Literature Update Immunology

Period: 1-31 October 2010

IBD

- Report of the **ECCO** pathogenesis workshop on **anti-TNF therapy failures** in **inflammatory bowel diseases**: **Definitions**, **frequency** and **pharmacological aspects**.
- Report of the **ECCO** workshop on **anti-TNF therapy failures** in **inflammatory bowel diseases**: **Biological roles** and **effects** of **TNF** and **TNF antagonists**.
- **Long-term outcome** in patients with **ulcerative colitis** treated with **intravenous cyclosporine A** is determined by previous exposure to **thiopurines**.
- The **pattern** and **outcome** of **acute severe colitis**.
- What options do we have for **induction therapy** for **Crohn's disease**?
- New keys to **maintenance** treatment in **ulcerative colitis**.
- How **rapidly** should **remission** be achieved?
- State-of-the-Art: **Immunosuppression** and **Biologic Therapy**.
- The **role** of **biologics** in **ulcerative colitis**.
- **Thiopurines** in **Crohn's disease**, is there something new?
- Maintenance of **clinical benefit** in **Crohn's disease** patients after **discontinuation** of **infliximab**: long-term follow-up of a single centre cohort.
- Additional **benefit** of **procalcitonin** to **C-reactive protein** to assess **disease activity** and **severity** in **Crohn's disease**.
- The **CHOICE trial**: **adalimumab** demonstrates **safety, fistula healing**, improved **quality of life** and increased **work productivity** in patients with **Crohn's disease** who failed **prior infliximab therapy**
- **Infliximab rescue therapy** in **ulcerative colitis**, and the effect on subsequent **colectomy rates**
- **Peripheral regulatory T cells** and **serum transforming growth factor-β**: Relationship with clinical response to **infliximab in Crohn's disease**
- Monitoring functional **serum antitumor necrosis factor antibody level** in **Crohn's disease** patients who maintained and those who **lost response to anti-TNF**
- **Mucosal healing** in patients with **ulcerative colitis** during a course of **selective leukocytapheresis therapy:** A prospective cohort study
- **Adalimumab** for **Crohn's disease** in **clinical practice** at Mayo clinic: The first 118 patients
- **Genetic predictors** of medically **refractory ulcerative colitis**
- **Ulcerative colitis** in Madrid, **Spain**: current **management**
- **Adherence of gastroenterologists** to **European Crohn's and Colitis Organisation consensus** on **ulcerative colitis**: A real-life survey in **Spain**
- **Long-term efficacy** of **adalimumab in Paediatric Crohn's disease** patients **naïve to other anti-TNF therapies**

Safety

- The **safety** profile of **biologic therapies** for **juvenile idiopathic arthritis**.
- **Etanercept** concentrations in **maternal serum**, **umbilical cord serum**, **breast milk** and **child serum** during **breastfeeding**.
- Therapy: **Immunogenicity** of **biologic** therapies—we need tolerance.
- **Incidence** of **tuberculosis** infection in **psoriatic patients** on **anti-TNF** therapy: report of a case series with 144 patients.
- A Systematic Review of Factors that Contribute to **Hepatosplenic T-cell Lymphoma** in Patients with **Inflammatory Bowel Disease**.
- **Risk Factors** Associated With **Progression** to **Intestinal Complications** of **Crohn's Disease** in a Population-Based Cohort.

- Are **accelerated infliximab infusions** safe in patients with **inflammatory bowel disease**?
- The **effect of immunomodulators** on the **immunogenicity of TNF-blocking therapeutic monoclonal antibodies**: a review
- **Infliximab** therapy increases **body fat mass** in **early rheumatoid arthritis** independently of changes in disease activity and levels of leptin and adiponectin: a randomized study over 21 months
- **European evidenced-based consensus** on **reproduction** in **inflammatory bowel disease**
- **Hepatosplenic T-cell lymphoma** and **inflammatory bowel disease**
- No evidence of association between **anti–tumor necrosis factor treatment** and **mortality** in patients with **rheumatoid arthritis**: Results from the **British Society for Rheumatology Biologics Register**
- A case of **progressive multifocal leukoencephalopathy** in a patient treated with **infliximab**

IBD

Journal of Crohn's and Colitis 2010 Oct: 4(4): 355-366
Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: Definitions, frequency and pharmacological aspects.
Matthieu Allez, Konstantinos Karmiris, Edouard Louis, Gert Van Assche, Shomron Ben-Horin, Amir Klein, Janneke Van der Woude, Filip Baert, Rami Eliakim, Konstantinos Katsanos, Jørn Brynskov, Flavio Steinwurz, Silvio Danese, Severine Vermeire, Jean-Luc Teillaud, Marc Lémann, Yehuda Chowers

No abstract available

Journal of Crohn's and Colitis 2010 Oct: 4(4): 367-376
Report of the ECCO workshop on anti-TNF therapy failures in inflammatory bowel diseases: Biological roles and effects of TNF and TNF antagonists.
Yehuda Chowers, Andreas Sturm, Miquel Sans, Konstantinos Papadakis, Maria Gazouli, Marcus Harbord, Jörg Jahnel, Gerassimos J. Mantzaris, Johannes Meier, Christian Mottet, Laurent Peyrin-Biroulet, Matthieu Allez

