed as an objective for achieving a lasting response.

J Crohn's and Colitis 2010; 4(2): 144-152
**Does fecal calprotectin predict relapse in patients with Crohn's disease and ulcerative colitis?**
Valle García-Sánchez, Eva Iglesias-Flores, Raúl González, Javier P. Gisbert, José María Gallardo-Valverde, Ángel González-Galilea, Antonio Naranjo-Rodríguez, Juan F. de Dios-Vega, Jordi Muntané, Federico Gómez-Camacho

No abstract available

J Crohn's and Colitis 2010; 4(2): 153-160
**Clinical trial: Preliminary efficacy and safety study of a new Budesonide-MMX® 9mg extended-release tablets in patients with active left-sided ulcerative colitis**
G.R. D'Haens, Á. Kovács, P. Vergauwe, F. Nagy, T. Molnár, Y. Bouhnik, W. Weiss, H. Brunner, A. Lavergne-Slove, D. Binelli, A.F.D. Di Stefano, P. Marteau

No abstract available

J Crohn's and Colitis 2010; 4(2): 176-182
**Pregnancy and IBD treatment: This challenging interplay from a patients' perspective**
R.E. Mountifield, R. Prosser, P. Bampton, K. Muller, J.M. Andrews

No abstract available

Gut 2010;59:752-759
**Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial**
Walter Reinisch, Sieglinde Angelberger, Wolfgang Petritsch, Olga Shonova, Milan Lukas, Simon Bar-Meir, Alexander Teml, Elke Schaeffeler, Matthias Schwab, Karin Dilger, Roland Greinwald, Ralph Mueller, Eduard F Stange, Klaus R Herrlinger

No abstract available

Gut 2010;59:760-766
**A randomised placebo-controlled multicentre trial of intravenous semapimod HCl for moderate to severe Crohn's disease**
Iris Dotan, Daniel Rachmilewitz, Stefan Schreiber, Rami Eliakim, C Janneke van der Woude, Asher Kornbluth, Alan L Buchman, Shimon Bar-Meir, Bernd Bokemeyer, Eran Goldin, Christian Maaser, Uma Mahadevan, Ursula Seidler, Jörg C Hoffman, Douglas Homoky, Terry Plasse, Barbara Powers, Paul Rutgeerts, Daniel Hommes

No abstract available

Aliment Pharmacol Ther. 2010 Mar 11. [Epub ahead of print]
**Clinical trial: five or ten cycles of granulocyte-monocyte apheresis (GMA) show equivalent efficacy and safety in ulcerative colitis.**
Dignass AU, Eriksson A, Kilander A, Pukitis A, Rhodes JM, Vavricka S.

BACKGROUND: Ulcerative colitis is characterized by leukocyte infiltration into the colonic mucosa. Granulocyte-monocyte-apheresis depletes these cells. Aim: To assess the non-inferiority of 5 to 10 apheresis treatments in patients with steroid-dependent or steroid-refractory ulcerative colitis. METHODS: 196 adults with moderate-severe ulcerative colitis were randomized 1:1 to 5 (n=96), or 10 (n=90) open label apheresis treatments. The primary endpoint was non-inferiority of clinical activity index (CAI) score

after 12 weeks. RESULTS: The intent-to-treat population comprised 82 and 80 patients for the 5- and 10-treatment groups, respectively. The difference between the two groups in mean CAI was 0.24 with an upper 95% confidence intervall of 1.17, which was below a predefined non-inferiority threshold of 1.33. CAI score improved from baseline in both groups (from 8.7 to 5.6 with 5 treatments, and from 8.8 to 5.4 with 10), with no significant difference between the groups (P=0.200). Outcomes for the 5- and 10-treatment groups were similar: Clinical remission: 44% and 40%, respectively (P=0.636); clinical response: 56% and 59%, respectively (P=0.753). Treatment was well tolerated in both groups. CONCLUSIONS: This first prospective study comparing apheresis regimens in ulcerative colitis demonstrates that 5 treatments were not inferior to 10 treatments in steroid-refractory or -dependent ulcerative colitis.

Aliment Pharmacol Ther. 2010 Mar 18. [Epub ahead of print]
**Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease.**
Panaccione R, Colombel JF, Sandborn WJ, Rutgeerts P, D'Haens GR, Robinson AM, Chao J, Mulani PM, Pollack PF.

Background In the randomized, double-blind, placebo-controlled CHARM trial, adalimumab was more effective than placebo in maintaining clinical remission for patients with moderate to severe Crohn's disease (CD) through 56 weeks. Aim To further substantiate the long-term safety and clinical benefits of adalimumab through 2 years of therapy in CHARM and its open-label extension (ADHERE). Methods Patients entering ADHERE on blinded therapy received adalimumab 40 mg every other week (eow). Patients who had already moved to open-label adalimumab eow or weekly in CHARM continued their regimens. Data were analyzed by originally randomized treatment group at CHARM baseline (adalimumab 40 mg eow, adalimumab 40 mg weekly, or placebo), regardless of whether patients entered ADHERE or received open-label adalimumab (eow or weekly). Results After up to 2 years of therapy, 37.6%, 41.9%, and 49.8% of patients originally randomized placebo, adalimumab eow, and adalimumab weekly, respectively, were in clinical remission. All groups experienced sustained improvements on the Inflammatory Bowel Disease Questionnaire. Decreasing hazard rates for both all-cause and CD-related hospitalizations were observed over time. Over a 2-year period, the rates of serious adverse events and malignancies (33.3 and 1.1 events/100-patient-years, respectively) were similar to those observed during the overall adalimumab CD clinical development program. Conclusions Adalimumab demonstrated sustained maintenance of clinical remission, improvements in quality of life, and reductions in hospitalization during long-term treatment for CD, with no new safety concerns identified.

