

Literature Update Immunology

Period: 01-31 December 2010

IBD

- **Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease**
- Development of the **crohn's disease digestive damage score**, the **Lémann score**.
- **Review article: medical, surgical and radiological management of perianal Crohn's fistulas.**
- **Review article: explaining risks of inflammatory bowel disease therapy to patients.**
- **Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab.**
- **Adalimumab in ulcerative colitis: hypes and hopes.**
- **Perioperative anti-tumor necrosis factor therapy does not increase the rate of early postoperative complications in Crohn's disease.**
- **Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease** - subgroup results from a placebo-controlled study.
- Evaluation of **adalimumab therapy** in multidisciplinary strategy for **perianal Crohn's disease** patients with **infliximab failure**.
- **Hepatosplenic T-cell lymphoma in inflammatory bowel disease: a possible thiopurine-induced chromosomal abnormality.**
- **Clinical variables as prognostic tools in pediatric-onset ulcerative colitis: A retrospective cohort study.**
- **Outcomes and adverse events in children and young adults undergoing tacrolimus therapy for steroid-refractory colitis.**
- **Real-time tool to display the predicted disease course and treatment response for children with Crohn's disease.**
- **Combined approach with infliximab, surgery, and methotrexate in severe fistulizing anoperineal Crohn's disease: Results from a prospective study.**
- **Short CDAI: Development and validation of a shortened and simplified Crohn's disease activity index.**
- **Risk-benefit analysis of adalimumab versus traditional non-biologic therapies for patients with Crohn's disease.**
- **Dosage adjustment during long-term adalimumab treatment for Crohn's disease: Clinical efficacy and pharmacoeconomics.**
- **Adherence to adalimumab therapy in Crohn's disease: A French multicenter experience.**
- **Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends.**
- **Acute severe ulcerative colitis in children: A systematic review.**
- **Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease** - subgroup results from a placebo-controlled study
- The **duration of effect of infliximab maintenance treatment in paediatric Crohn's disease** is limited
- **Predicting the need for colectomy in severe ulcerative colitis: a critical appraisal of clinical parameters and currently available biomarkers**
- **Management of acute severe ulcerative colitis**
- **Improvement in growth of children with Crohn disease following anti-TNF- α therapy can be independent of pubertal progress and glucocorticoid reduction**
- The **efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab**

Safety

- **Rectal non-Hodgkin's lymphoma in an infliximab treated patient with ulcerative colitis and primary sclerosing cholangitis**

- **Legionella pneumophila pneumonia** in a **pregnant woman** treated with **anti-TNF- α antibodies** for **Crohn's disease**: A case report
- **Inflammatory polypoid mass** treated with **infliximab** in a **Crohn's disease patient**
- A 24-year-old patient with **Crohn's disease** starting **immunosuppressive therapy**: **vaccination issues to consider**
- **Severe skin lesions** cause patients with **inflammatory bowel disease** to discontinue **anti-tumor necrosis factor therapy**
- **Psoriasis** is associated with clinically significant **cardiovascular risk**: a **Danish nationwide cohort study**.
- **Pregnancy outcome** in patients with **inflammatory bowel disease** treated with **thiopurines**: cohort from the **CESAME Study**
- **Infliximab** as therapeutic option in **steroid-refractory ulcerative colitis** after **kidney transplantation**: case report.
- **Injection-site burning and stinging** in patients with **rheumatoid arthritis** using **injectable biologics**.
- Presentation and outcome of **histoplasmosis** in **pediatric inflammatory bowel disease** patients treated with **antitumor necrosis factor alpha therapy**: A case series.
- **QuantiFERON TB** gold testing for **tuberculosis screening** in an **inflammatory bowel disease** cohort in the United States.
- Factors impacting the **results of interferon- release assay and tuberculin skin test** in routine screening for **latent tuberculosis** in patients with **inflammatory bowel diseases**.
- Formation of **antinuclear and double-strand DNA antibodies** and frequency of **lupus-like syndrome** in **anti-TNF- antibody-treated** patients with **inflammatory bowel disease**.
- **Characterization** of patients with **infliximab-induced lupus erythematosus** and outcomes after **retreatment** with a **second anti-TNF agent**.
- **Long-term complications, extraintestinal manifestations, and mortality** in **adult Crohn's disease** in population-based cohorts.
- **Liver diseases** associated with **anti-tumor necrosis factor-alpha (TNF-)** use for **inflammatory bowel disease**.
- **Cancer risk** with **tumor necrosis factor alpha (TNF) inhibitors**: **meta-analysis** of **randomized controlled trials** of **adalimumab, etanercept, and infliximab** using patient level data
- The **London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD** with the **European Crohn's and Colitis Organisation: Pregnancy and Pediatrics**
- **Diagnosing latent tuberculosis infection** in patients with **psoriasis under antitumour necrosis factor- α treatment**: every new solution breeds new doubts
- **Acute infusion reactions** induced by **monoclonal antibody therapy**
- **Drug-specific risk of non-tuberculosis opportunistic infections** in patients receiving **anti-TNF therapy** reported to the 3-year prospective **French RATIO registry**
- **Appropriate infliximab infusion dosage and monitoring**: results of a panel **meeting of rheumatologists, dermatologists and gastroenterologists**

IBD

Clin Gastroenterol Hepatol. 2010 Dec;8(12):1099. Epub 2010 Aug 20.

Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease.

Fraser GM.

No abstract available

Inflamm Bowel Dis. 2010 Nov 28. [Epub ahead of print]

Development of the crohn's disease digestive damage score, the Lémann score.

Pariante B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, Chowers Y, D'Haens G, Feagan BG, Hibi T, Hommes DW, Irvine EJ, Kamm MA, Loftus EV Jr, Louis E, Michetti P, Munkholm P, Oresland T, Panés J, Peyrin-Biroulet L, Reinisch W, Sands BE, Schoelmerich J, Schreiber S, Tilg H, Travis S, van Assche G, Vecchi M, Mary JY, Colombel JF, Lémann M.

Crohn's disease (CD) is a chronic progressive destructive disease. Currently available instruments measure disease activity at a specific point in time. An instrument to measure cumulative structural damage to the bowel, which may predict long-term disability, is needed. The aim of this article is to outline the methods to develop an instrument that can measure cumulative bowel damage. The project is being conducted by the International Program to develop New Indexes in Crohn's disease (IPNIC) group. This instrument, called the Crohn's Disease Digestive Damage Score (the Lémann score), should take into account damage location, severity, extent, progression, and reversibility, as measured by diagnostic imaging modalities and the history of surgical resection. It should not be "diagnostic modality driven": for each lesion and location, a modality appropriate for the anatomic site (for example: computed tomography or magnetic resonance imaging enterography, and colonoscopy) will be used. A total of 24 centers from 15 countries will be involved in a cross-sectional study, which will include up to 240 patients with stratification according to disease location and duration. At least 120 additional patients will be included in the study to validate the score. The Lémann score is expected to be able to portray a patient's disease course on a double-axis graph, with time as the x-axis, bowel damage severity as the y-axis, and the slope of the line connecting data points as a measure of disease progression. This instrument could be used to assess the effect of various medical therapies on the progression of bowel damage.

Aliment Pharmacol Ther. 2011 Jan;33(1):5-22. doi: 10.1111/j.1365-2036.2010.04486.x. Epub 2010 Oct 29.

Review article: medical, surgical and radiological management of perianal Crohn's fistulas.

Tozer PJ, Burling D, Gupta A, Phillips RK, Hart AL.

Aliment Pharmacol Ther 2011; 33: 5-22 SUMMARY: Background Crohn's anal fistulas are common and cause considerable morbidity. Their management is often difficult; medical and surgical treatments rarely lead to true healing with frequent recurrence and complications. Aim To examine medical treatments previously and currently used, surgical techniques and the important role of optimal imaging. Methods We conducted a literature search in the Pub Med database using Crohn's, Anal Fistula, Surgery, Imaging and Medical Treatment as search terms. Results Antibiotics and immunosuppressants have a role, but slow initial response, side effects and relatively low remission rates of up to around a third with frequent recurrence limit their value. Long-term infliximab produces clinical remission in 36-58% of patients with combined medical and surgical management achieving optimal outcomes. Traditional and newer surgical procedures often have a high rate of recurrence with a significant risk of temporary or, in up to 10% of cases, permanent stomas, incontinence and unhealed or slowly healing wounds in 30%. Conclusions Management of Crohn's anal fistulas remains challenging. Established principles are to drain infection, use setons as required, aggressively manage active proctitis, give antibiotics, immunosuppressants and employ anti-TNF α therapy, and they demand significant co-operation between gastroenterologists and surgeons.

Aliment Pharmacol Ther. 2011 Jan;33(1):23-32. doi: 10.1111/j.1365-2036.2010.04489.x. Epub 2010 Oct 26.

Review article: explaining risks of inflammatory bowel disease therapy to patients.

Siegel CA.

Aliment Pharmacol Ther 2011; 33: 23-32 SUMMARY: Background Medical treatment for inflammatory bowel disease (IBD) has advanced significantly over the past decade, but it is important to communicate effectively the balance of benefits and risks of therapy to patients to facilitate informed medical decisions. Aim To review the available data describing the risk of side effects of IBD medications and to describe effective methods for communicating risk. Methods To identify relevant articles for this review, a PubMed search was conducted using relevant key words and phrases. In addition, reference lists from identified manuscripts were searched and recent abstracts from National meetings were reviewed. Results The steroid-sparing medications used for the treatment of IBD all carry risks of both common and rare adverse events. Trade-offs need to be made between the risks of these medications vs. the risks of poorly treated disease and corticosteroids. There has been significant research on how best to present risk data to patients, which is summarized in this review. Conclusions To ensure that our patients understand their choices and feel comfortable with their treatment, we need to communicate risk data to patients clearly. Patients comprehend absolute numbers better than relative risk, and when available, pictorial representations of data are preferred over solely presenting numerical outcomes.