No abstract available

Journal of Crohn's and Colitis 2010 Oct: 4(4): 398-404
Long-term outcome in patients with ulcerative colitis treated with intravenous cyclosporine A is determined by previous exposure to thiopurines.
Andrea Walch, Miena Meshkat, Harald Vogelsang, Gottfried Novacek, Clemens Dejaco, Sieglinde Angelberger, Andrea Mikulits, Wolfgang Miehsler, Alfred Gangl, Walter Reinisch

No abstract available

Journal of Crohn's and Colitis 2010 Oct: 4(4): 431-437
The pattern and outcome of acute severe colitis.
Lotte C. Dinesen, Alissa J. Walsh, Marijana Nedeljkovic Protic, Graham Heap, Fraser Cummings, Bryan F. Warren, Bruce George, Neil J.M. Mortensen, Simon P.L. Travis

No abstract available

Dig Dis. 2010;28(3):543-7
What options do we have for induction therapy for Crohn's disease?
Siegel CA.

The first goal of Crohn's disease treatment is to induce a response. The choice of induction therapy depends on a number of factors. First, disease severity will dictate the level of intensity of treatment. Moderate to severely active Crohn's disease needs to be treated more aggressively than mild disease. Second, it is important to consider the disease distribution, since some medications (e.g. 5-aminosalicylates, budesonide, antibiotics) are more effectively delivered to the small bowel or the colon. Third, prior medications need to be considered. A patient naïve to immunomodulators and anti-TNF agents will be managed very differently from a patient who has already failed two anti-TNF drugs. A fourth critical factor is considering the individual patient. The balance of benefits and risks will depend upon the patient's expected disease course, and how much risk they are at personally for serious adverse events related to treatment. In addition, patients' preferences for treatment need to be addressed since they will choose therapies differently based on their personal experience with symptoms, thresholds for risk taking, and fears about their disease and treatment. The basic armamentarium for induction therapy for Crohn's disease includes: 5-aminosalicylates, antibiotics, budesonide, systemic corticosteroids, thiopurines, methotrexate, and anti-TNF agents. These drugs can be used alone or combined in difference treatment algorithms to optimize therapy. The art of treating the IBD patient is in understanding the options and being able to apply an individualized regimen based upon unique patient and disease factors.

Dig Dis. 2010;28(3):483-9
New keys to maintenance treatment in ulcerative colitis.
Higgins PD.

Maintenance treatment in ulcerative colitis often fails to prevent flares and long term complications. The first key to maintenance is to use effective therapy, even when patients become asymptomatic. The second key is to communicate the importance of adherence to patients, and to help them achieve long term adherence. Simplified dosing schedules are of some benefit, but the bond between patient and doctor, and the patient's belief in the efficacy of the therapy are essential. Decreased co-pays (a fixed amount paid by patients seeking care that is not reimbursed my medical insurance) have been associated with increased adherence, and incentives for patients may be a cost-effective approach to improving adherence. While the most substantial data on the association between adherence and clinical outcomes is in 5-ASAs, non-adherence can also limit the efficacy of thiopurines and biologics. The third key to maintenance treatment is monitoring and maintaining control of inflammation. Decreased histologic and endoscopic damage to the colon has been associated with decreased risk of colon cancer. The most cost-effective way to monitor smoldering inflammation is not known, but endoscopy, structured symptom indices, and biomarkers may be valuable approaches. The fourth key to maintenance treatment is optimizing immunomodulator therapy with thiopurines, and possibly methotrexate in the future. The fifth key to maintenance treatment in ulcerative colitis is maintaining biologic efficacy by avoiding low trough levels and being vigilant for subclinical inflammation and symptom recurrence at the end of dose intervals. Combination therapy with immunomodulators improves trough levels in Crohn's, and may prove to have benefits for the maintenance of biologic efficacy in ulcerative colitis.

Dig Dis. 2010;28(3):548-55. Epub 2010 Sep 30.
How rapidly should remission be achieved?
Isaacs KL.

The major goal of therapy in inflammatory bowel disease is to induce remission. Remission has multiple definitions - clinical remission, where the patient's symptoms have remitted, and endoscopic remission, in which there has been complete mucosal healing. Mucosal healing is a harder endpoint of remission but may be more difficult to achieve. In clinical trials we are forced to use activity indices such as the Crohn's disease activity index that may not completely reflect the endoscopic and histologic state of the bowel. Ideally we would like to see remission as quickly as possible to improve patient quality of life. The time to remission varies between different therapeutic approaches. Steroids tend to have a rapid clinical effect with remission seen in some patients as early as two weeks. In early anti-TNF trials, a single dose of infliximab lead to 27% remission at two weeks compared to 4% of placebo patients. Adalimumab and certolizumab have similar reports of early induction of remission. Mesalamine in Crohn's disease has inconsistent and delayed remission rates, whereas in ulcerative colitis, response and remission rates are more consistent in the three-week time frame. Azathioprine and 6-mercaptopurine have delayed onset of action but may induce remission as early as six weeks if dosing is optimized. In this presentation induction of clinical remission and mucosal healing in Crohn's disease and ulcerative colitis will be discussed. The impact of early remission on disease course will also be reviewed.

Dig Dis. 2010;28(3):536-42. Epub 2010 Sep 30
State-of-the-Art: Immunosuppression and Biologic Therapy.
Sandborn WJ.