Expert Opin Emerg Drugs. 2010 Jun;15(2):309-22.
**Emerging drugs to treat Crohn's disease**
Strauch U, Schölmerich J.

IMPORTANCE OF THE FIELD: Inflammatory bowel diseases are chronic inflammatory diseases that comprise of two forms - Crohn's disease (CD) and ulcerative colitis (UC) - characterized by aberrant responses to luminal bacteria in genetically susceptible individuals. Whereas inflammation is limited to the large intestine in patients with UC, CD can affect all parts of the gastrointestinal tract. During disease exacerbations, pharmacological or surgical intervention is usually needed to re-establish remission; however, current therapeutic interventions cannot cure CD. As a subgroup of patients with CD will not be able to remain in remission with available drugs or suffer from side effects, new therapeutic strategies are needed. AREAS COVERED IN THIS REVIEW: This review focuses on emerging drugs in the treatment of CD and reviews data on their efficacy and safety. An extensive review of the available literature was undertaken using MEDLINE to identify relevant studies. WHAT THE READER WILL GAIN: The reader will learn about current therapeutic strategies in patients with CD and gain insights into emerging new drugs. TAKE HOME MESSAGE: As modification of the clinical course of CD becomes the therapeutic paradigm, potential future treatments have to induce mucosal healing in order to prevent long-term complications. New biologics show promising results.

Tohoku J Exp Med. 2010;220(3):207-15.
**Scheduled maintenance therapy with infliximab improves the prognosis of Crohn's disease: a single center prospective cohort study in Japan.**

Takahashi S, Takagi S, Shiga H, Umemura K, Endo K, Kakuta Y, Takahashi S, Kinouchi Y, Shimosegawa T.

The main goal of Crohn's disease (CD) treatment at present is to induce and maintain remission for as long as possible, and several approaches have been used as induction and maintenance therapies. There are no reports that have compared the effects on mid- and long-term prognosis among the induction and maintenance therapies, especially between infliximab, a chimeric antibody to tumor necrosis factor-alpha, and nutritional therapies. A total of 262 CD patients with induced remission were enrolled in the cohort study. Patients who failed to achieve remission, and patients who were lost to follow-up within 12 months were excluded. Induction therapies for CD included total elemental enteral nutrition, total parenteral nutrition, infliximab, prednisolone, and surgical resection. Maintenance therapies included home elemental diet, 5-aminosalicylates, immunomodulators, and scheduled infliximab therapy. We evaluated the possible predictive factors of relapse and surgical recurrence including the clinical backgrounds of the patients and medical therapies, using the Cox multivariate hazard analysis. The main factors that strongly affected the first relapse were scheduled infliximab therapy (hazard ratio (HR) = 0.24, $p < 0.0001$), surgical induction (HR = 0.19, $p < 0.0001$) and high frequency of previous relapse (HR = 2.56, $p = 0.002$). Penetrating (HR = 3.33, $p = 0.009$) and stricturing (HR = 6.60, $p < 0.0001$) disease behavior were main risk factors of surgical recurrence. Scheduled infliximab therapy is the most effective maintenance therapy in a real clinical setting with respect to the mid- and long-term prognosis.

J Pediatr Gastroenterol Nutr. 2010 Jun;50(6):628-33.
**Effectiveness of infliximab in Brazilian children and adolescents with Crohn disease and ulcerative colitis according to clinical manifestations, activity indices of inflammatory bowel disease, and corticosteroid use**
Tiemi J, Komati S, Sdepanian VL.

OBJECTIVE: The objective of the study was to evaluate the response to infliximab in children and adolescents with Crohn disease and ulcerative colitis up to week 22. PATIENTS AND METHODS: A total of 21 patients with inflammatory bowel disease (IBD) received 5 mg/kg of infliximab at weeks 0, 2, 6, and 14. The following parameters were evaluated: clinical manifestations; activity indices of IBD, including the Pediatric Crohn Disease Activity Index for Crohn disease, the Lightiger Colitis Activity Index and the Pediatric Ulcerative Colitis Activity Index for ulcerative colitis, and the modified Harvey-Bradshaw Index for Crohn disease and ulcerative colitis; and the reduction or suspension of corticosteroid use. RESULTS: All of the patients had improvements in clinical manifestations after the first infusion of infliximab. At week 22, 18 of 21 (85.7%) patients were categorized as being in remission, 3 of 21 (14.3%) patients were categorized as having clinical improvement, and none of the patients were categorized as having no response. There was a statistically significant difference in all of the IBD activity indices at weeks 2, 6, 14, and 22 compared with time 0. The corticosteroid use was completely discontinued in 6 of 15 patients by week 22. CONCLUSIONS: Infliximab is effective in the treatment of Crohn disease and ulcerative colitis in children and adolescents up to week 22.