Aliment Pharmacol Ther. 2010 Dec 7. doi: 10.1111/j.1365-2036.2010.04531.x. [Epub ahead of print]

Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab.

Taxonera C, Estellés J, Fernández-Blanco I, Merino O, Marín-Jiménez I, Barreiro-de Acosta M, Saro C, García-Sánchez V, Gento E, Bastida G, Gisbert JP, Vera I, Martínez-Montiel P, Garcia-Morán S, Sánchez MC, Mendoza JL.

Background The long-term efficacy of adalimumab in patients with ulcerative colitis is not well known. Aim To evaluate the short- and long-term outcomes of adalimumab in ulcerative colitis patients previously treated with infliximab. Methods Patients with active ulcerative colitis were treated with adalimumab after failure of other therapies including infliximab. Short-term clinical response and remission were assessed at weeks 4 and 12. The proportion of patients who continued on adalimumab and the proportion of patients who remained colectomy free were assessed over the long term. Results Clinical response at weeks 4 and 12 was achieved in 16 (53%) and 18 (60%) patients, respectively, and clinical remission was obtained in 3 (10%) and 8 (27%) patients, respectively. After a mean 48 weeks' follow-up, 15 patients (50%) continued on adalimumab. Six patients (20%) required colectomy. All patients who achieved clinical response at week 12 were colectomy free at long term. Conclusions Adalimumab was well tolerated and induced durable clinical response in many patients with otherwise medically refractory ulcerative colitis. Patients achieving clinical response at week 12 avoided colectomy over the long term.

Expert Opin Biol Ther. 2011 Jan;11(1):109-16.

Adalimumab in ulcerative colitis: hypes and hopes.

Fiorino G, Peyrin-Biroulet L, Repici A, Malesci A, Danese S.

Importance of the field: The advent of anti-TNF- α monoclonal antibodies has dramatically changed the management of inflammatory bowel diseases (IBD). Unlike Crohn's disease (CD), only one anti-TNF- α agent, infliximab, is currently approved for active moderate-to-severe ulcerative colitis (UC). Adalimumab is a fully human anti-TNF- α antibody that is effective and safe for the treatment of luminal and fistulising CD. Areas covered in this review: This review of the literature summarizes available data on of efficacy and safety profile adalimumab in patients with UC. What the reader will gain: Adalimumab may be effective in inducing and maintaining clinical remission in patients with moderate-to-severe UC. It may also induce mucosal healing and reduce the need for colectomy in patients with severe disease. The safety profile of the drug in UC is consistent with previous experience with this drug in CD. Take home message: Adalimumab may be effective and well tolerated in UC. Its efficacy in maintaining clinical remission needs to be confirmed in a randomized controlled trial.

J Gastrointest Surg. 2010 Dec;14(12):1859-65; discussion 1865-6. Epub 2010 Sep 25.

Perioperative anti-tumor necrosis factor therapy does not increase the rate of early postoperative complications in Crohn's disease.

Nasir BS, Dozois EJ, Cima RR, Pemberton JH, Wolff BG, Sandborn WJ, Loftus EV, Larson DW.

BACKGROUND: There have been numerous studies with conflicting results regarding the use of anti-tumor necrosis factor (TNF) therapy and its relationship to postoperative outcome in Crohn disease. The aim of our study was to examine the rate of postoperative morbidity in patients receiving anti TNF therapy in the perioperative period.

METHODS: All patients undergoing surgery for Crohn disease from 2005 till 2008 were abstracted from a prospective database. Patients undergoing surgery which included a suture or staple line at risk for leaking were selected for the study. A retrospective review of medical records was performed. The study group comprised patients treated with perioperative anti TNF therapy (defined as treatment within 8 weeks preoperatively or up to 30 days postoperatively). The remainder of the patients did not receive perioperative anti TNF therapy. Patient characteristics, disease severity, medication use, operative intervention and 30-day complication were compared between the two groups.

RESULTS: Three hundred and seventy patients were selected for analysis in this study, of which 119 received perioperative anti TNF therapy and 251 did not. The groups were similar in baseline characteristics, perioperative risk factors and procedures. The group who received perioperative anti TNF therapy had a more severe disease overall as measured by the American College of Gastroenterology (ACG) categories of disease (50% severe fulminant disease in the perioperative anti-TNF therapy group versus 18% in the group that did not receive perioperative anti-TNF therapy, $p < 0.001$). There was no significant association of perioperative anti TNF therapy and any postoperative complications (27.9% in anti-TNF group versus 30.1% in no anti-TNF group, $p = 0.63$) nor intra-abdominal infectious complications (5.0% in anti-TNF group versus 7.2% in no anti-TNF group, $p = 0.44$). Univariate analysis showed that the only factors associated with an increase in postoperative intra-abdominal infections were age and penetrating disease.

CONCLUSIONS: The use of anti-TNF therapy in the perioperative period is safe and is not associated with an increase in overall or infectious complications in Crohn disease patients undergoing surgery.

Aliment Pharmacol Ther. 2010 Nov 17. doi: 10.1111/j.1365-2036.2010.04509.x. [Epub ahead of print]

Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease - subgroup results from a placebo-controlled study.

Schreiber S, Lawrance IC, Thomsen OO, Hanauer SB, Bloomfield R, Sandborn WJ.

Background Treatment options for fistulizing Crohn's disease (CD) are limited. **Aim** To examine whether fistula closure is maintained at week 26 following treatment with certolizumab pegol. **Methods** Patients with draining fistulas at baseline from PRECiSE 2 ($n = 108$) received open-label induction with certolizumab pegol 400 mg at weeks 0 (baseline), 2 and 4. Response was defined as ≥ 100 -point decrease from baseline in the Crohn's Disease Activity Index. Nonresponders (50/108) were excluded. At week 6, responders with draining fistulas ($N = 58$) were randomised to certolizumab pegol 400 mg ($n = 28$) or placebo ($n = 30$) every 4 weeks across weeks 8-24. Fistula closure was evaluated throughout the study, with a final assessment at week 26. **Results** The majority of patients (55/58) had perianal fistula. At week 26, 36% of patients in the certolizumab pegol group had 100% fistula closure compared with 17% of patients receiving placebo ($P = 0.038$). Protocol-defined fistula closure ($\geq 50\%$ closure at two consecutive post-baseline visits ≥ 3 weeks apart) was not statistically significant ($P = 0.069$) with 54% and 43% of patients treated with certolizumab pegol and placebo achieving this end point, respectively. **Conclusion** Continuous treatment with certolizumab pegol improves the likelihood of sustained perianal fistula closure compared with placebo.

J Crohns Colitis. 2010 Dec;4(6):654-60. Epub 2010 Sep 17.

Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure.

Echarri A, Castro J, Barreiro M, Carpio D, Pereira S, Lorenzo A.

BACKGROUND: Infliximab has improved the management of perianal Crohn's disease, but intolerance and loss of efficacy can occur. The use of a second antibody can be less effective.

OBJECTIVE: Our aim was to determine if the use of adalimumab, based on a multidisciplinary strategy, can enhance outcomes for patients with fistulizing disease and infliximab failure.

MATERIAL AND METHODS: Sixteen patients with perianal disease and infliximab failure were treated with adalimumab. Complex fistulas were assessed using magnetic resonance imaging (MRI). Patients with severe conditions as determined by radiology were examined under anesthesia, and seton placement was performed when appropriate. Setons were removed when external discharge had ceased and there was no radiological evidence of fistula activity.

RESULTS: Nine patients (56%) underwent MRI. Setons were inserted in seven (43%). The baseline perianal disease activity index (PDAI) decreased after 4 weeks and remained at similar levels 24 and 48 weeks after treatment. The complete response rate was 50% after four weeks and 87.5% of these patients remained in remission after 48 weeks of treatment.

CONCLUSIONS: For patients with Crohn's perianal fistulas and infliximab failure, adalimumab as a multidisciplinary approach to management, using MRI to guide surgical drainage when necessary, results in a favourable response and low recurrence rate.

Am J Gastroenterol. 2010 Oct;105(10):2299-301.

Hepatosplenic T-cell lymphoma in inflammatory bowel disease: a possible thiopurine-induced chromosomal abnormality.

Kotlyar DS, Blonski W, Diamond RH, Wasik M, Lichtenstein GR.

No abstract available

Inflamm Bowel Dis. 2011 Jan;17(1):15-21. doi: 10.1002/ibd.21393.

Clinical variables as prognostic tools in pediatric-onset ulcerative colitis: A retrospective cohort study.

Moore JC, Thompson K, Lafleur B, Book LS, Jackson WD, O'Gorman MA, Black RE, Downey E Jr, Johnson DG, Matlak ME, Meyers RL, Scaife E, Guthery SL.

BACKGROUND: Clinical variables may identify a subset of patients with pediatric-onset ulcerative colitis (UC) (≤ 18 years at diagnosis) at risk for adverse outcomes. We postulated that routinely measured clinical variables measured at diagnosis would predict colectomy in patients with pediatric-onset UC.

METHODS: We conducted a chart review of patients with pediatric-onset UC at a single center over a 10-year period. We compared patients with and without colectomy across several variables, used proportional hazards regression to adjust for potential confounders, and assessed the ability of a UC risk score to predict colectomy.