Azathioprine and 6-mercaptopurine are orally administered immunosuppressive drugs which are effective for the treatment of Crohn's disease and ulcerative colitis. Azathioprine is rapidly converted to 6-mercaptopurine after administration. 6-Mercaptopurine is then either converted to the putative active metabolites, the 6-thioguinine nucleotides, or inactivated by the enzyme xanthine oxidase to 6-thiouric acid or alternatively inactivated to 6-methylmercaptopurine by the enzyme thiopurine methyltransferase. Thiopurine methyltransferase activity is genetically determined, with one in 300 patients having low or absent enzyme activity, one in 10 patients having intermediate enzyme activity, and 9 in 10 patients having normal enzyme activity. Patients with intermediate or low thiopurine methyltransferase activity are at risk for early leukopenia. Higher erythrocyte 6-thioguinine nucleotide concentrations are associated with a greater likelihood of clinical response. Azathioprine is modestly effective for Crohn's disease and ulcerative colitis. Toxicity associated with azathioprine includes infection and lymphoma. Anti-TNF therapy with infliximab, adalimumab, and certolizumab pegol is effective for induction and maintenance treatment

of Crohn's disease, and infliximab is effective for ulcerative colitis. Toxicity associated with anti-TNF therapy includes infection and lymphoma. Combination therapy with infliximab and azathioprine is more effective for inducing and maintaining steroid-free remission and mucosal healing then monotherapy with either drug alone. Strategies to reduce immunogenicity of anti-TNF agents include combination therapy with azathioprine and administration of a loading dose followed by systematic maintenance dosing. Higher serum trough concentrations of infliximab occur more frequently in patients receiving combination therapy with azathioprine and are associated with better clinical outcomes. Combination therapy is associated with an increased relative risk of opportunistic infection, but is not associated with an increased absolute risk of serious infection. Clinical practice should change such that combination therapy with an anti-TNF agent and azathioprine replace azathioprine in patients failing first line therapy with mesalamine and/or steroids.

Dig Dis. 2010;28(3):497-500. Epub 2010 Sep 30
The role of biologics in ulcerative colitis.
Hanauer SB.

Since the introduction of anti-TNF agents for the treatment of Crohn's disease there has been interest in the potential for treating ulcerative colitis with biological therapies. Early observational series suggested a benefit in the setting of severe, hospitalized patients. However, the recent completion of two large multi-center, double-blind placebo-controlled trials confirmed a role for infliximab for outpatients with refractory, moderate-severe disease with evidence for clinical remissions, mucosal healing, and a reduction in colectomies. Despite this evidence, there are numerous questions remaining regarding the optimal positioning in the setting of moderate-severe disease, potential benefits of concomitant immune suppression and the need for maintenance treatment after induction therapy. Additional clinical trials have demonstrated a less profound benefit for adalimumab at similar doses that are used in Crohn's disease. Other biological agents that have targeted T cells such as visiluzimab and abatacept were not demonstrated to be effective in controlled trials.

Expert Opin Drug Metab Toxicol. 2010 Oct 5. [Epub ahead of print]
Thiopurines in Crohn's disease, is there something new?
Miheller P, Lakatos PL.

Importance of the field: Traditional immunosuppressants, including azathioprine, remain the mainstay of therapy in steroid dependent/refractory patients with inflammatory bowel diseases (IBD). The main limitations of its use are its side effects appearing in about a fifth of the patients, including myelosuppression and liver toxicity. Major complications occur in patients with low thiopurine-S-methyltransferase (TPMT) enzyme activity; however, the clinical relevance of these tests remains conflictive. Areas covered in this review: In this review, the authors aim to summarize the new data regarding the relationship between the pharmacology of thiopurines and pathogenesis of adverse events. What the reader will gain: Readers will gain an understanding of the metabolism of thiopurines, side effect profile, pharmacological background of side effects, importance of metabolite monitoring, clinical relevance of inherited differences in drug metabolism and other conditions (e.g., concomitant use of allopurinol) which can modify enzyme activity. By gaining an understanding of the pharmacology and metabolism of thiopurines, clinicians will be able to optimize thiopurine therapy in IBD. Take home message: TPMT testing and metabolite monitoring are still not considered the standard of care, and clinicians will continue to choose the approach that best suits their clinical practice and patient needs. Regardless of what strategy is chosen, patients need to be carefully monitored and well informed about the potential risks.

Aliment Pharmacol Ther. 2010 Nov, 32(9): 1129–1134: Article first published online: 30 Aug 2010
Maintenance of clinical benefit in Crohn’s disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort.
A. W. G. Waugh, S. Garg, K. Matic, L. Gramlich, C. Wong, D. C. Sadowski, M. Millan, R. Bailey, D. Todoruk, R. Cherry, C. W. Teshima, L. Dieleman and R. N. Fedorak

Background Tumour necrosis factor-blockade with infliximab has advanced the treatment of Crohn's disease. While infliximab is efficacious, it remains to be determined whether patients who enter clinical remission with an anti-tumour necrosis factor therapy can have their treatment stopped and retain the

state of remission. Aim To assess in patients with Crohn's disease who obtained infliximab-induced remission, the proportion who relapsed after infliximab discontinuation. Methods This longitudinal cohort study examined patients from a University-based IBD referral centre. Forty eight patients with Crohn's disease in full clinical remission and who then discontinued infliximab were followed up for up to 7 years. Crohn's disease relapse was defined as an intervention with Crohn's disease medication or surgery. Results Kaplan-Meier analysis of the proportion of patients with sustained clinical benefit demonstrated that 50% relapsed within 477 days after infliximab discontinuance. In contrast, 35% of patients remained well, and without clinical relapse, up to the end of the nearly 7-year follow-up. Conclusion In patients with Crohn's disease with an infliximab-induced remission, stopping infliximab results in a predictable relapse in a majority of patients. Nevertheless, a small percentage of patients sustain a long-term remission.