Minerva Gastroenterol Dietol. 2010 Jun;56(2):233-43.
**Anti-TNF therapy in inflammatory bowel diseases: a huge review.**
Peyrin-Biroulet L.

Anti-tumour necrosis factor-alpha (TNF-a) agents have changed the way of treating inflammatory bowel diseases (IBD) refractory to conventional medications (corticosteroids, immu-nomodulators). Infliximab, adalimumab, and certolizumab are more effective than placebo for induction and maintenance of remission in luminal Crohn's disease. Infliximab and adalimumab are also effective for maintenance of fistula closure in Crohn's disease. Only infliximab is Food and Drug Administra-tion (FDA)-approved for ulcerative colitis. Only adalimumab has demonstrated its efficacy in a randomized controlled trial to induce remission after infliximab failure in Crohn's disease. Anti-TNF therapy leads to mucosal healing, reduces hospitalizations and surgeries, and improves patients' quality of life. Safety data indicate that serious infections occur in 2-4% of patients treated with anti-TNF therapy, with no statistical difference when compared to controls. The risk of rare events such as malignancies and lymphoma, in IBD patients treated with anti-TNF agents, will require a longer duration of follow-up. Currently, the risk-benefit ratio of anti-TNF therapy supports its use in IBD. Several questions remain to be answered: can an indiscriminate use of anti-TNF agents modify the natural course of the disease, should mucosal healing be used in

clinical practice, and should anti-TNF therapy be used alone or in combination with immunomodulators in the long-term?

Minerva Gastroenterol Dietol. 2010 Jun;56(2):213-31.
**An approach to the management of re-fractory ulcerative colitis.**
Sonu I, Blonski W, Lin MV, Lichtenstein GR.

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology associated with dysregulation of the gastrointestinal mucosal immune system. It is characterized by a waxing and waning course and approximately 15% of UC patients will experience a severe episode. The first line treatment for severe colitis includes IV corticosteroids, however, 40% of patients are non-responsive to corticosteroid therapy and may require either colectomy, intravenous infliximab or intravenous cyclosporine within 3-5 days of presentation. This review focuses on the management and treatment approaches to refractory UC.

## Safety

J Rheumatol. 2010 May;37(5):887-9.
**The challenges of quantifying the risk of serious infection with tumor necrosis factor antagonist therapy.**
Leombruno J.

No abstract available

J Rheumatol. 2010 May;37(5):928-31. Epub 2010 Apr 1.
**Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists.**
Bernatsky S, Habel Y, Rahme E.

OBJECTIVE: Published metaanalyses of tumor necrosis factor (TNF) antagonists and infection have focused on randomized controlled trials, which tend to have short duration, relatively small size, and stringent inclusion/exclusion criteria that may limit enrollment to patients at low risk of infection. We performed a systematic review and synthesis of observational studies of TNF antagonists and infection risk. METHODS: We conducted a systematic literature search of studies estimating overall risk of serious infection after anti-TNF exposure in rheumatoid arthritis (RA). We estimated a pooled relative risk (RR) for the relevant observational studies, using a random-effects model. RESULTS: Five cohort studies and 2 nested case-control studies were included in the metaanalysis. Anti-TNF therapy appeared to significantly increase risk of serious infection (pooled adjusted RR 1.37, 95% CI 1.18, 1.60). CONCLUSION: Our metaanalysis of observational data demonstrated an increased risk of serious infection in subjects with RA receiving anti-TNF therapy, versus those not receiving these agents.

Ann Rheum Dis. 2010 May 5. [Epub ahead of print]
**Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register.**
Dixon WG, Hyrich KL, Watson KD, Lunt M; BSRBR Control Centre Consortium, Symmons DP; on behalf of the British Society for Rheumatology Biologics Register.

BACKGROUND: /st> Anti-tumour necrosis factor (anti-TNF) therapy has been associated with reports of rapid severe progression of rheumatoid arthritis-associated interstitial lung disease (RA-ILD). However, reports also exist of favourable responses to anti-TNF therapy in patients with ILD. The aim of this study was to examine the influence of anti-TNF therapy on mortality in patients with pre-existing RA-ILD. METHODS: /st> Using data from the British Society for Rheumatology Biologics Register, a national prospective observational study, 367 patients with pre-existing RA-ILD were identified (299 treated with anti-TNF therapy and 68 treated with traditional disease-modifying antirheumatic drugs (DMARDs)). RESULTS: /st> 70/299 patients (23%) in the anti-TNF cohort died after a median follow-up of 3.8 years

compared with 14/68 (21%) in the DMARD cohort after a median follow-up of 2.1 years. The mortality was 68 deaths/1000 person years (pyrs) (95% CI 53 to 86) in the anti-TNF cohort and 92/1000 pyrs (95% CI 50 to 155) in the DMARD cohort, generating an age- and sex-adjusted mortality rate ratio (aMRR) of 1.26 (95% CI 0.69 to 2.31). After further adjustment for potential confounders, the aMRR fell to 0.81 (95% CI 0.38 to 1.73) for the anti-TNF cohort compared with the DMARD cohort. RA-ILD was the underlying cause of death in 15/70 (21%) and 1/14 (7%) patients in the anti-TNF and DMARD cohorts, respectively. CONCLUSION: /st> The mortality in patients with RA-ILD is not increased following treatment with anti-TNF therapy compared with traditional DMARDs. The proportion of deaths attributable to RA-ILD is higher in patients treated with anti-TNF therapy, although reporting bias may exist.