RESULTS: Among 470 patients with inflammatory bowel disease ICD9-coded encounters, 155 patients had UC and 135 were eligible for analysis. The 1- and 3-year colectomy rates were 16.7% (95% confidence interval [CI]: 11.0%-24.8%) and 35.6% (26.7%-45.4%). White blood cell (WBC) count and hematocrit measured at diagnosis were associated with colectomy at 3 years, even after correcting for potential confounding variables. A UC Risk Score derived from the WBC count and hematocrit was strongly associated with colectomy risk, with a high negative predictive value (NPV) for colectomy at 1 and 3 years (NPV = 0.95 and 0.89, respectively), but low positive predictive value (PPV = 0.22 and 0.38, respectively).

CONCLUSIONS: A risk score calculated from WBC and hematocrit measured at diagnosis was associated with, but incompletely predictive of, colectomy in pediatric-onset UC. These data suggest 1) routinely measured clinical variables may have a prognostic role in risk stratification, and 2) multicenter prospective studies are needed to optimize risk stratification in pediatric UC. Our findings have impact on the design of such studies. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):22-29. doi: 10.1002/ibd.21418. Epub 2010 Aug 18.

Outcomes and adverse events in children and young adults undergoing tacrolimus therapy for steroid-refractory colitis.

Watson S, Pensabene L, Mitchell P, Bousvaros A.

BACKGROUND: Children with severe corticosteroid-resistant ulcerative colitis either need to undergo surgery or be treated with more intensive immunosuppression. Our aim was to characterize the short- and long-term outcomes and adverse events associated with the use of tacrolimus in a steroid-refractory pediatric population.

METHODS: We retrospectively reviewed the medical records of 46 children with steroid-refractory colitis treated with tacrolimus at Children's Hospital Boston between 1994 and 2008. Oral tacrolimus was

initiated at a dose of 0.1 mg/kg twice a day and titrated to yield trough levels of 10-15 ng/mL for induction, and 5-10 ng/mL once in remission. The Pediatric Ulcerative Colitis Activity Index (PUCAI) and other measures of disease activity, adverse events, and long-term outcomes were assessed. Statistical analysis of outcomes was performed using SAS statistical software.

RESULTS: Ninety-three percent of patients were discharged without undergoing surgery. The median length of stay after starting tacrolimus was 10 days (range 4-37 days). The mean PUCAI score was 68 ± 13 prior to initiating tacrolimus, and 27 ± 18 at the time of hospital discharge. The probability of avoiding colectomy after starting tacrolimus was 40% at 26 months. The most common adverse events included hypertension (52%) and tremor (44%). There was one seizure and no deaths.

CONCLUSIONS: Tacrolimus is useful as induction therapy in pediatric patients with corticosteroid-refractory colitis and side effects are generally mild and reversible. Despite these findings, many patients develop exacerbations of colitis upon transition to maintenance therapies. The long-term colectomy rate in this challenging population remains $\approx 60\%$ over time. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):30-38. doi: 10.1002/ibd.21386. Epub 2010 Sep 1.

Real-time tool to display the predicted disease course and treatment response for children with Crohn's disease.

Siegel CA, Siegel LS, Hyams JS, Kugathasan S, Markowitz J, Rosh JR, Leleiko N, Mack DR, Crandall W, Evans J, Keljo DJ, Otlej AR, Oliva-Hemker M, Farrior S, Langton CR, Wrobel IT, Wahbeh G, Quiros JA, Silber G, Bahar RJ, Sands BE, Dubinsky MC.

BACKGROUND: Immunomodulators and biologics are effective treatments for children with Crohn's disease (CD). The challenge of communicating the anticipated disease course with and without therapy to patients and parents is a barrier to the timely use of these agents. The aim of this project was to develop a tool to graphically display the predicted risks of CD and expected benefits of therapy.

METHODS: Using prospectively collected data from 796 pediatric CD patients we developed a model using system dynamics analysis (SDA). The primary model outcome is the probability of developing a CD-related complication. Input variables include patient and disease characteristics, magnitude of serologic immune responses expressed as the quartile sum score (QSS), and exposure to medical treatments.

RESULTS: Multivariate Cox proportional analyses show variables contributing a significant increase in the hazard ratio (HR) for a disease complication include female gender, older age at diagnosis, small bowel or perianal disease, and a higher QSS. As QSS increases, the HR for early use of corticosteroids increases, in contrast to a decreasing HR with early use of immunomodulators, early or late biologics, and early combination therapy. The concordance index for the model is 0.81. Using SDA, results of the Cox analyses are transformed into a simple graph displaying a real-time individualized probability of disease complication and treatment response.

CONCLUSIONS: We have developed a tool to predict and communicate individualized risks of CD complications and how this is modified by treatment. Once validated, it can be used at the bedside to facilitate patient decision making. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):69-76. doi: 10.1002/ibd.21405.

Combined approach with infliximab, surgery, and methotrexate in severe fistulizing anoperineal Crohn's disease: Results from a prospective study.

Roumeguère P, Bouchard D, Pigot F, Castinel A, Juguet F, Gaye D, Capdepon M, Zerbib F, Laharie D.

BACKGROUND: Infliximab is the only medical therapy that has been proven to be effective in fistulizing Crohn's disease (CD), but the recurrence rate of fistulas is high despite maintenance therapy. The aim of this prospective study was to evaluate the short- and long-term efficacy of a combined schedule with infliximab, methotrexate, and sphincter-sparing surgery in patients with severe fistulizing anoperineal CD.

METHODS: From January 2006 to November 2007, all consecutive patients in three referral centers with severe fistulizing anoperineal CD were prospectively included after primary drainage. At inclusion, patients received three infliximab infusions at weeks 0, 2, and 6, and maintenance therapy with methotrexate. A second optimized surgical step consisting of at least removal of setons was performed between the second and the third infliximab infusions.

RESULTS: Thirty-four CD patients (26 women; median age 38.5 years) with complex anoperineal fistula were enrolled (including 9 with recto-vaginal fistulas, and 10 with anorectal stenosis). At week 14 the response rate was 85% with 74% complete responders. At 1 year, 50% were still responders; luminal CD

worsening was the major cause of relapse. Median Perineal Disease Activity Index (PDAI) and magnetic resonance imaging (MRI) scores significantly decreased from baseline to week 50.

CONCLUSIONS: A combined approach with infliximab induction, two surgical sphincter-sparing steps and methotrexate is effective in achieving short-term response in severe fistulizing anoperineal CD. The best maintenance regimen remains to be determined. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):105-111. doi: 10.1002/ibd.21400.

Short CDAI: Development and validation of a shortened and simplified Crohn's disease activity index.

Thia K, Faubion WA Jr, Loftus EV Jr, Persson T, Persson A, Sandborn WJ.

BACKGROUND: The aim of this study was to develop a shortened Crohn's Disease Activity Index (CDAI).

METHODS: A short CDAI was developed retrospectively using patient-level data from four budesonide clinical trials to select variables from the full CDAI which best predicted health-related quality of life as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ), using the multiple linear regression model. The validity, reliability, and responsiveness of the short CDAI compared to the original CDAI were determined using data from nine clinical trials of budesonide.

RESULTS: The variables selected for the short CDAI were abdominal pain, diarrhea frequency, and general well-being. In all nine studies involving 1373 patients with active and inactive CD (5863 visits), the Pearson correlation coefficients between the short CDAI scores and the original CDAI scores at baseline ($r = 0.899$, $P < 0.001$), and the score differences ($r = 0.963$, $P < 0.001$) were excellent. The short CDAI accounted for 82.4% of the variance of the original CDAI. The intraclass correlation coefficient for the short CDAI was marginally better than that for the full CDAI, and both demonstrated good reliability ($r = 0.600$ versus $r = 0.549$). In patients with active CD who remitted during follow-up, the mean short CDAI scores decreased from 247 to 97, a score difference of 150 ± 60 points ($P < 0.001$). In patients with stable CD who relapsed, the mean short CDAI scores increased from 109 to 244 points, a score difference of 135 ± 62 points ($P < 0.001$).

CONCLUSIONS: The short CDAI is a valid, reliable, and responsive tool for the measurement of CD activity. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):127-140. doi: 10.1002/ibd.21341.

Risk-benefit analysis of adalimumab versus traditional non-biologic therapies for patients with Crohn's disease.

Loftus EV Jr, Johnson SJ, Wang ST, Wu E, Mulani PM, Chao J.

BACKGROUND: Adalimumab is indicated for the treatment of moderately to severely active Crohn's disease (CD). A systematic analysis of risks and benefits of adalimumab versus traditional non-biologic therapies for patients refractory to non-biologic therapy is lacking.

METHODS: A base-case analysis compared expected benefits of adalimumab therapy with a 12-week stopping rule for non-responders versus non-biologic therapies using data from clinical trials (CHARM, CLASSIC I). Adverse events (AEs) recorded in clinical trials (CHARM, CLASSIC I, CLASSIC II, GAIN, open-label extensions) were compiled. Sensitivity analyses incorporated all observed benefits of adalimumab and placebo (CHARM, CLASSIC I, GAIN) and observed AEs from a systematic literature review of non-biologic therapies (MEDLINE search of randomized trials 1990-2007). Distributional information from maintenance clinical trial observations and benefit model predictions were used in a probabilistic simulation. Incremental net benefits were estimated based on utility estimates from the literature.

RESULTS: Average time in remission (i.e., CDAI < 150) over 1 year of therapy was 39.9% for adalimumab versus 6.6% for traditional non-biologic therapies. Adalimumab was associated with fewer expected hospitalizations, better fistula closure rates, and lower AE rates. These findings were robust in sensitivity analyses. In the probabilistic simulation, with serious AEs as a composite of risks, adalimumab provided greater benefits with fewer AEs versus non-biologic therapies ($P < 0.01$). Adalimumab demonstrated greater incremental net quality-adjusted life-years (0.12) versus non-biologic therapies.