Aliment Pharmacol Ther. 2010 Nov, 32(9): 1135–1144: Article first published online: 16 Sep 2010
Additional benefit of procalcitonin to C-reactive protein to assess disease activity and severity in Crohn's disease.
A. Oussalah, V. Laurent, O. Bruot, J.-L. Guéant, D. Régent, M.-A. Bigard and L. Peyrin-Biroulet

No abstract available

Aliment Pharmacol Ther. 2010 Nov;32(10):1228-39. doi: 10.1111/j.1365-2036.2010.04466.x. Epub 2010 Sep 28.
The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy.
Lichtiger S, Binion DG, Wolf DC, Present DH, Bensimon AG, Wu E, Yu AP, Cardoso AT, Chao J, Mulani PM, Lomax KG, Kent JD.

BACKGROUND: Adalimumab induces and maintains remission in adults with Crohn's disease.
AIM: To evaluate safety, fistula healing, quality of life and work productivity in adalimumab-treated patients who failed infliximab, including primary nonresponders.
METHODS: After a ≥8-week infliximab washout, patients with moderate-to-severe Crohn's disease received open-label adalimumab as induction (160/80 mg at weeks 0/2) and maintenance (40 mg every other week) therapies. At/after 8 weeks, patients with flare/nonresponse could receive weekly therapy. Minimum study duration was 8 weeks, continuing until the commercial availability of adalimumab for Crohn's disease.
RESULTS: Of 673 patients enrolled, 17% were infliximab primary nonresponders and 83% were initial responders. Three percent of patients had serious infections (mainly abscesses). Complete fistula healing was achieved by 34/88 (39%) patients with baseline fistulas. Improvements in quality of life and work productivity were sustained from week 4 to week 24 for all patients, as well as the subgroup of primary nonresponders.
CONCLUSIONS: Blinded clinical trials have shown adalimumab to be both an effective first-line therapy for anti-TNF-naïve patients and an important treatment option for infliximab-refractory or -intolerant patients. This trial presents open-label experience to support further the safety and effectiveness of adalimumab in patients who failed infliximab therapy, including primary nonresponders (NCT00338650).

Aliment Pharmacol Ther. 2010 Nov;32(10):1294-5. doi: 10.1111/j.1365-2036.2010.04478.x.
Infliximab rescue therapy in ulcerative colitis, and the effect on subsequent colectomy rates.
Halpin SJ, Hamlin PJ, Ford AC.

No abstract available

Inflamm Bowel Dis. 2010 Nov;16(11):1891-7.
Peripheral regulatory T cells and serum transforming growth factor-β: relationship with clinical response to infliximab in Crohn's disease.
Di Sabatino A, Biancheri P, Piconese S, Rosado MM, Ardizzone S, Rovedatti L, Ubezio C, Massari A, Sampietro GM, Foschi D, Porro GB, Colombo MP, Carsetti R, MacDonald TT, Corazza GR.

BACKGROUND: CD4(+)Foxp3(+) regulatory T cells (Treg) inhibit T-cell proliferation in vitro and are effective in suppressing colitis in mouse models. Tumor necrosis factor (TNF)-α, which is centrally

involved in Crohn's disease (CD) pathogenesis, also impairs Treg function. Here we investigated the influence of anti-TNF therapy on Treg frequency and function in CD.
METHODS: Twenty CD patients were treated with infliximab administered at weeks 0, 2, and 6. Blood was collected immediately before the first infusion and after 10 weeks. Treg frequency was quantified by flow cytometry. Treg function was measured using a standard coculture assay. Serum levels of transforming growth factor (TGF)-β1 and interleukin (IL)-10 were measured by enzyme-linked immunosorbent assay (ELISA).
RESULTS: Pretreatment Treg frequency and serum TGF-β1 levels were significantly higher in nonresponder than responder patients. Clinical improvement in 12 CD patients was associated with a significant increase of Treg frequency after 10 weeks. Treg were functionally active before and after treatment with infliximab, both in responder and nonresponder CD patients. In responder patients the restoration of Treg pool was accompanied by a parallel significant increase of serum TGF-β1 and IL-10. No significant change in the elevated Treg or serum TGF-β1 was seen in nonresponder patients.
CONCLUSIONS: This study suggests that there may be a relationship between numbers of Treg in the blood, serum TGF-β1, and response to infliximab; however, further prospective studies are needed.

Inflamm Bowel Dis. 2010 Nov;16(11):1898-904.
Monitoring functional serum antitumor necrosis factor antibody level in Crohn's disease patients who maintained and those who lost response to anti-TNF.
Yamada A, Sono K, Hosoe N, Takada N, Suzuki Y.