Ann Rheum Dis. 2010 May 6. [Epub ahead of print]
**Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis.**
Sokolove J, Strand V, Greenberg JD, Curtis JR, Kavanaugh A, Kremer JM, Anofrei A, Reed G, Calabrese L, Hooper M, Baumgartner S, Furst DE; on behalf of the CORRONA Investigators.

OBJECTIVE: /st> Liver function test (LFT) elevations are reported with the use of tumour necrosis factor inhibitors (TNF-Is). The aim of this study was to compare LFT elevations in patients with rheumatoid arthritis receiving adalimumab (ADA), etanercept (ETN) or infliximab (INF) enrolled in the Consortium of Rheumatology Researchers of North America from October 2001 to March 2007. METHODS: /st> Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >1x upper limit of normal (ULN) were considered elevations and ALT/AST levels >2x ULN were considered abnormalities. Treatments included TNF-Is, methotrexate (MTX), leflunomide and other disease-modifying antirheumatic agents (DMARDs). Patients were censored after their first LFT elevation. Three analytical models were evaluated: (1) individual TNF-I vs non-biological DMARDs (primary model); (2) individual TNF-I plus MTX vs MTX monotherapy; and (3) limited to new users of individual TNF-I vs non-biological DMARDs. ORs for LFT elevations were estimated using generalised estimating equation logistic regression. RESULTS: /st> 6861 patients (ADA: 849; ETN: 1383; INF: 1449) with 22 522 determinations were analysed. LFT elevations >1x ULN with TNF-I use were seen in 5.9% of AST/ALT determinations and abnormalities >2x ULN in 0.77%. In the primary model the adjusted ORs for LFT elevations >1x ULN were ADA 1.35 (95% CI 1.09 to 1.66), ETN 1.00 (95% CI 0.83 to 1.21) and INF 1.58 (95% CI 1.35 to 1.86). For 2x ULN, adjusted ORs were ADA 1.72 (95% CI 0.99 to 3.01), ETN 1.10 (95% CI 0.64 to 1.88) and INF 2.40 (95% CI 1.53 to 3.76). Similar results were obtained in other models. CONCLUSION: /st> The overall incidence of LFT elevations >1x ULN with TNF-I use was uncommon and abnormalities >2x ULN were rarely observed. Significant differences were most consistently observed with INF, less commonly with ADA and were not observed with ETN compared with comparator DMARDs.

Acta Derm Venereol. 2010 Mar;90(2):183-5.
**Paradoxical reactions to targeted biological treatments: A way to treat and trigger?**
Brunasso AM, Laimer M, Massone C.

No abstract available

Intern Med J. 2010 Feb;40(2):139-49.
**Practical guidelines for treating inflammatory bowel disease safely with anti-tumour necrosis factor therapy in Australia.**
Connell W, Andrews JM, Brown S, Sparrow M.

Anti-tumour necrosis factor (TNF) therapy is an effective but expensive option for treating inflammatory bowel disease (IBD). Its use is generally reserved for patients with severe refractory disease, often involving long-term administration. Anti-TNF therapy has the potential to be associated with various adverse effects, such as infection, malignancy and immunogenicity. Clinicians and patients should be familiar with these possibilities and adopt appropriate precautions prior to and during treatment to minimize risk. Guidelines have been developed for Australian prescribers intending to use anti-TNF therapy in IBD by a Working Party commissioned by IBD-Australia, a Special Interest Group affiliated with the Gastroenterology Society of Australia.

J Crohn's and Colitis 2010; 4(2): 215-216
**Necrotizing external otitis on a Crohn's disease patient treated with infliximab**
Gabriela Duque, Francisco Portela, Maria Carmo Migueis

No abstract available

J Am Acad Dermatol. 2010 Jun;62(6):968-78. Epub 2010 Apr 14.
**The safety profile and sustained remission associated with response to multiple courses of intramuscular alefacept for treatment of chronic plaque psoriasis.**
Roberts JL, Ortonne JP, Tan JK, Jaracz E, Frankel E; Alefacept Clinical Study Group.

BACKGROUND: Safety and efficacy of up to 3 courses of alefacept intramuscular (IM) in the treatment of chronic plaque psoriasis have been demonstrated in earlier trials. OBJECTIVE: We sought to determine the safety and efficacy of up to 5 courses of alefacept IM in treating plaque psoriasis. METHODS: A standard treatment course was defined as 15 mg of alefacept IM once weekly for 12 weeks, followed by 12 weeks of treatment-free observation. Patients with chronic plaque psoriasis, who had previously received alefacept IM, received up to 3 additional courses (A, B, and C). Efficacy was evaluated by Physician Global Assessment. RESULTS: Safety profiles were similar to those for a single course of treatment. There were no cumulative adverse effects. At 2 weeks postdosing, 16%, 22%, and 19% of patients were rated clear or almost clear by Physician Global Assessment in courses A, B, and C, respectively, with 35%, 42%, and 42% achieving this response at any time during these courses. Patients who achieved clear or almost clear at 2 weeks postdosing remained so for a median duration of 214 and 126 days after courses A and B, respectively. LIMITATIONS: This was an extension study and therefore contained no control group. CONCLUSIONS: Up to 5 courses of alefacept IM may provide extended treatment-free, symptom-free periods in responders while maintaining the safety profile.