CONCLUSIONS: Adalimumab demonstrated greater benefits and lower rates of AEs versus traditional non-biologic therapies for patients with moderately to severely active CD who were refractory to non-biologic therapies. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):141-151. doi: 10.1002/ibd.21328.

Dosage adjustment during long-term adalimumab treatment for Crohn's disease: Clinical efficacy and pharmacoeconomics.

Sandborn WJ, Colombel JF, Schreiber S, Plevy SE, Pollack PF, Robinson AM, Chao J, Mulani P.

BACKGROUND: Data from CHARM, a 56-week, randomized controlled trial of adalimumab for patients with moderately to severely active Crohn's disease (CD), were used to evaluate outcomes of adalimumab dosage adjustment.

METHODS: Patients randomized to blinded adalimumab 40 mg every other week (EOW) in CHARM were the focus of the analysis. At ≥ 12 weeks, patients with flares or lack of response versus baseline (including patients who responded and then lost response) could move sequentially to open-label (OL) adalimumab EOW and then to OL adalimumab weekly.

RESULTS: Of 260 patients randomized to adalimumab EOW, 140 (54%) continued blinded EOW therapy and 120 (46%) moved to OL therapy. Of patients on OL therapy, 49 (19%) continued EOW therapy and 71 (27%) moved to weekly therapy; 36 (14%) completed the trial on weekly therapy. Of 71 patients on weekly therapy, 37% achieved clinical remission (Crohn's Disease Activity Index [CDAI] < 150), 58% achieved CR-100 (CDAI decreased ≥ 100 points), and 63% achieved CR-70 (CDAI decreased ≥ 70 points). Of the 49 patients who remained on OL EOW therapy, 39% achieved clinical remission, 59% achieved CR-100, and 63% achieved CR-70. In a logistic regression, greater baseline CDAI predicted changing to weekly therapy. A model of dosage-adjustment cost indicated a modest per-patient drug-acquisition cost increase (\$574 over yearly EOW dosing cost [\$22,518]).

CONCLUSIONS: Of patients randomized to blinded EOW therapy, 19% moved to OL EOW therapy and 27% moved to OL weekly therapy for flares or lack of response versus baseline. Weekly therapy was associated with clear clinical benefits and a small cost increase. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):152-159.

Adherence to adalimumab therapy in Crohn's disease: A French multicenter experience.

Billioud V, Laharie D, Filippi J, Roblin X, Oussalah A, Chevaux JB, Hébuterne X, Bigard MA, Peyrin-Biroulet L.

BACKGROUND: We evaluated adherence to adalimumab therapy in Crohn's disease (CD).

METHODS: This was an observational multicenter study conducted in four French university hospitals between April 4, 2008 and January 1, 2010. Patients were systematically asked, at each clinical visit, whether or not they delayed or missed an injection of adalimumab over the past 3 months. Patients were also asked about the reasons for their nonadherence.

RESULTS: Of the 108 patients analyzed, 33 (30.6%) delayed the administration of at least one injection and 16 (14.8%) missed at least one injection over the past 3 months. The main reasons for overall nonadherence were: forgetfulness (24.6%), infection (24.6%), and travel (20%). Other reasons for nonadherence were intentional nonadherence (10.8%), pharmaceutical supply issues (9.2%), side effects (7.7%), pregnancy (1.5%), and CD-related hospitalization (1.5%). Adalimumab regimen of 40 mg every other week was a positive predictor for injection delays ($P = 0.02$, odds ratio [OR] = 3.76, 95% confidence interval [CI], 1.28-11.05), whereas having at least one relapse in the past 12 months was associated with fewer delays ($P = 0.02$, OR = 0.37, 95% CI, 0.15-0.87). [correction made here after initial online publication]. Disease duration over 90 months negatively predicted failure to inject adalimumab ($P = 0.009$, OR = 0.17, 95% CI, 0.05-0.64).

CONCLUSIONS: The overall nonadherence rate for adalimumab use was 45.4%. Most of the reasons for nonadherent behaviors could be avoided. An adalimumab regimen of 40 mg every other week was negatively related to adalimumab adherence; both the occurrence of at least one relapse in the past 12 months and disease duration over 90 months were positively related to adherence. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):423-439. doi: 10.1002/ibd.21349.

Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends.

Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM.

BACKGROUND: Temporal trends in the incidence of pediatric-onset inflammatory bowel disease (IBD) are controversial and a wide range of estimates have been reported worldwide. We conducted a

systematic review of research describing the epidemiology of childhood-onset IBD to assess changes in incidence rates over time and to evaluate international differences.

METHODS: The following electronic databases were searched for articles published 1950-2009: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane IBD/Functional Bowel Disorders Group Specialised Trial Register. All included studies reported incidence or prevalence of IBD, Crohn's disease (CD) or ulcerative colitis (UC). Two authors independently completed the data extraction form for each eligible study. Choropleth maps demonstrated the international incidence of IBD, CD, and UC. Incidence of CD and UC was graphed using data from studies reporting rates in multiple time periods.

RESULTS: The search yielded 2209 references and review resulted in 139 included studies from 32 countries. A wide range of incidence was reported internationally; however, rates of IBD were not described in most countries. Twenty-eight studies (20.1%) used statistical analysis to assess trends over time, and 77.8% reported statistically significantly increased incidence of pediatric IBD. Of studies calculating statistical trends in CD incidence, 60% reported significantly increased incidence. Of similar UC studies, 20% reported significantly increased incidence.

CONCLUSIONS: Globally rising rates of pediatric IBD (due primarily to the rising incidence of CD) was demonstrated in both developed and developing nations; however, most countries lack accurate estimates. Analyzing incidence trends may help identify specific environmental and genetic risk factors for pediatric IBD. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):440-449. doi: 10.1002/ibd.21383.

Acute severe ulcerative colitis in children: A systematic review.

Turner D, Griffiths AM.

Pediatric ulcerative colitis (UC) has a more severe phenotype, reflected by more extensive disease and a higher rate of acute severe exacerbations. The pooled steroid-failure rate among 291 children from five studies is 34% (95% confidence interval [CI]: 27%-41%). It is suggested that corticosteroids should be dosed between 1-1.5 mg/kg up to 40-60 mg daily. Food restriction has a limited role in severe UC and should be generally discouraged in children who do not have a surgical abdomen. Appraisal of radiologic findings in children must recognize the variation in colonic width with age and size. Data suggest that the Pediatric UC Activity Index (PUCAI), determined at day 3, should be used to screen for patients likely to fail corticosteroids (>45 points), and at day 5 to dictate the introduction of second-line therapy (>65-70 points). Cyclosporine is successful in children with severe colitis but its use should be restricted to 3-4 months while bridging to thiopurine treatment (pooled short-term success rate 81% [95% CI: 76%-86%]; n = 94 from eight studies). Infliximab may be as effective as cyclosporine (75% pooled short-term response [95% CI: 67%-83%]; n = 126, six studies) with a pooled 1-year response of 64% (95% CI: 56%-72%). In toxic megacolon, in patients refractory to one salvage medical therapy, and in chronic severe disease, colectomy may be preferred. Decision-making regarding colectomy in children must consider the toxicity of medication consumed over many future years, the quality of life and self-image associated with either choice, as well as both functional outcomes and, in females, fertility following pouch procedures. (Inflamm Bowel Dis 2011;).

Aliment Pharmacol Ther. 2011 Jan;33(2):185-93. Epub 2010 Nov 17.

Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease - subgroup results from a placebo-controlled study.

Schreiber S, Lawrance IC, Thomsen OØ, Hanauer SB, Bloomfield R, Sandborn WJ.

BACKGROUND: Treatment options for fistulizing Crohn's disease (CD) are limited.

AIM: To examine whether fistula closure is maintained at week 26 following treatment with certolizumab pegol.

METHODS: Patients with draining fistulas at baseline from PRECiSE 2 (n = 108) received open-label induction with certolizumab pegol 400 mg at weeks 0 (baseline), 2 and 4. Response was defined as ≥ 100 -point decrease from baseline in the Crohn's Disease Activity Index. Nonresponders (50/108) were excluded. At week 6, responders with draining fistulas (N = 58) were randomised to certolizumab pegol 400 mg (n = 28) or placebo (n = 30) every 4 weeks across weeks 8-24. Fistula closure was evaluated throughout the study, with a final assessment at week 26.

RESULTS: The majority of patients (55/58) had perianal fistula. At week 26, 36% of patients in the certolizumab pegol group had 100% fistula closure compared with 17% of patients receiving placebo (P = 0.038). Protocol-defined fistula closure ($\geq 50\%$ closure at two consecutive post-baseline visits ≥ 3 weeks

apart) was not statistically significant ($P = 0.069$) with 54% and 43% of patients treated with certolizumab pegol and placebo achieving this end point, respectively.

CONCLUSION: Continuous treatment with certolizumab pegol improves the likelihood of sustained perianal fistula closure compared with placebo.

Aliment Pharmacol Ther. 2011 Jan;33(2):243-50. Epub 2010 Nov 14.

The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited.

De Bie CI, Hummel TZ, Kindermann A, Kokke FT, Damen GM, Kneepkens CM, Van Rheezen PF, Schweizer JJ, Hoekstra JH, Norbruis OF, Tjon A Ten WE, Vreugdenhil AC, Deckers-Kocken JM, Gijsbers CF, Escher JC, De Ridder L.

BACKGROUND: Infliximab is effective for induction and maintenance of remission in children with moderately to severely active Crohn's disease (CD).

AIM: To evaluate the long-term efficacy of infliximab treatment in paediatric CD.

METHODS: In this observational, multicentre study, all paediatric CD patients in The Netherlands treated with infliximab from October 1992 to November 2009 and with minimal follow-up of 3 months since start of infliximab, were studied.