BACKGROUND: Infliximab (IFX) is an antitumor necrosis factor (TNF)-α antibody used to treat Crohn's disease (CD). However, antibodies to IFX (ATI) emerge, which can impair its efficacy. A fluid-phase enzyme immunoassay (FP-EIA) was established for measuring serum functional IFX (f-IFX) in CD patients receiving maintenance IFX.
METHODS: In 31 patients, 16 had maintained response (GI) and 15 had lost response to IFX despite good initial response (GII) were selected. Serum f-IFX was measured just before and immediately after IFX infusion and the values together with CD activity index (CDAI) and C-reactive protein (CRP) were compared.
RESULTS: IFX therapy in GI and GII were 1.8 ± 1.2 years and 2.7 ± 1.5 years, respectively, while the median dose frequency was 56 days in GI and 29 days in GII. Our FP-EIA for f-IFX showed TNF-α binding increasing with the IFX dose, which was suppressed by antibodies to IFX. On the infusion day, CRP and CDAI in GII were significantly higher than in GI, while median trough f-IFX for GI and GII were 4.7 μg/mL and 6.3 μg/mL, respectively. The median f-IFX immediately after IFX infusion for GI and GII were 149.5 μg/mL and 126.3 μg/mL, respectively (P = 0.0488), and binary logistic regression showed conditional maximum likelihood estimate to be -0.0258 (P = 0.0395), supporting association of low postinfusion f-IFX to the loss of response.
CONCLUSIONS: FP-EIA could accurately measure f-IFX. High serum ATI strongly impacted f-IFX levels immediately after an infusion. The postinfusion f-IFX level was associated with clinical response. f-IFX level should be valuable in decision-making to optimize treatment efficacy.

Inflamm Bowel Dis. 2010 Nov;16(11):1905-11.
Mucosal healing in patients with ulcerative colitis during a course of selective leukocytapheresis therapy: a prospective cohort study.
Yamamoto T, Umegae S, Matsumoto K.

BACKGROUND: During active ulcerative colitis (UC), vast numbers of granulocytes, monocytes/macrophages (GM) infiltrate the mucosal tissue and can potentially exacerbate inflammation and injury. Accordingly, we were interested to see if selective depletion of GM by adsorption (GMA) impacts mucosal healing (MH) in UC patients.
METHODS: In all, 124 patients with clinically and endoscopically active UC received 5 or 10 GMA sessions at one or two sessions/week. The endoscopic severity of mucosal inflammation at entry and 1 week after the last GMA session were scored as follows: 0 = normal mucosa and inactive disease; 1 = mild inflammation; 2 = moderate inflammation; 3 = severe inflammation. Likewise, a score 0 or 1 at post-GMA course was defined as MH.
RESULTS: At entry the endoscopic severity of the mucosal inflammation was 2 in 100 patients (81%) and 3 in 24 patients (19%). Following the course of GMA, 56 patients (45%) achieved clinical remission (normal stool frequency and no rectal bleeding). Thirty-four of these 56 responders achieved MH; 32 (94%) of the 34 patients with MH had an endoscopic score of 2 (moderate inflammation) at entry. The

maintained clinical remission rate was significantly higher in the 34 patients who achieved MH as compared with 22 patients who achieved clinical remission without MH (P = 0.0005).
CONCLUSIONS: MH is achieved more frequently in patients with moderate than with severe endoscopic severity at entry. Further, patients with MH have a reduced risk of future clinical relapse as compared with patients who achieve remission without MH.

Inflamm Bowel Dis. 2010 Nov;16(11):1912-21.
Adalimumab for Crohn's disease in clinical practice at Mayo clinic: the first 118 patients.
Swoger JM, Loftus EV Jr, Tremaine WJ, Faubion WA, Pardi DS, Kane SV, Hanson KA, Harmsen WS, Zinsmeister AR, Sandborn WJ.

BACKGROUND: We sought to assess the effectiveness and safety of adalimumab for the treatment of Crohn's disease (CD) in clinical practice.
METHODS: Demographic, clinical, and treatment data were abstracted from the medical record. The primary outcome was clinical response to induction therapy with adalimumab for CD (complete, partial, or nonresponse).
RESULTS: In all, 118 patients were prescribed adalimumab for CD between January 2003 and June 2007. All but five subjects (96%) had received prior infliximab and 50 were on systemic corticosteroids at the time of initial adalimumab dose (44%). A complete response was achieved in 53 patients and 20 patients had no response. The cumulative probability of any response (complete or partial) was 81.3% at 1 year. Dose escalation was required in 59 patients (1-year cumulative probability, 54.0%). Among patients with complete response, 18 lost response during follow-up (1-year cumulative probability, 21.4%). Among 50 patients on corticosteroids at baseline the median daily dose was 20 mg, which decreased to a median of 0 mg during treatment. Sixty-four patients (54%) experienced a total of 117 adverse events. Thirteen patients (11%) experienced 15 serious adverse events. Sixteen patients (14%) discontinued adalimumab due to an adverse event.
CONCLUSIONS: Adalimumab was both effective and well tolerated for the treatment of CD in this tertiary practice with a high prevalence of past infliximab exposure. This experience largely predates FDA approval of adalimumab for CD.

Inflamm Bowel Dis. 2010 Nov;16(11):1830-40.
Genetic predictors of medically refractory ulcerative colitis.
Haritunians T, Taylor KD, Targan SR, Dubinsky M, Ippoliti A, Kwon S, Guo X, Melmed GY, Berel D, Mengesha E, Psaty BM, Glazer NL, Vasiliauskas EA, Rotter JI, Fleshner PR, McGovern DP.