J Am Acad Dermatol. 2010 Jun;62(6):1067-9.
**Safety of etanercept in patients with psoriasis and hepatitis C virus assessed by liver histopathology: preliminary data.**
Paradisi A, Caldarola G, Capizzi R, Siciliano M, Annichiarico E, Vecchio FM, Amerio PL, De Simone C.

No abstract available

Rev Esp Enferm Dig. 2010 Feb;102(2):145-6.
**Infliximab therapy in a patient with refractory ileocolic Crohn's disease and Takayasu arteritis.**
[Article in English, Spanish]
Calderón R, Estrada S, Ramírez de la Piscina P, Salvador M, Zabaleta S, Enciso C, Delgado E, García-Campos F.

No abstract available

Rheumatology (Oxford). 2010 Jun;49(6):1209; *author reply* 1210. Epub 2010 Mar 17.
**Comment on: Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-alpha blockers: perioperative interruption of tumour necrosis factor-alpha blockers decreases complications?**
Backhouse MR, Helliwell PS, Redmond AC.

No abstract available

Lancet. 2010 May 15;375(9727):1689; *author reply* 1690-1.
**Disease activity and venous thromboembolism in inflammatory bowel disease.**
Koutroubakis IE, Pena AS.

No abstract available

Lancet. 2010 May 15;375(9727):1689; *author reply* 1690-1.
**Disease activity and venous thromboembolism in inflammatory bowel disease.**
Thachil J.

No abstract available

Lancet. 2010 May 15;375(9727):1690; *author reply* 1690-1.
**Disease activity and venous thromboembolism in inflammatory bowel disease.**
Valsecchi ME, Damilano CP.

No abstract available

Lancet. 2010 May 15;375(9727):1690; *author reply* 1690-1.
**Disease activity and venous thromboembolism in inflammatory bowel disease.**
Ghosh T, Ford AC, Everett S.

No abstract available

Lancet. 2010 Feb 20;375(9715):657-63. Epub 2010 Feb 8.
**Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study**.
Grainge MJ, West J, Card TR.

BACKGROUND: Patients with inflammatory bowel disease who develop deep vein thrombosis or pulmonary embolism often have active disease at the time of thromboembolism. We therefore aimed to quantify the risk of venous thromboembolism prospectively during different activity phases of inflammatory bowel disease. METHODS: From the General Practice Research Database, we matched patients with prospectively recorded inflammatory bowel disease from November, 1987, until July, 2001 with up to five controls by age, sex, and general practice. A flare was defined as the period 120 days after a new corticosteroid prescription. We used Cox regression analysis with time-varying covariates to accommodate changes in the state of inflammatory bowel disease, and whether patients were at high risk of venous thromboembolism after hospitalisation. FINDINGS: 13 756 patients with inflammatory bowel disease and 71 672 matched controls were included in the analysis, and of these 139 patients and 165 controls developed venous thromboembolism. Overall, patients with inflammatory bowel disease had a higher risk of venous thromboembolism than did controls (hazard ratio 3.4, 95% CI 2.7-4.3; p<0.0001; absolute risk 2.6 per 1000 per person-years). At the time of a flare, however, this increase in risk was much more prominent (8.4, 5.5-12.8; p<0.0001; 9.0 per 1000 person-years). This relative risk at the time of a flare was higher during non-hospitalised periods (15.8, 9.8-25.5; p<0.0001; 6.4 per 1000 person-years) than during hospitalised periods (3.2, 1.7-6.3; p=0.0006; 37.5 per 1000 person-years). INTERPRETATION: Trials of primary prophylaxis of venous thromboembolism are warranted to find out whether this important complication can be prevented.

Br J Dermatol. 2010 Feb 22. [Epub ahead of print]
**Safety of antitumour necrosis factor-alpha therapy in psoriatic patients with hepatitis B virus infection**
Nosotti L, Francesconi F, Izzi S, Berardesca E, Morrone A, Bonifati C.

No abstract available

Aliment Pharmacol Ther. 2010 Mar 17. [Epub ahead of print]
**Nationwide linkage analysis in Scotland implicates age as the critical overall determinant of mortality in ulcerative colitis**
Nicholls RJ, Clark DN, Kelso L, Crowe AM, Knight AD, Hodgkins P, Satsangi J.

Background Recent data associated higher mortality with medical rather than surgical intervention in ulcerative colitis (UC) patients requiring hospitalisation. Factors influencing UC-related mortality in Scotland were examined. Method Using the national record linkage database 1998-2000, three year mortality was determined after four admission types: colectomy elective, emergency; no colectomy elective, emergency. Results Of 1078 patients crude three year mortality rates were: colectomy elective 5.6% (177) and emergency 9.0% (100); no colectomy elective 9.8% (244) and emergency 16.0% (557). Using elective colectomy as reference, multivariate analysis (OR ([95% CI]) showed admission age >50 years (OR 5.46 [2.29-11.95]), male gender (OR 1.92 [1.23-3.02]), comorbidity (OR 2.2 [1.38-3.51]), length of stay >15 days (OR 2.04 [1.08-3.84]) and prior IBD admission (OR 1.66 [1.06-2.61] were independently related to mortality. Age was the strongest determinant. No patient <30 years died. Mortality <50 years (10/587 [1.7%]) was significantly lower than from 50-64 (26/246 [10.6%]) (chi(2) = 32.91;p<0.0000001) and >65 (96/245 [39.2%]) (chi(2) = 218.2;p<0.0000001). Over 65, mortality in the four groups was 29.4%, 33.3%, 28.1% and 44.7%; all greater than expected in the Scottish population on assessment of standardised mortality ratios. Conclusion Hospital admission in UC patients >65 is associated with high mortality. Management strategies should consider this by treatment in specialist units, early investigation, focussed medical treatment and earlier surgical referral.