RESULTS: One hundred and fifty-two CD patients [81M; median age at start of infliximab 15.0 years (IQR 13.1-16.4)] received a median number of 10.5 infliximab infusions (IQR 6-21). Median follow-up after start of infliximab was 25 months (IQR 13-40). Kaplan-Meier analysis showed that the cumulative probability of losing response to infliximab in patients who initially required repeated infusions was 13%, 40% and 50% after 1, 3 and 5 years, respectively. Seventy-four patients (49%) needed dose adjustments, with a median time to any adjustment of 6 months.

CONCLUSIONS: Duration of effect of infliximab is limited as 50% of patients on infliximab maintenance treatment lose their therapeutic response after 5 years. Dose adjustments after start of infliximab are frequently needed to regain therapeutic benefit. These findings emphasise the need for effective, long-term treatment strategies for paediatric CD.

Gut. 2011 Jan;60(1):3-9.

Predicting the need for colectomy in severe ulcerative colitis: a critical appraisal of clinical parameters and currently available biomarkers.

Travis S, Satsangi J, Lémann M.

No abstract available

Gut. 2011 Jan;60(1):130-3. Epub 2010 Oct 28.

Management of acute severe ulcerative colitis.

Van Assche G, Vermeire S, Rutgeerts P.

Acute severe ulcerative colitis is a potentially lethal condition that requires a pro-active approach with either effective medical treatment or timely colectomy. Although intravenous corticosteroids remain the first line treatment, in patients not responding after 3-5 days rescue medical therapy with either intravenous (IV) cyclosporine 2 mg/kg or infliximab 5 mg/kg IV should be considered. Controlled evidence supports the use of both treatments but medical rescue therapy should not defer the decision for colectomy in patients with inadequate response. Providing clear guidance for the choice between both agents is impossible due to the lack of comparative trials. The better short-term safety profile and the option for maintenance treatment favour infliximab specifically in patients already exposed to immunosuppressives. The rapid onset of action and the short half-life are advantages of cyclosporine in patients with imminent risk of colectomy. Even if cyclosporine and probably also infliximab only postpone colectomy in at least half of the patients, elective colectomy in a later stage of the disease may offer better outcomes. Whereas prolonged exposure to steroids predisposes to an increased rate of peri-operative complications it is still debated whether cyclosporine or infliximab increase peri-operative morbidity in ulcerative colitis.

J Pediatr Gastroenterol Nutr. 2011 Jan;52(1):31-7.

Improvement in growth of children with Crohn disease following anti-TNF- α therapy can be independent of pubertal progress and glucocorticoid reduction.

Malik S, Wong S, Bishop J, Hassan K, McGrogan P, Ahmed S, Russell R.

BACKGROUND AND AIM: Treatment with antitumour necrosis factor- α therapy such as infliximab may improve growth in children with Crohn disease (CD), but the extent of improvement in growth and its relation to pubertal progress and glucocorticoid (GC) therapy are unclear. This is a retrospective study of growth, puberty, and disease activity during the 6 months before starting infliximab (T - 6), at baseline (T0), and for the following 6 months (T + 6) and 12 months (T + 12) in children with CD.

PATIENTS AND METHODS: The growth and treatment details of 28 children (male, 17) who were given infliximab at a median (10th, 90th) age of 13.1 years (10.0, 15.7) were reviewed. Data on disease markers (C-reactive protein, erythrocyte sedimentation rate, and albumin), total alkaline phosphatase, and a physician's global assessment were also collected. Results are expressed as median (10th, 90th).

RESULTS: Of the 28 cases, 21 (75%) demonstrated a clinical response to infliximab treatment. Overall, height velocity (HV) increased from 3.6 cm/y (0.4-7.8) at T0 to 5.5 cm/y (2.1-9.2) at T + 6 ($P = 0.003$). In infliximab responders, HV increased from 2 cm/y (0.3-7.1) to 6.4 cm/y (2.3-9.1) ($P = 0.004$) and in the nonresponders, HV remained static at 4.3 cm/y (2.5-8.6) at T0 and 3.0 cm/y (2.0-11.3) ($P = 0.701$) at T + 6. HV also increased in the subgroup of 13 children who had remained prepubertal from 4.5 cm/y (0.4-8) to 5.5 cm/y (3.3-8.4) ($P = 0.050$). In the subgroup of 11 children who had a reduction ($n = 2$) or cessation in GC ($n = 9$), HV increased from 1.8 cm/y (0.3-8.3) at T0 to 5.6 cm/y (2.2-9.2) at T + 6 ($P = 0.14$), whereas those children who did not receive GC during the 12 months had an increase from 3.7 cm/y (0.6-6.5) to 6.4 cm/y (2.9-9.0) ($P < 0.05$). HV at T0 and T + 6 showed a significant association with the average alkaline phosphatase during the prior 6 months ($r = 0.39$, $P < 0.05$). HV did not show any association with individual markers of disease activity.

CONCLUSIONS: Clinical response to infliximab therapy is associated with an improvement in linear growth in the short term in children with CD. This increase in height may not be simply due to progress in pubertal status or reduction in GC dose.

Aliment Pharmacol Ther. 2010 Dec 1. doi: 10.1111/j.1365-2036.2010.04523.x. [Epub ahead of print]

The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab.

Kopylov U, Mantzaris GJ, Katsanos KH, Reenaers C, Ellul P, Rahier JF, Israeli E, Lakatos PL, Fiorino G, Cesarini M, Tsianos EV, Louis E, Ben-Horin S.

Background Patients treated with infliximab for Crohn's disease (CD) frequently require intensified dosage due to loss of response. There are scant data regarding the efficacy of shortening the dosing interval to 6 weeks. **Aim** We sought to investigate the efficacy of a once every 6 weeks' strategy compared with dose-doubling. **Methods** This work was a multicentre retrospective study of infliximab-treated CD patients who required dose escalation. The clinical outcome of patients treated by intensification to 5 mg/kg/6 weeks (6-week group) was compared with the outcome of patients whose infliximab was double-dosed (10 mg/kg/8 weeks or 5 mg/kg/4 weeks). **Results** Ninety-four patients (mean age: 29.8 years) were included in the study, 55 (59%) in the 6-week group and 39 (41%) in the double-dose group. Demographics and disease characteristics were similar between the two groups, although patients with re-emerging symptoms 5-7 weeks postinfusion were more likely to receive 5 mg/kg/6 weeks dosing (OR: 3.4, 95% CI: 1.4-8.8, $P < 0.01$). Early response to dose-intensification occurred in 69% of patients in the 6-week group and 67% in the double-dose group ($P = \text{N.S.}$). Regained response was maintained for 12 months in 40% compared with 29% of the patients respectively ($P = \text{N.S.}$). **Conclusion** In CD patients who lost response to standard infliximab dose, especially when symptoms re-emerge 5-7 weeks postinfusion, shortening the dosing interval to 6 weeks appears to be at least as effective as doubling the dose to 10 mg/kg or halving the infusion intervals to once in 4 weeks.

Safety

J Crohns Colitis. 2010 Dec;4(6):683-6. Epub 2010 Jul 14.

Rectal non-Hodgkin's lymphoma in an infliximab treated patient with ulcerative colitis and primary sclerosing cholangitis.

Van Hauwaert V, Meers S, Verhoef G, Vermeire S, Rutgeerts P, Van Assche G.

A 20-year old man with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) was diagnosed with a rectal non-Hodgkin's lymphoma (NHL) at surveillance endoscopy while being in remission on infliximab therapy. Further staging identified a diffuse large B-cell NHL, EBV negative restricted to the rectal submucosa (stage IA). Until now, there has not been any evidence of an increased risk of NHL in patients with UC nor of an increased risk of lymphoproliferative disorders in IBD patients. Hence, the role of concomitant PSC in the pathogenesis of intestinal NHL is unclear. However, IBD patients treated with purine analogues and with anti-TNF are at risk of NHL, especially hepatosplenic T-cell lymphoma. The management of this particular young patient is further complicated by the possibility of a future colectomy due to intractable disease which compromises the use of radiotherapy for this localized disease.

J Crohns Colitis. 2010 Dec;4(6):687-9. Epub 2010 Sep 15.

Legionella pneumophila pneumonia in a pregnant woman treated with anti-TNF- α antibodies for Crohn's disease: A case report.

Epping G, van der Valk PD, Hendrix R.

Anti-TNF- α antibodies are widely used. The indications for their usage are still increasing. With their emerging use, their infectious complications are seen more often. We describe the first case of a pneumonia with Legionella pneumophila in a pregnant women with Crohn's disease, during treatment with anti-TNF- α antibodies. She was treated with erythromycin and made a full recovery.

J Crohns Colitis. 2010 Dec;4(6):707-8. Epub 2010 Oct 30.

Inflammatory polypoid mass treated with Infliximab in a Crohn's disease patient.

Liatsos C, Kyriakos N, Panagou E, Karagiannis S, Salemis N, Mavrogiannis C.

No abstract available

Clin Gastroenterol Hepatol. 2010 Dec;8(12):1013-6. Epub 2010 Jul 23.

A 24-year-old patient with Crohn's disease starting immunosuppressive therapy: vaccination issues to consider.

Wasan SK, Skolnik PR, Farraye FA.

No abstract available

Clin Gastroenterol Hepatol. 2010 Dec;8(12):1048-55. Epub 2010 Aug 20.

Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy.

Rahier JF, Buche S, Peyrin-Biroulet L, Bouhnik Y, Duclos B, Louis E, Papay P, Allez M, Cosnes J, Cortot A, Laharie D, Reimund JM, Lémann M, Delaporte E, Colombel JF; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID).