BACKGROUND: Acute severe ulcerative colitis (UC) remains a significant clinical challenge and the ability to predict, at an early stage, those individuals at risk of colectomy for medically refractory UC (MR-UC) would be a major clinical advance. The aim of this study was to use a genome-wide association study (GWAS) in a well-characterized cohort of UC patients to identify genetic variation that contributes to MR-UC.
METHODS: A GWAS comparing 324 MR-UC patients with 537 non-MR-UC patients was analyzed using logistic regression and Cox proportional hazards methods. In addition, the MR-UC patients were compared with 2601 healthy controls.
RESULTS: MR-UC was associated with more extensive disease (P = 2.7 × 10(-6)) and a positive family history of UC (P = 0.004). A risk score based on the combination of 46 single nucleotide polymorphisms (SNPs) associated with MR-UC explained 48% of the variance for colectomy risk in our cohort. Risk scores divided into quarters showed the risk of colectomy to be 0%, 17%, 74%, and 100% in the four groups. Comparison of the MR-UC subjects with healthy controls confirmed the contribution of the major histocompatibility complex to severe UC (peak association: rs17207986, P = 1.4 × 10(-16)) and provided genome-wide suggestive association at the TNFSF15 (TL1A) locus (peak association: rs11554257, P = 1.4 × 10(-6)).
CONCLUSIONS: A SNP-based risk scoring system, identified here by GWAS analyses, may provide a useful adjunct to clinical parameters for predicting the natural history of UC. Furthermore, discovery of genetic processes underlying disease severity may help to identify pathways for novel therapeutic intervention in severe UC.

Inflamm Bowel Dis. 2010 Nov;16(11):1826-7.
Ulcerative colitis in Madrid, Spain: current management.

López-Serrano P, Pérez-Calle JL, Fernández-Rodríguez C.

No abstract available

J Crohn Colitis 2010; 4(5): 567-574
Adherence of gastroenterologists to European Crohn's and Colitis Organisation consensus on ulcerative colitis: A real-life survey in Spain
J.P. Gisbert, F. Gomollón, J. Hinojosa, A. López San Román

No abstract available

J Crohn Colitis 2010; 4(5): 594-598
Long-term efficacy of adalimumab in Paediatric Crohn's disease patients naïve to other anti-TNF therapies
J. Martín-de-Carpi, N. Pociello, V. Varea

No abstract available

Safety

Nat Rev Rheumatol. 2010 Oct;6(10):561-71. Epub 2010 Aug 31.
The safety profile of biologic therapies for juvenile idiopathic arthritis.
Hashkes PJ, Uziel Y, Laxer RM.

The treatment of juvenile idiopathic arthritis (JIA) has been revolutionized by the use of novel biologic agents that have much improved patients' short-term and, according to early evidence, long-term outcomes. Currently available biologic agents used to treat patients with JIA include tumor necrosis factor (TNF) blockers, various agents that target interleukin (IL)-1 and the IL-6 receptor, T-cell co-stimulation inhibitors and antibodies to B-lymphocyte antigen CD20. These agents are increasingly used early in the course of the disease (often in combination with other immunosuppressive medications) and often for long periods of time, as patients can be difficult to wean from their use. Safety concerns (especially the long-term effects of biologic therapy) are, therefore, being examined more closely. For instance, in 2009, the FDA issued a warning related to the development of malignancies in patients with JIA who had used anti-TNF medications for >2.5 years. In this Review, data related to the safety profile of all currently available biologic agents used to treat JIA are examined, with a particular focus on anti-TNF therapy, the most studied biologic agent for JIA. Safety issues that need further study, including the implementation of registries to monitor long-term drug safety, are also discussed.

Rheumatology (Oxford). 2010 Nov;49(11):2225-7. Epub 2010 Jun 26.
Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding.
Berthelsen BG, Fjeldsøe-Nielsen H, Nielsen CT, Hellmuth E.

No abstract available

Nat Rev Rheumatol. 2010 Oct;6(10):558-9.
Therapy: Immunogenicity of biologic therapies—we need tolerance.
Krieckaert CL, Bartelds GM, Wolbink GJ.

No abstract available

Journal of the European Academy of Dermatology and Venereology 2010 epub
Incidence of tuberculosis infection in psoriatic patients on anti-TNF therapy: report of a case series with 144 patients.
Al Sánchez-Moya and E Dauden

No abstract available

Clin Gastroenterol Hepatol. 2010 Sep 29. [Epub ahead of print]
A Systematic Review of Factors that Contribute to Hepatosplenic T-cell Lymphoma in Patients with Inflammatory Bowel Disease.
Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, Sampat S, Mendizabal M, Lin MV, Lichtenstein GR.

BACKGROUND & AIMS: Hepatosplenic-T cell lymphoma (HSTCL) is a rare and usually fatal lymphoma that primarily affects men younger than 35 years old. Treatment of patients with Inflammatory Bowel Disease (IBD) using antibodies to Tumor Necrosis Factor (anti-TNFs) and thiopurines has been associated with HSTCL. We investigated the medications, duration of therapy, and ages of patients associated with HSTCL.
METHODS: We collected and analyzed data on the association between HSTCL, and anti-TNF agents along with thiopurine therapies in patients with IBD from published reports and the MedWatch reporting system of the US Food and Drug Administration (FDA).
RESULTS: Of 36 patients with HSTCL, 20 received therapy with infliximab and a thiopurine and 16 received a thiopurine as monotherapy for IBD. Four patients who had been treated with infliximab and a thiopurine also received adalimumab. One of these patients had been given infliximab, adalimumab, and natalizumab. Of 31 patients of known gender, only 2 were female. Twenty-seven of the 30 patients of known age were younger than 35 years old.
CONCLUSION: Most patients with HSTCL were men younger than 35 years old who received long-term therapy (at least 2 years) with thiopurines for IBD. There were no reported cases of HSTCL in patients with IBD who received only anti-TNF therapy. Physicians should consider giving thiopurines and anti-TNF agents to young male patients with IBD only in cases in which a clear benefit is expected, such as in early-stage disease in untreated patients or possibly in very severe cases.