Dig Liver Dis. 2010 May 14. [Epub ahead of print]
**Inflammatory bowel disease-patients are insufficiently educated about the basic characteristics of their disease and the associated risk of colorectal cancer**
Baars JE, Siegel CA, Van't Spijker A, Markus T, Kuipers EJ, van der Woude CJ.

BACKGROUND/AIM: Limited data are available about inflammatory bowel disease-patients' knowledge of disease and associated risks. We assessed patients' knowledge of disease and its associated risks/complications, and their perspectives on current recommendations for colectomy when low-grade dysplasia is found. METHODS: Inflammatory bowel disease-patients at a regional patient-information-day were asked to anonymously complete a survey (group-A). A 2nd group was recruited online through the Dutch inflammatory bowel disease-patients' association (group-B). RESULTS: In group-A, 109 inflammatory bowel disease-patients completed the survey (76% Crohn's disease, 24% ulcerative colitis, 78% female). Thirty-three patients (30%) were unaware of their disease-localization; 30% thought inflammatory bowel disease shortened their life-expectancy; 26% thought it was likely for a severe complication to occur during colonoscopy. Patients estimated their 10-year colorectal carcinoma-risk at 25%. Mean perceived colorectal carcinoma-associated mortality-risk was 13%. Patients would agree to colectomy if their current colorectal carcinoma-risk was at least 53% and 70% would refuse physicians' recommendation for colectomy if dysplasia were detected with a 20% risk of concomitant colorectal carcinoma. Group-B (n=393 inflammatory bowel disease-patients) verified the results above. However, fewer patients (52%) would refuse physicians' recommendation for colectomy, p=0.01. CONCLUSION: Inflammatory bowel disease-patients are ill-informed about their disease and its associated risks. Improvement of patient-education is necessary to appropriately involve patients in the decision-making process.

J Med Microbiol. 2010 May;59(Pt 5):617-21. Epub 2010 Feb 4.
**Mycobacterium marinum infection complicated by anti-tumour necrosis factor therapy.**
Ramos JM, García-Sepulcre MF, Rodríguez JC, Padilla S, Gutiérrez F.

Mycobacteria other than tuberculosis infections in patients taking various tumour necrosis factor (TNF)-alpha inhibitors have been reported in the literature. We describe sporotrichoid spread of Mycobacterium marinum in a man with Crohn's disease treated with infliximab. After starting ethambutol and rifampicin and discontinuing infliximab, a worsening appeared. M. marinum infection may have a potential local spread and systemic dissemination in patients treated with TNF-alpha inhibitors.

Joint Bone Spine. 2010 May 13. [Epub ahead of print]
**Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients.**
Finckh A, Dudler J, Wermelinger F, Ciurea A, Kyburz D, Gabay C, Bas S; on behalf of the physicians of the SCQM.

BACKGROUND: Infliximab (IFX) can be immunogenic for humans and lead to the formation of antibodies against IFX (anti-IFX Ab), which could induce acquired IFX resistance. OBJECTIVE: To test whether the

presence of anti-IFX Ab and residual circulating IFX levels are associated with acquired IFX resistance in RA. METHODS: A multivariate logistic regression was used to analyze the relationship between anti-IFX Ab, residual IFX concentrations, and acquired IFX resistance in a nested cohort within the Swiss RA registry (SCQM-RA). RESULTS: Sixty-four RA patients on longstanding IFX therapy were included; 24 with an acquired therapeutic resistance to IFX and 40 with continuous good response to IFX. The two groups had similar disease characteristics, but patients with acquired IFX resistance required significantly higher dosage of IFX (5.4mg/kg versus 4.3mg/kg, p=0.02) and shorter infusion intervals (7.1 versus 8.7 weeks, p=0.01) than long-term good responders. The presence of residual IFX tended to be associated with a decreased risk of acquired therapeutic resistance (OR 0.4 [95% CI: 0.1-1.5]), while the presence of anti-IFX Ab tended to be associated with an increased risk of acquired therapeutic resistance (OR: 1.8 [95% CI: 0.4 - 9.0]). The presence of either high anti-IFX Ab levels or low residual IFX concentrations was strongly associated with acquired therapeutic resistance to IFX (OR 5.9, 95% CI 1.3 - 26.6). However, just 42% of patients with acquired IFX resistance had either low IFX or high anti-IFX Ab levels. CONCLUSION: These results suggest that the assessment of anti-IFX Ab and residual IFX levels is of limited value for individual patients in routine clinical care. Copyright © 2010 Société française de rhumatologie.

Rheumatol Int. 2010 May 15. [Epub ahead of print]
**Antibodies against cyclic citrullinated peptide don't decrease after 6 months of infliximab treatment in refractory rheumatoid arthritis.**
Kolarz B, Majdan M, Dryglewska M, Darmochwal-Kolarz D.