BACKGROUND & AIMS: Psoriasiform and eczematiform lesions are associated with anti-tumor necrosis factor (TNF)- α therapies. We assessed clinical characteristics, risk factors, and outcomes of skin disease in patients with inflammatory bowel diseases that presented with psoriasiform and eczematiform lesions induced by anti-TNF- α agents.

METHODS: We studied 85 patients (69 with Crohn's disease, 15 with ulcerative colitis, and 1 with indeterminate colitis; 62 women) with inflammatory skin lesions (62 psoriasiform and 23 eczematiform lesions).

RESULTS: Twenty-four patients had a history of inflammatory skin lesions and 15 had a familial history of inflammatory skin disease. Locations of eczematiform lesions varied whereas scalp and flexural varieties were mostly psoriasiform. Skin lesions emerged but inflammatory bowel disease was quiescent in 69 patients following treatment with any type of anti-TNF- α agent (60 with infliximab, 20 with adalimumab, and 5 with certolizumab). Topical therapy resulted in partial or total remission in 41 patients. Patients with psoriasiform lesions that were resistant to topical therapy and that changed anti-TNF- α therapies once or twice developed recurring lesions. Overall, uncontrolled skin lesions caused 29 patients to stop taking TNF- α inhibitors.

CONCLUSIONS: Inflammatory skin lesions following therapy with TNF- α inhibitors occurred most frequently among women and patients with a personal or familial history of inflammatory skin disease; lesions did not correlate with intestinal disease activity. Recurring and intense skin lesions caused 34% of patients in this study to discontinue use of anti-TNF- α agents.

J Intern Med. 2010 Oct 29. doi: 10.1111/j.1365-2796.2010.02310.x. [Epub ahead of print]

Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study.

Ahlehoff O, Gislason GH, Charlott M, Jørgensen CH, Lindhardsen J, Olesen JB, Abildstrøm SZ, Skov L, Torp-Pedersen C, Hansen PR.

From the Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup Department of Cardiovascular Medicine, Copenhagen University Hospital Bispebjerg, Copenhagen National Institute of Public Health, University of Southern Denmark, Copenhagen Department of Dermatology, Copenhagen University Hospital Gentofte, Hellerup Faculty of Health Sciences, University of Copenhagen, Copenhagen; Denmark.

Objective. The magnitude of the cardiovascular risk from psoriasis and psoriatic arthritis is debated. We therefore investigated the psoriasis-related risk of adverse cardiovascular events and mortality. **Design, setting and subjects.** We conducted a cohort study of the entire Danish population aged ≥ 18 years followed from 1997 to 2006 by individual-level linkage of nationwide registers. Psoriasis was defined by prescription claims and classified as severe if patients received hospital-based treatment. Time-dependent Poisson regression models were applied to assess cardiovascular risk in patients with psoriasis and psoriatic arthritis. **Main outcome measures.** All-cause mortality, cardiovascular mortality and hospitalizations for myocardial infarction (MI), stroke and coronary revascularization were recorded. **Results.** A total of 34 371 patients with mild psoriasis and 2621 with severe psoriasis, including 607 with psoriatic arthritis, were identified and compared with 4 003 265 controls. The event rates and rate ratios (RRs) of all-cause mortality, cardiovascular death, MI, coronary revascularization, stroke and a composite of MI, stroke and cardiovascular death were increased in patients with psoriasis. The rate ratio increased with disease severity and decreased with age of onset. The overall RRs for the composite endpoint were 1.20 (95% confidence interval [CI] 1.14-1.25) and 1.58 (95% CI 1.36-1.82) for mild and severe psoriasis, respectively. The corresponding RRs for cardiovascular death were 1.14 (95% CI 1.06-1.22) and 1.57 (95% CI 1.27-1.94). The risk was similar in patients with severe skin affection alone and those with psoriatic arthritis. **Conclusions.** Psoriasis is associated with increased risk of adverse cardiovascular events and all-cause mortality. Young age, severe skin affection and/or psoriatic arthritis carry the most risk. Patients with psoriasis may be candidates for early cardiovascular risk factor modification.

Gut. 2010 Nov 29. [Epub ahead of print]

Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study.

Coelho J, Beaugerie L, Colombel JF, Hébuterne X, Lerebours E, Lémann M, Baumer P, Cosnes J, Bourrille A, Gendre JP, Seksik P, Blain A, Metman EH, Nisard A, Cadiot G, Veyrac M, Coffin B, Dray X, Carrat F, Marteau P; for the CESAME pregnancy study group (France).

Background and aims Few studies have been conducted addressing the safety of thiopurine treatment in pregnant women with inflammatory bowel disease (IBD). The aim of this study was to evaluate the pregnancy outcome of women with IBD who have been exposed to thiopurines. **Methods** 215 pregnancies in 204 women were registered and documented in the CESAME cohort between May 2004 and October 2007. Physicians documented the following information from the women: last menstrual date, delivery term, details of pregnancy outcome, prematurity, birth weight and height, congenital abnormalities, medication history during each trimester, smoking history and alcohol ingestion. Data were compared between three groups: women exposed to thiopurines (group A), women receiving a drug other than thiopurines (group B) and women not receiving any medication (group C). **Results** Mean age at pregnancy was 28.3 years. 75.7% of the women had Crohn's disease and 21.8% had ulcerative colitis, with a mean disease duration of 6.8 years at inclusion. Of the 215 pregnancies, there were 138 births (142 newborns), and the mean birth weight was 3135 g. There were 86 pregnancies in group A, 84 in group B and 45 in group C. Interrupted pregnancies occurred in 36% of patients enrolled in group A, 33% of patients enrolled in group B, and 40% of patients enrolled in group C;

congenital abnormalities arose in 3.6% of group A cases and 7.1% of group B cases. No significant differences were found between the three groups in overall pregnancy outcome. Conclusions The results obtained from this cohort indicate that thiopurine use during pregnancy is not associated with increased risks, including congenital abnormalities.

Transplant Proc. 2010 Nov;42(9):3880-2.

Infliximab as therapeutic option in steroid-refractory ulcerative colitis after kidney transplantation: case report.

Temme J, Koziolok M, Bramlage C, Schaefer IM, Füzesi L, Ramadori G, Müller GA, Schwörer H.

In inflammatory bowel disease refractory to established therapies, treatment with biological agents such as monoclonal tumor necrosis factor- α antibodies is an established therapeutic option. However, application in renal allograft recipients is either not licensed or has not yet been systematically examined. Herein, we present 2 case reports of renal allograft recipients who had steroid-refractory ulcerative colitis who demonstrated improvement of symptoms after treatment with infliximab, without signs of effect on transplant function. In both patients, stool frequency decreased significantly. Colonoscopy controls and histologic examination after initiation of treatment revealed a state of remission. Renal function parameters and drug concentrations remained constant.

Curr Med Res Opin. 2010 Nov 22. [Epub ahead of print]

Injection-site burning and stinging in patients with rheumatoid arthritis using injectable biologics.

Curtis JR, Hobar C, Hansbrough K.

Abstract Objective: Some patients with rheumatoid arthritis (RA) who receive injectable biologics experience injection-site burning and stinging (ISBS); however, the prevalence of ISBS in the general RA population is unknown and may impact preference for an injectable biologic. This study assessed the prevalence of ISBS and associated comorbidities in patients with RA who receive injectable biologics. **Research design and methods:** The physician and patient survey consisted of a retrospective chart review and a prospective assessment. In the former, each participating US rheumatologist reviewed the medical records of five randomly selected RA patients receiving an injectable biologic. In the prospective assessment, each rheumatologist was asked to report data based on interviews with up to 50 RA patients currently treated with an injectable biologic, who were asked whether they had ISBS during or after their most recent injection. **Results:** Data were analyzed for 504 patients in the retrospective chart review and 3326 patients in the prospective assessment; data were provided by 101 physicians. The overall prevalence of ISBS was 17% and 58% in the retrospective chart review and prospective analyses, respectively. Out of the 1939 prospectively assessed patients who experienced at least some ISBS, 429 (22%) rated the level of ISBS as moderate to severe (13% of total). Increased risk of ISBS was associated with female gender, fibromyalgia, depression, and more severe RA. **Conclusions:** The prevalence of ISBS is likely underestimated in many rheumatology practices. Specifically asking about it may identify patients who experience this side effect, provide a more accurate understanding of how significantly it affects them, and provide an opportunity for intervention in light of their preferences.

Inflamm Bowel Dis. 2011 Jan;17(1):56-61. doi: 10.1002/ibd.21378.

Presentation and outcome of histoplasmosis in pediatric inflammatory bowel disease patients treated with antitumor necrosis factor alpha therapy: A case series.

Dotson JL, Crandall W, Mousa H, Honegger JR, Denson L, Samson C, Cunningham D, Balint J, Dienhart M, Jaggi P, Carvalho R.

BACKGROUND: Antitumor necrosis factor alpha (aTNF) therapies are commonly used in the treatment of pediatric inflammatory bowel disease (IBD). However, inhibition of the TNF-alpha pathway predisposes to serious infections, including histoplasmosis, which is the most common invasive fungal infection in individuals on aTNF therapy and carries a high mortality rate when associated with delayed diagnosis. Few data exist on the frequency, presentation, and appropriate treatment of pediatric patients with histoplasmosis on aTNF therapy.

METHODS: Following Institutional Review Board approval, cases were identified then reviewed with their primary gastroenterologist and infectious disease specialists.

RESULTS: Herein we describe histoplasmosis in five pediatric patients receiving aTNF therapy for IBD in an endemic area.

CONCLUSIONS: Histoplasmosis is an important complication of treatment with TNF-alpha neutralizing agents. Children with IBD treated with aTNF therapy who develop the infection may present with minimal pulmonary symptoms. While discontinuation of aTNF therapy is important initially, few data exist to determine when and how aTNF therapy can be reinstated. Recognition of Histoplasma capsulatum is often delayed due to the overlap of symptoms with some of the extraintestinal manifestations of IBD and other more prevalent infectious complications. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):77-83. doi: 10.1002/ibd.21329.

QuantIFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States.

Qumseya BJ, Ananthakrishnan AN, Skaros S, Bonner M, Issa M, Zadvornova Y, Naik A, Perera L, Binion DG.

BACKGROUND: Reactivation of latent Mycobacterium tuberculosis (TB) is a rare, yet devastating infectious complication associated with anti-tumor necrosis factor alpha (TNF- α) therapy. We evaluated the performance of the QuantiFERON TB Gold test (QFT-G) for TB screening in a cohort of inflammatory bowel disease (IBD) patients in the United States.

METHODS: We performed a retrospective, observational study of patients initiated and/or maintained on an anti-TNF- α agent in a single IBD referral center and recorded the frequency and the test results of QFT-G testing and the rate of TB reactivation.

RESULTS: 512 QFT-G tests were done in 340 patients. Five patients (1.5%) had a positive, nine (2.7%) indeterminate, and 326 patients (95.8%) had a negative QFT-G. After a mean follow-up of 17 months there was one case of TB reactivation (0.3%). The use of immunosuppressive therapy or anti-TNF therapy at the time of testing did not affect the results of the QFT-G testing. Test-retest had substantial concordance ($\kappa = 0.72$). 25% of patients ($n = 85$) had TST testing. Concordance between the TST and QFT-G was found to be moderate ($\kappa = 0.4152$, $P = 0.0041$).

CONCLUSIONS: Most patients with negative QFT-G tolerated anti-TNF therapy with no evidence of TB reactivation. Concomitant use of immunosuppressive therapy or anti-TNF did not seem to affect QFT-G results. One patient had an indeterminate QFT-G while on infliximab and later developed miliary TB. Concordance with TST is moderate. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):84-90. doi: 10.1002/ibd.21427. Epub 2010 Aug 18.

Factors impacting the results of interferon- γ release assay and tuberculin skin test in routine screening for latent tuberculosis in patients with inflammatory bowel diseases.

Papay P, Eser A, Winkler S, Frantal S, Primas C, Miehsler W, Novacek G, Vogelsang H, Dejaco C, Reinisch W.

BACKGROUND: Screening for latent tuberculosis (LTB) including chest x-ray, tuberculin skin test (TST), and facultative whole blood interferon- γ assay (IGRA) is part of routine management in inflammatory bowel disease (IBD) patients before starting therapy with tumor necrosis factor (TNF)- α inhibitors. However, in patients with immunomodulators (IM) TST and IGRA might show limitations.

METHODS: We aimed to evaluate the results from an IGRA (QuantiFERON-TB Gold in Tube) and TST as well as their concordance in 208 consecutive IBD patients with indications for anti-TNF- α therapy. Associations of both tests with risk factors for LTB were determined by logistic regression.

RESULTS: During screening, 149 patients (71.6%) were under IM therapy. In 26 (12.5%) patients TST was positive, whereas 15 (7.2%) patients showed a positive result from IGRA. IGRA failed on samples from 16/208 (7.7%) patients, resulting in 192/208 (92.3%) patients in whom results from both screening tests were available. Correlation between IGRA and TST results was fair (84.9%, $\kappa = 0.21$). The presence of risk factors for LTB showed association with positive results of TST (odds ratio [OR] 3.7, 1.5-9.6) and IGRA (OR 3.5, 1.2-11.3). TST was associated furthermore with age (OR 1.06, 1.02-1.10) and signs indicative of LTB in chest x-ray (OR 4.9, 1.1-19.9). The IGRA was negatively influenced by IM therapy (OR 0.3, 0.1-0.9).

CONCLUSION: Our study reveals that results of IGRA are negatively affected by IM therapy. Thus, current guidelines for TB screening prior anti-TNF- α therapy appear inaccurate in patients under IM. Therefore, LTB screening might be best performed prior to initiation of IM treatment. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):91-98. doi: 10.1002/ibd.21362.

Formation of antinuclear and double-strand DNA antibodies and frequency of lupus-like syndrome in anti-TNF- α antibody-treated patients with inflammatory bowel disease.

Beigel F, Schnitzler F, Paul Laubender R, Pfennig S, Weidinger M, Göke B, Seiderer J, Ochsenkühn T, Brand S.

BACKGROUND: Anti-tumor necrosis factor (TNF) therapy used in patients with inflammatory bowel disease (IBD) has been associated with induction of autoantibodies including antinuclear antibodies (ANA), double-strand (ds) DNA antibodies, and the occurrence of lupus-like syndrome (LLS). However, the clinical relevance of autoantibody formation and predictive factors are unclear.

METHODS: 180 IBD patients treated with anti-TNF antibodies (infliximab or adalimumab, or infliximab and adalimumab consecutively) were analyzed regarding ANA and dsDNA antibody values and the development of LLS, including factors predicting the development of LLS.

RESULTS: In all, 44.4% of anti-TNF-treated patients had ANA titers $\geq 1:240$, while 15.6% had dsDNA serum levels ≥ 9 U/mL. However, only a minority of these patients experienced clinical symptoms of LLS; 8.9% presented with mild lupus-like symptoms with no need for intervention; 1.1% had severe symptoms consistent with LLS requiring immediate stop of anti-TNF therapy. Multivariate logistic regression analyses identified age as an independent risk factor for developing ANA $\geq 1:240$ ($P < 0.001$) and LLS ($P = 0.002$), while concomitant immunosuppressive therapy was protective against autoantibody formation (ANA: $P = 0.05$) and LLS development ($P = 0.04$). There was a significant association between dsDNA antibody values ≥ 9 U/mL and LLS ($P = 0.02$) but not between ANA titers and LLS.

CONCLUSIONS: dsDNA antibody levels ≥ 9 U/mL, but not ANA titers $\geq 1:240$, are associated with clinical symptoms of LLS. IBD patients of higher age treated with anti-TNF- α antibodies are at increased risk for development of ANA and LLS, while concomitant immunosuppressive therapy may have a protective effect. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):99-104. doi: 10.1002/ibd.21370.

Characterization of patients with infliximab-induced lupus erythematosus and outcomes after retreatment with a second anti-TNF agent.

Subramanian S, Yajnik V, Sands BE, Cullen G, Korzenik JR.

BACKGROUND: Drug-induced lupus erythematosus (DILE) due to infliximab therapy for inflammatory bowel disease (IBD) is an uncommon occurrence. It remains uncertain whether patients with infliximab-induced DILE could tolerate another antitumor necrosis factor (TNF) agent without recurrent DILE.

METHODS: We reviewed the case records of patients with infliximab-induced DILE diagnosed at our institute and noted details of their clinical and immunological profile at presentation. In addition, case notes of patients who were treated with a second anti-TNF agent were examined for evidence of recurrent DILE.

RESULTS: Thirteen patients with infliximab-induced DILE were identified with a female-to-male ratio of 11:2. Symmetric large joint arthralgias and high titers of antinuclear and antidouble-stranded DNA antibody were noted in all patients. Eight patients were retreated with a second anti-TNF agent (six certolizumab pegol and two adalimumab) of whom two patients (one adalimumab and certolizumab pegol each) developed recurrent DILE following 3 months of therapy with a second anti-TNF agent. One patient discontinued therapy after 2 months despite no recurrence of DILE, due to fear of side effects. Five patients remain well with no recurrence of DILE after a median of 5 months (range 2-6) therapy.

CONCLUSIONS: Rechallenge with a further anti-TNF agent in patients who have developed DILE with infliximab is associated with a low rate of recurrence. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):471-478. doi: 10.1002/ibd.21417. Epub 2010 Aug 19.

Long-term complications, extraintestinal manifestations, and mortality in adult Crohn's disease in population-based cohorts.

Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ.

BACKGROUND: Crohn's disease (CD) is a chronic, progressive, destructive disease. Numerous intestinal and extraintestinal complications and manifestations can occur during its clinical course. This literature review summarizes our current knowledge of the long-term complications, extraintestinal complications, and mortality in CD in adults as reported in population-based studies that include long-term follow-up results.

METHODS: A literature search of English and non-English language publications listed in the electronic databases of Medline (source PubMed, 1935 to July, 2009).

RESULTS: The relative risk of incident fractures is increased in CD patients by ≈30%-40%. These patients have also have a 3-fold increased risk of deep venous thrombosis and pulmonary embolism. A variety of extraintestinal manifestations (primary sclerosing cholangitis, ankylosing spondylitis, iritis/uveitis, pyoderma gangrenosum, erythema nodosum) and diseases (asthma, bronchitis, pericarditis, psoriasis, rheumatoid arthritis, and multiple sclerosis) are associated with CD. The risks of colorectal and small bowel cancers relative to the general population are 1.4-1.9 and 21.1-27.1, respectively. A slightly increased risk of lymphoma, irrespective of medication use, has been reported in a recent meta-analysis of population-based studies. Overall mortality is slightly increased in CD, with a standardized mortality ratio of 1.4.

CONCLUSIONS: CD is frequently associated with disease complications and extraintestinal conditions. Whether the impact of changing treatment paradigms with increased use of immunosuppressives and biologic agents can reduce disease complications and associated conditions is unknown. (Inflamm Bowel Dis 2011;).

Inflamm Bowel Dis. 2011 Jan;17(1):479-484. doi: 10.1002/ibd.21336.

Liver diseases associated with anti-tumor necrosis factor-alpha (TNF-α) use for inflammatory bowel disease.

Coffin CS, Fraser HF, Panaccione R, Ghosh S.