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Risk Factors Associated With Progression to Intestinal Complications of Crohn's Disease in a Population-Based Cohort
Kelvin T. Thia, William J. Sandborn, William S. Harmsen, Alan R. Zinsmeister, et al.

AB BACKGROUND AND AIMS: We sought to assess the evolution of Crohn's disease behavior in an American population-based cohort. METHODS: Medical records of all Olmsted County, Minnesota residents who were diagnosed with Crohn's disease from 1970 to 2004 were evaluated for their initial clinical phenotype, based on the Montreal Classification. The cumulative probabilities of developing structuring and/or penetrating complications were estimated using the Kaplan-Meier method. Proportional hazards regression was used to assess associations between baseline risk factors and changes in behavior. RESULTS: Among 306 patients, 56.2% were diagnosed between the ages of 17 and 40 years. Disease extent was ileal in 45.1%, colonic in 32.0%, and ileocolonic in 18.6%. At baseline, 81.4% had nonstricturing nonpenetrating disease, 4.6% had stricturing disease, and 14.0% had penetrating disease. The cumulative risk of developing either complication was 18.6% at 90 days, 22.0% at 1 year, 33.7% at 5 years, and 50.8% at 20 years after diagnosis. Among 249 patients with nonstricturing, nonpenetrating disease at baseline, 66 changed their behavior after the first 90 days from diagnosis. Relative to colonic extent, ileal, ileocolonic, and upper GI extent were significantly associated with changes in behavior, whereas the association with perianal disease was barely significant. CONCLUSIONS: In a population-based cohort study, 18.6% of patients with Crohn's disease experienced penetrating or stricturing complications within 90 days after diagnosis; 50% experienced intestinal complications 20 years after diagnosis. Factors associated with development of complications were the presence of ileal involvement and perianal disease.

Inflamm Bowel Dis. 2010 Nov;16(11):1922-5.
Are accelerated infliximab infusions safe in patients with inflammatory bowel disease?

Bhat S, Sharma D, Doherty P, Tham TC, Caddy GR.

BACKGROUND: Infliximab is a monoclonal antibody used in the treatment of inflammatory bowel disease (IBD). The manufacturer-recommended administration is over 2 hours followed by 2 hours of patient observation. The data relating to adverse outcomes in patients receiving accelerated infusions for IBD are limited.
METHODS: Our unit utilizes an accelerated protocol for infliximab infusion in selected patients with IBD (those with no adverse reaction in their first four standard infusions). Our aim was to assess if the accelerated infusion protocol (infusion over 1 hour or 30 minutes with 1 hour or no monitoring according to protocol) was associated with any increase in adverse outcomes. Data were collected retrospectively on protocol used and adverse outcomes for all infliximab infusions between October 2005 and June 2008.
RESULTS: Out of 69 patients, 27 received the accelerated protocol (130 infusions). All patients received a total of 306 infusions on the standard protocol. No adverse reactions were reported in the accelerated protocol patients. In patients on the standard protocol, 16 adverse reactions were observed: seven were acute (occurring during infusion); nine were delayed (occurring within 1-7 days following infusion). No patient required intramuscular adrenaline or hospitalization.
CONCLUSIONS: Our findings suggest that an accelerated protocol for infliximab infusion is well tolerated in selected patients. The monitoring period following infusion may not be necessary, as all acute reactions occurred within an hour of initiating infusion and did not warrant hospitalization. The accelerated infusion may allow more efficient utilization of hospital resources and reduce patient inconvenience.

Arthritis Res Ther. 2010 Oct 20;12(5):217. [Epub ahead of print]
The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review.
Krieckaert CL, Bartelds GM, Lems WF, Wolbink GJ.

ABSTRACT: Therapeutic monoclonal antibodies have revolutionized the treatment of various inflammatory diseases. Immunogenicity against these antibodies has been shown to be clinically important: it is associated with shorter response duration because of diminishing concentrations in the blood and with infusion reactions. Concomitant immunomodulators in the form of methotrexate or azathioprine reduced the immunogenicity of therapeutic antibodies in rheumatoid arthritis, Crohn disease, and juvenile idiopathic arthritis. The occurrence of adverse events does not increase when immunomodulators are added to therapeutic antibodies. The mechanism whereby methotrexate and azathioprine influence immunogenicity remains unclear. Evidence-based consensus on prescribing concomitant immunomodulators is needed.

Arthritis Res Ther. 2010 Oct 21;12(5):R197. [Epub ahead of print]
Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomized study over 21 months.
Engvall IL, Tengstrand B, Brismar K, Hafstrohm I.