Anti-citrullinated peptide antibodies (ACPA) and the rheumatoid factor (RF) are well-established serological markers for rheumatoid arthritis (RA). ACPA are very useful in the diagnosis of RA, especially at the early stages of the disease when ACPA have a greater diagnostic value than RF. The aim of the study was to assess the influence of infliximab treatment on RF IgM and ACPA serum levels and RA activity during 6 months of treatment. Thirty-two patients with refractory RA were treated with infliximab during a 6-month period. At baseline, 3 and 6 months of treatment the patients were examined for the number swollen and tender joints out of 28 (SJC, TJC) and the visual analogue scale of arthritis activity according to the patient (VAS). Serum samples were tested for erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP), ACPA and RF IgM. The disease activity score (DAS-28) parameter was also calculated at the same time. During the course of our study, we observed statistically significant improvement in ESR, CRP, TJC, SJC, VAS DAS-28, and RF IgM after 3 and 6 months of infliximab treatment when compared to the baseline, whereas the ACPA level remained unchanged after 3 and 6 months of treatment (P = 0.96 and P = 0.85). The changes in the ACPA level are not a factor for evaluation of successful infliximab treatment but the changes in RF IgM are. According to different behavior of these antibodies during infliximab treatment, we suggest that the roles of ACPA and RF in the pathogenesis of RA are different.

Ann Intern Med. 2010 May 18;152(10):JC5-13.
**ACP Journal Club. Anti-TNFalpha therapy did not increase short- or medium-term risk for cancer in patients with rheumatoid arthritis.**
Smith M.

No abstract available

Ann Rheum Dis. 2010 May 14. [Epub ahead of print]
**Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection.**
Vassilopoulos D, Apostolopoulou A, Hadziyannis E, Papatheodoridis GV, Manolakopoulos S, Koskinas J, Manesis EK, Archimandritis AI.

OBJECTIVES: /st> The aim of this prospective study was to examine the safety of anti-tumour necrosis factor (TNF) therapy in patients with rheumatic disease and hepatitis B virus (HBV) infection. METHODS: /st> 14 patients with chronic HBV infection, 19 HBV-vaccinated patients and 19 patients with resolved HBV infection were included in the study. All HBV-infected patients received combination therapy with oral antivirals and anti-TNF agents. During treatment the levels of hepatitis B surface antibodies (anti-HBs) in HBV-vaccinated patients and of serum HBV DNA in patients with chronic or resolved HBV

infection were monitored. RESULTS: /st> No viral reactivation was observed in patients with resolved HBV infection while anti-HBs titres decreased during anti-TNF treatment in vaccinated patients, similarly to patients treated with methotrexate alone. None of the HBV-infected patients developed liver decompensation or a significant increase in alanine aminotransferase levels. One patient (7%) treated with lamivudine and etanercept showed viral reactivation due to the emergence of a lamivudine-resistant mutant strain. CONCLUSIONS: /st> Anti-TNF agents represent a safe option for patients with chronic HBV infection when combined with antiviral therapy, as well as in patients previously exposed to HBV receiving no HBV prophylaxis. Resistant HBV strains may arise in patients with chronic hepatitis B, necessitating the initial use of anti-HBV agents with a low risk of resistance.

Semin Arthritis Rheum. 2010 Jun;39(6):442-7. Epub 2009 Feb 26.
**The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis.**
Elkayam O, Bashkin A, Mandelboim M, Litinsky I, Comaheshter D, Levartovsky D, Mendelson E, Wigler I, Caspi D, Paran D.

OBJECTIVES: To assess the effect of the timing of vaccination in relation to administration of infliximab on the efficacy and safety of influenza vaccine in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS). METHODS: The study population comprised 38 patients treated with infliximab at a mean dosage of 3 mg/kg (20 RA patients; 18 AS patients; 23 RA controls (treated with disease modifying antirheumatic drugs other than anti-tumor necrosis factor-alpha; and 17 healthy controls). Split-virion inactivated vaccine containing 15 mug hemagglutinin/dose of each of A/New Caledonan/20/1999 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 (M) was used. Patients treated with infliximab were divided into 2 groups: 22 were vaccinated on the day of administration of infliximab, while 16 received the vaccine 3 weeks after infliximab. Baseline and 4- to 6-week clinical assessment of disease activity included erythrocyte sedimentation rate and C-reactive protein for all patients, the 28-joint disease-activity score for RA patients, and Bath Ankylosing Spondylitis Disease Activity Index for AS patients. Hemagglutination inhibition (HI) antibodies were tested by a standard World Health Organization procedure. Response was defined as >or=4-fold rise in HI antibodies 4 to 6 weeks after vaccination, or seroconversion in patients with a nonprotective baseline level of antibodies (<1/40). Geometric mean titers (GMT) were calculated to assess the immunity of the whole group. RESULTS: At baseline, RA patients and controls had similar occurrence of protective levels of HI antibodies and GMT, while AS patients had lower levels reflecting lower rates of previous vaccination. Four weeks after vaccination, a significant and similar increase in GMT for each antigen was observed in all groups ($P < 0.004$) except in the RA-infliximab group, vaccinated 3 weeks after administration of infliximab, in whom the increase in GMT was not significant for H1N1 ($P = 0.12$) and H3 ($P = 0.06$). AS patients demonstrated an increase in GMT, independently of the time of vaccination. The percentage of responders was similar in all groups. The response was not affected by variables such as age, gender, methotrexate, or prednisone use. Parameters of disease activity remained unchanged. No adverse effects other than injection site pain were recorded. CONCLUSIONS: Influenza virus vaccine generated a good humoral response in RA and AS patients treated with infliximab.