The conventional treatment of inflammatory bowel disease (IBD) has focused on nonspecifically targeting mucosal inflammation. In the last decade, with the advent of novel biological agents that directly inhibit proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), rapid progress has been made in clinical management of complex and challenging patients with IBD. However, there remain many unanswered questions about the short and long-term side effects; this article focuses on hepatic complications. This review aims to provide a concise update to gastroenterologists on the well-known, as well as the potential rare consequences of anti-TNFα therapy on the liver and recommendations for clinical management. We performed a focused literature review for reports of the effect of anti-TNF therapy on preexisting liver disease as well as de novo hepatitis and drug-induced hepatotoxicity. Search terms used included anti-TNF therapy, biologics, liver disease, inflammatory bowel disease, hepatitis, hepatotoxicity, opportunistic infections,, and hepatitis virus reactivation. There are multiple potential effects of anti-TNF therapy on the liver during treatment of patients with IBD. Often treatment may be complicated by preexisting chronic liver disease. Clinicians should be aware of potential hepatic side effects and appropriate management options. (Inflamm Bowel Dis 2011;).

Pharmacoepidemiol Drug Saf. 2010 Dec 7. [Epub ahead of print]

Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data.

Askling J, Fahrback K, Nordstrom B, Ross S, Schmid CH, Symmons D.

PURPOSE: Uncertain short- and long-term cancer risks with anti-TNF therapies is a concern, and led to a recent black box warning. This meta-analysis, requested by the European Medicines Agency, aimed at better assessing short-term risks by using meta-analytic techniques based on individual patient data from all corporate-sponsored randomized controlled trials (RCTs) of adalimumab, etanercept, and infliximab.

METHODS: All 74 RCTs of TNF inhibitors of at least 4 weeks duration were provided to independent investigators, including case narratives for events occurring between trial start until 30 days after planned end of treatment and indicating a possible cancer. Relative risks were estimated using Bayesian piecewise exponential models.

RESULTS: One hundred thirty (0.84%) of 15 418 individuals randomized to anti-TNF therapy were diagnosed with cancer, compared to 48 (0.64%) of 7486 individuals randomized to comparators. The relative risks associated with all anti-TNF were 0.99 (95%CI 0.61-1.68) for cancers excluding non-melanoma skin cancer (NMSC), and 2.02 (95%CI 1.11-3.95) for NMSC. There were indications of differences in the relative risks for the three anti-TNF drugs, but also of differences across the cancer rates in the three comparator arms for adalimumab, etanercept, and infliximab.

CONCLUSIONS: Despite a reassuring overall short-term risk, we could neither refute nor verify that individual anti-TNF therapies affect the short-term clinical emergence of cancer. Despite representing the best available evidence, statistical precision, and differences in baseline cancer risk and reporting detail between trials of adalimumab, etanercept, and infliximab hampered distinction of drug-specific from trial effects, illustrating the challenges in safety-assessments using RCT meta-analyses. Long-term risk assessment requires observational studies.

Am J Gastroenterol. 2010 Dec 14. [Epub ahead of print]

The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organisation: Pregnancy and Pediatrics.

Mahadevan U, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, Sandborn WJ, Colombel JF.

Women with inflammatory bowel disease (IBD) have similar rates of fertility to the general population, but have an increased rate of adverse pregnancy outcomes compared with the general population, which may be worsened by disease activity. Infertility is increased in those undergoing ileal pouch-anal anastomosis. Anti-tumor necrosis factor therapy in pregnancy is considered to be low risk and compatible with use during conception in men and women and during pregnancy in at least the first two trimesters. Infliximab (IFX) and certolizumab pegol are also compatible with breastfeeding, but safety data for adalimumab (ADA) are awaited. The safety of natalizumab during pregnancy is unknown. For children with Crohn's disease (CD), IFX is effective at inducing and maintaining remission. Episodic therapy is not as effective as scheduled infusions. Disease duration in children does not appear to affect the efficacy of IFX. IFX promotes growth in prepubertal and early pubertal Crohn's patients. It is also effective for the treatment of extraintestinal manifestations. ADA is effective for children with active CD and for maintaining remission, even if they have lost response to IFX, although there are fewer data. Vaccination of infants exposed to biological therapy in utero should be given at standard schedules during the first 6 months of life, except for live-virus vaccines such as rotavirus. Inactivated vaccines may be safely administered to children with IBD, even when immunocompromised. Am J Gastroenterol advance online publication, 14 December 2010; doi:10.1038/ajg.2010.464.

Br J Dermatol. 2011 Jan;164(1):208-9. doi: 10.1111/j.1365-2133.2010.10028.x. Epub 2010 Nov 4.

Diagnosing latent tuberculosis infection in patients with psoriasis under antitumour necrosis factor- α treatment: every new solution breeds new doubts.

Sánchez-Moya AI, Daudén E.

No abstract available

Expert Rev Clin Immunol. 2011 Jan;7(1):55-63.

Acute infusion reactions induced by monoclonal antibody therapy.

Maggi E, Vultaggio A, Matucci A.

This article reports recent evidence on epidemiological data concerning monoclonal antibody (mAb) infusion-related anaphylaxis, as well as recent data on the correlation between mAb immunogenicity and safety profiles. Pathogenic mechanisms of mAb-related adverse reactions including hypersensitivity, IgE- and non-IgE-mediated events and cytokine release syndrome are also highlighted. Finally, the role of serum anti-mAb antibodies as markers to monitor the safety of such therapeutical compounds are extensively evaluated. The anaphylaxis occurring during therapy with the anti-TNF- α mAb infliximab, largely used in immune-mediated diseases, has been taken as a paradigm.

Ann Rheum Dis. 2010 Dec 21. [Epub ahead of print]

Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry.

Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, Cuillerier E, Fautrel B, Michelet C, Morel J, Puéchal X, Wendling D, Lemann M, Ravaud P, Mariette X; for the RATIO group.

BACKGROUND: Anti-tumour necrosis factor (TNF) therapy may be associated with opportunistic infections (OIs).

OBJECTIVE: To describe the spectrum of non-tuberculosis OIs associated with anti-TNF therapy and identify their risk factors.

METHODS: A 3-year national French registry (RATIO) collected all cases of OI in patients receiving anti-TNF treatment for any indication in France. A case-control study was performed with three controls treated with anti-TNF agents per case, matched for gender and underlying inflammatory disease.

RESULTS: 45 cases were collected of non-TB OIs in 43 patients receiving infliximab (n=29), adalimumab (n=10) or etanercept (n=4) for rheumatoid arthritis (n=26), spondyloarthritis (n=3), inflammatory colitis (n=8), psoriasis (n=1) or other conditions (n=5). One-third (33%) of OIs were bacterial

(4 listeriosis, 4 nocardiosis, 4 atypical mycobacteriosis, 3 non-typhoid salmonellosis), 40% were viral (8 severe herpes zoster, 3 varicella, 3 extensive herpes simplex, 4 disseminated cytomegalovirus infections), 22% were fungal (5 pneumocystosis, 3 invasive aspergillosis, 2 cryptococcosis) and 4% were parasitic (2 leishmaniasis). Ten patients (23%) required admission to the intensive care unit, and four patients (9%) died. Risk factors for OIs were treatment with infliximab (OR=17.6 (95% CI 4.3 - 72.9); $p < 0.0001$) or adalimumab (OR=10.0 (2.3 to 44.4); $p = 0.002$) versus etanercept, and oral steroid use > 10 mg/day or intravenous boluses during the previous year (OR=6.3 (2.0 to 20.0); $p = 0.002$).

CONCLUSION: Various and severe OIs, especially those with intracellular micro-organisms, may develop in patients receiving anti-TNF treatment. Monoclonal anti-TNF antibody rather than soluble TNF receptor therapy and steroid use > 10 mg/day are independently associated with OI.

Br J Clin Pharmacol. 2011 Jan;71(1):7-19. doi: 10.1111/j.1365-2125.2010.03760.x.

Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists.

de Vries HS, van Oijen MG, Driessen RJ, de Jong EM, Creemers MC, Kievit W, de Jong DJ.

WHAT THIS STUDY ADDS: This study is the first study which compared current international, national and local guidelines from the medical specialties involved in the treatment with infliximab on the following topics: indication, dosage, synergy and monitoring of vital signs.

AIMS: Infliximab, an anti-TNF biologic agent, is currently indicated and reimbursed for rheumatoid arthritis, ankylosing spondylitis, Crohn's disease (both adult and paediatric), ulcerative colitis, psoriatic arthritis and plaque psoriasis. Development of national and international guidelines for rheumatology, gastroenterology and dermatology, was mostly based on clinical studies and expert opinion. The aim of this study was to compare available guidelines and local protocols for rheumatology, dermatology and gastroenterology, regarding dosage of infliximab, synergy of infliximab with concomitant medication and monitoring of vital signs during infliximab administration, for achieving optimal care.

METHODS: Current international, national and local guidelines on the use of infliximab were reviewed and compared, differences and shortcomings were identified, and optimal treatment schedules discussed during a meeting (July 2008) of clinical experts and researchers from three departments of a Dutch university hospital.

RESULTS: Recommended dosages of infliximab are not equal for different indications. Loss of response to infliximab is a common problem encountered within the three medical specialties, but indications for adjustments in treatment schedules are lacking in all of the guidelines. Monitoring of vital signs (blood pressure, pulse, temperature) during infusion with infliximab is common practice and recommended by some guidelines. Routine measurement of vital signs is not of any value in predicting or recognizing acute infusion reactions, in our experience, and this is confirmed by literature on inflammatory bowel disease.

CONCLUSION: Different indications encompass different dosing schedules. National and internal guidelines do not provide advice regarding loss of response. Routine measurement of vital signs during infusion is not valuable in detecting acute infusion reactions and should only be performed in case of an acute infusion reaction. These topics need to be studied in future studies and covered in future guidelines.