INTRODUCTION: Rheumatoid arthritis (RA) is associated with changes in body composition and bone mineral density (BMD). The purpose of this study was to evaluate if anti-tumor necrosis factor alpha (TNF) treatment in early RA has an impact on body composition and BMD besides that which could be achieved by intensive disease modifying anti rheumatic drugs (DMARD) combination therapy.
METHODS: Forty patients with early RA who failed treatment with methotrexate (MTX) up to 20 mg/week for 3 months were randomized to addition of sulfasalazine and hydroxychloroquine, treatment A, or addition of infliximab, treatment B. At 3, 12 and 24 months body composition and BMD were assessed by total-body dual-energy X-ray absorptiometry. At the same time points, leptin, adiponectin, apo-lipoproteins, insulin-like growth factor-1 (IGF-1) and markers of bone remodelling were analysed. Compliance to treatment was considered in the analyses. Data were analysed with a mixed, linear model.
RESULTS: Patients treated with anti-TNF had a significant increase in fat mass, at 2 years 3.8(1.6-5.9) kg, in contrast to patients in treatment A, 0.4 (-1.5-2.2) kg, P = 0.040, despite similar reduction in disease activity. Both treatment strategies prevented loss of muscle mass and bone. Leptin concentrations increased significantly in both groups at 2 years and adiponectin increased significantly at 2 years in treatment A and at 1 year in treatment B. There were no significant changes in apo-lipoproteins or IGF-1. The markers of bone resorption decreased at 12 months in both treatment groups with no significant difference between the treatment groups.

CONCLUSIONS: Infliximab therapy increased body fat mass, an effect that was not achieved with the combination of DMARDs, despite a similar reduction in disease activity, and thus seemed to be drug specific. The increase of fat mass was not associated with an exacerbated atherogenic lipid profile. Leptin and adiponectin concentrations increased in both treatment groups. The increase of adiponectin may partially explain the reduced frequency of cardiovascular diseases found when disease activity is reduced in RA. Trial Registration: ISRCTN39045408.

J Crohn Colitis 2010; 4(5): 493-510
European evidenced-based consensus on reproduction in inflammatory bowel disease
C. Janneke van der Woude, Sanja Kolacek, Iris Dotan, Tom Øresland, Séverine Vermeire, Pia Munkholm, Uma Mahadevan, Lucy Mackillop, Axel Dignass, for the European Crohn's Colitis Organisation (ECCO)

No abstract available

J Crohn Colitis 2010; 4(5): 511-522
Hepatosplenic T-cell lymphoma and inflammatory bowel disease
Anne Thai, Thomas Prindiville

No abstract available

Arthritis Rheum. 2010 Nov;62(11):3145-53. doi: 10.1002/art.27660.
No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register.
Lunt M, Watson KD, Dixon WG, Symmons DP, Hyrich KL.

OBJECTIVE: To study the association between anti-tumor necrosis factor (anti-TNF) therapy and mortality in a national cohort of patients with rheumatoid arthritis.
METHODS: We prospectively followed up 12,672 patients who were beginning anti-TNF therapy and 3,522 biologic-naive patients receiving disease-modifying antirheumatic drugs (DMARDs) until either July 31, 2008, or death, whichever occurred first. Notification of death and cause of death was received from the UK National Death Register. Mortality was compared using Cox proportional hazards models. Inverse probability of treatment weighting was used to adjust for the confounding effects of baseline differences between groups, including age, sex, disease severity, disability, and comorbidity. Missing baseline data were accounted for using multiple imputation.
RESULTS: When compared with the DMARD cohort, the anti-TNF cohort was younger (median age 57 years versus 61 years), had greater disease activity (median Disease Activity Score in 28 joints 6.6 versus 5.1), and had greater disability (median Health Assessment Questionnaire score 2.1 versus 1.6). Patients in the DMARD cohort were more likely to have a history of myocardial infarction (4.8% versus 3.1%) and chronic obstructive pulmonary disease (8.1% versus 4.8%) but were less likely to have had depression (16.5% versus 18.9%). There were 9,445 and 50,803 person-years of followup in the DMARD and anti-TNF cohorts, respectively, during which time 204 DMARD-treated and 856 anti-TNF-treated patients died. The weighted mortality hazard ratios in the anti-TNF cohort were as follows: all-cause 0.86 (95% confidence interval [95% CI] 0.64-1.16), circulatory disease 0.73 (95% CI 0.44-1.23), neoplasm 0.65 (95% CI 0.39-1.09), and respiratory disease 0.81 (95% CI 0.36-1.83).
CONCLUSION: Our results indicate that, compared with standard DMARD therapy, treatment with anti-TNF therapies was not associated with an increase in mortality.

Arthritis Rheum. 2010 Nov;62(11):3191-5. doi: 10.1002/art.27687.
A case of progressive multifocal leukoencephalopathy in a patient treated with infliximab.
Kumar D, Bouldin TW, Berger RG.

We describe a 72-year-old white man with erosive rheumatoid arthritis in whom subacute neurologic and psychiatric symptoms developed after 3 years of treatment with infliximab, prednisone, and methotrexate. White matter demyelination was seen on magnetic resonance imaging of the brain, and progressive multifocal leukoencephalopathy (PML) was ultimately confirmed by brain biopsy. The patient was treated with supportive therapy and discontinuation of disease-modifying antirheumatic drugs, resulting in stabilization of the disease process. The patient survived, but neurologic and cognitive deficits persisted.

The distribution and pathology of this patient's disease are unique from almost all reported incidents of oral methotrexate-associated leukoencephalopathy. The pathogenesis of disease may be linked to a T cell-mediated process that is potentially impacted by infliximab. This case provides the first reported evidence that PML can be seen in association with infliximab therapy.