Ann Rheum Dis. 2010 Jun;69(6):1044-8. Epub 2009 Jul 5.
**Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study.**
Verstappen SM, Bakker MF, Heurkens AH, van der Veen MJ, Kruize AA, Geurts MA, Bijlsma JW, Jacobs JW; Utrecht Rheumatoid Arthritis Cohort Study Group.

OBJECTIVE: To evaluate toxicity profiles in patients with rheumatoid arthritis (RA) treated either according to an intensive or a conventional treatment strategy approach with methotrexate (MTX) and to study factors associated with MTX-related toxicity. METHODS: Data were used from the Computer-Assisted Management in Early Rheumatoid Arthritis (CAMERA) study, in which clinical efficacy of an intensive treatment strategy with MTX was more beneficial than a conventional treatment strategy approach. In this study, data on adverse events (AEs) were compared between the two strategy groups. Logistic regression analyses were used to identify possible associations between factors assessed at baseline and withdrawal due to MTX-related AEs or liver toxicity at follow-up. RESULTS: Although significantly more patients in the intensive strategy group experienced MTX-related AEs than in the conventional strategy group, all recorded AEs were relatively mild. A higher body mass index (BMI) was significantly associated with withdrawal due to MTX-related AEs in the multiple regression analyses (odds

ratio=1.207, 95% confidence interval 1.02 to 1.44, p=0.033). There was a trend towards an association between diminished creatinine clearance and MTX withdrawal. For liver toxicity, increased serum liver enzymes at baseline were associated with liver toxicity during follow-up. CONCLUSION: Although the occurrence of AEs in the intensive strategy group was higher than in the conventional strategy group, the previously observed clinical efficacy of an intensive treatment strategy seems to outweigh the observed toxicity profiles. When starting MTX, attention should be given to patients with a high BMI and those with increased levels of liver enzymes and decreased renal function.

Ann Rheum Dis. 2010 Jun;69(6):1086-91. Epub 2010 May 5.
**Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register.**
Dixon WG, Hyrich KL, Watson KD, Lunt M; BSRBR Control Centre Consortium, Symmons DP; British Society for Rheumatology Biologics Register.

BACKGROUND: Anti-tumour necrosis factor (anti-TNF) therapy has been associated with reports of rapid severe progression of rheumatoid arthritis-associated interstitial lung disease (RA-ILD). However, reports also exist of favourable responses to anti-TNF therapy in patients with ILD. The aim of this study was to examine the influence of anti-TNF therapy on mortality in patients with pre-existing RA-ILD. METHODS: Using data from the British Society for Rheumatology Biologics Register, a national prospective observational study, 367 patients with pre-existing RA-ILD were identified (299 treated with anti-TNF therapy and 68 treated with traditional disease-modifying antirheumatic drugs (DMARDs)). RESULTS: 70/299 patients (23%) in the anti-TNF cohort died after a median follow-up of 3.8 years compared with 14/68 (21%) in the DMARD cohort after a median follow-up of 2.1 years. The mortality was 68 deaths/1000 person years (pyrs) (95% CI 53 to 86) in the anti-TNF cohort and 92/1000 pyrs (95% CI 50 to 155) in the DMARD cohort, generating an age- and sex-adjusted mortality rate ratio (aMRR) of 1.26 (95% CI 0.69 to 2.31). After further adjustment for potential confounders, the aMRR fell to 0.81 (95% CI 0.38 to 1.73) for the anti-TNF cohort compared with the DMARD cohort. RA-ILD was the underlying cause of death in 15/70 (21%) and 1/14 (7%) patients in the anti-TNF and DMARD cohorts, respectively. CONCLUSION: The mortality in patients with RA-ILD is not increased following treatment with anti-TNF therapy compared with traditional DMARDs. The proportion of deaths attributable to RA-ILD is higher in patients treated with anti-TNF therapy, although reporting bias may exist.

Clin Exp Immunol. 2010 May 18. [Epub ahead of print]
**How tumour necrosis factor blockers interfere with tuberculosis immunity**
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Summary Tumour necrosis factor (TNF) is a potent inflammatory cytokine that plays an important role in immunity to numerous bacterial infections, including Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB) in humans. Infliximab, adalimumab, certolizumab pegol and etanercept are anti-TNF agents used to treat a range of inflammatory/autoimmune diseases, such as rheumatoid arthritis. The use of some of these drugs has been linked to reactivation TB. In addition to blocking TNF-mediated immune responses, some anti-TNF drugs have been found to interfere with innate immune responses, such as phagolysosomal maturation and monocyte apoptosis, as well as cell-mediated responses, including interferon-gamma secretion by memory T cells, complement-mediated lysis of Mtb-reactive CD8(+) T cells and increased regulatory T cell activity. This review summarizes some of the reported effects of TNF blockers on immune cell responses in the context of the observed clinical data on TB reactivation in patients on anti-TNF therapy.