

Literature Update Immunology

Period: 01-31 July 2010

IBD

- **SONIC** finds **2-drug combo** twice as effective for **Crohn's remission**
- Is it time for **dosing anti-tnf antibody therapy by serum level?**
- 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
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- **Pediatric inflammatory bowel diseases**: coming of age
- **Systematic review: steroid withdrawal in anti-TNF-treated patients with inflammatory bowel disease**
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- **Pre-operative management** is associated with low **rate of post-operative morbidity** in penetrating **Crohn's disease**
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- **Postoperative CD**: how can we prevent it?
- Role of **IL-21** in **IBD**
- **Drug targeting strategies** for the **treatment of IBD**: a mechanistic update
- **Leukocyte traffic control**: a novel therapeutic strategy for **IBD**
- **Stem cell treatment for CD**
- **Current status of monoclonal antibody therapy** for the treatment of **IBD**
- **Use of immunomodulators and biologic therapies** in **children with IBD**
- **Treatment of UC with ADA or IFX**: long-term follow-up of a single-centre cohort
- **Serum anti-glycan antibodies predict complicated CD behavior**: A cohort study
- Efficacy of **methotrexate** in **UC**: Failure or promise
- **Nonfistulizing perianal CD**: Clinical features, epidemiology, and treatment
- **Ultrastructural evidence of mucosal healing after IFX** in patients with **UC**
- **Response to medical treatment** in patients with **CD**: the role of **NOD2/CRAD15**, disease phenotype, and age of diagnosis
- **New biological agents** for the treatment of the **"high risk" IBD patients**
- **Extraintestinal manifestations of pediatric IBD** and their relation to disease type and severity
- **Postoperative outcome of colectomy** for pediatric patients with **UC**
- **Quality of life in children with CD**

Safety

- **Tumor necrosis factor- blocker** induced **tuberculosis**
- **Dermatomyositis** during **adalimumab** therapy for **rheumatoid arthritis**
- Measuring multiple **etanercept levels** in the **breast milk of a nursing mother with rheumatoid arthritis**
- Review article: **malignancy on thiopurine treatment** with special reference to **inflammatory bowel disease**

- **Hepatosplenic T-cell lymphoma and inflammatory bowel disease**
- Early years of **biological agents therapy in Crohn's disease** and risk of the human polyomavirus **JC reactivation**
- Risk of **diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis.**
- **Psoriatic skin lesions** induced by **tumor necrosis factor antagonist therapy**: clinical features and possible immunopathogenesis
- Common **vaccinations among adults** do not increase the risk of developing **rheumatoid arthritis**: results from the Swedish EIRA study
- **Risk of cancer in inflammatory bowel disease** treated with **azathioprine**: a UK population-based case-control study
- Update on the **risk of lymphoma following immunosuppressive therapy for IBD**
- Should patients under **long-term anti-TNF therapies** be followed for **TB contamination**?
- The good, the bad, and the ugly: **Adverse events and Crohn's therapies**
- Safety and retention rate of **off-label uses of TNF antagonists** in rheumatic conditions: **data from the Spanish registry BIOBADASER 2.0**
- **Whipple's endocarditis** as a complication of TNF- antagonist treatment in a man with AS
- **Autoimmune hepatitis** in two PSO patients treated with IFX
- TNF inhibitor-associated **dermatomyositis**
- Management of **PSO in pregnancy**: time to deliver?
- Potentially modifiable risk factors for **adverse pregnancy outcomes** in women with PSO
- **Pregnancy during ADA** use for PSO
- **Impact of anti-TNF therapy** on the **weight of patients with RA**
- **A systematic review of the effect of TNF- α antagonists** on **lipid profiles in patients** with rheumatoid arthritis
- **Use of TNF- α inhibitors in hepatitis B surface antigen-positive patients**: a literature review and potential mechanisms of action
- **Angioedema occurring in pediatric patients** with CD treated with ADA
- **Infliximab-related vasculitis** in patients affected by UC
- **Obesity in early adulthood** as a risk factor for PsA

IBD

Gastroenterology. 2010 May 22. [Epub ahead of print]

SONIC finds 2-drug combo twice as effective for Crohn's remission

Lang L.

No abstract available

Gastroenterology 2010; 139: 344-346

Is it time for dosing anti-tnf antibody therapy by serum level?

Kerner C, Aberra F

No abstract available

Journal of Crohn's and Colitis, Published online: 30 June 2010

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, Published online: 01 July 2010

Report of the ECCO workshop on anti-TNF therapy failures in inflammatory bowel diseases: Biological roles and effects of TNF and TNF antagonists

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

Curr Opin Gastroenterol. 2010 Jul;26(4):337-43.

Preventive therapy in postoperative Crohn's disease

Swoger JM, Regueiro M.

PURPOSE OF REVIEW: Recurrence of Crohn's disease following surgical resection is common, but the optimal strategy to assess, prevent, and treat postoperative recurrence remains unclear. Recent developments in the prevention and management of postoperative recurrence have provided additional information. **RECENT FINDINGS:** Predictors of Crohn's disease recurrence after surgery include cigarette smoking, disease behavior, number of prior resections, family history, anastomotic type, and time to first surgery. Only penetrating disease behavior and continued cigarette smoking after surgery remain clear predictors of postoperative Crohn's disease recurrence. Ileocolonoscopy is the only modality to detect mucosal recurrence after surgery; however, surrogate markers of inflammation, specifically stool lactoferrin and calprotectin as well as small intestine contrast ultrasound, are promising. Due to the high rate of surgery for the treatment of complications of Crohn's disease, prevention of postoperative disease has received considerable attention. Recent studies of azathioprine/6-mercaptopurine, nitroimidazole antibiotics, and infliximab have broadened the spectrum of medication options postoperatively. **SUMMARY:** Smoking cessation and ileocolonoscopy for early detection of Crohn's disease recurrence should be part of any postoperative management strategy. The selection of medication and optimal time to initiate treatment after surgery is less certain. Postoperative immunomodulators and antitumor necrosis factor agents may prevent Crohn's disease in those at high risk for recurrence. Treatment of patients by predictors of recurrence and personalization of management based on genotypes/phenotypes will be the focus of future study.

Expert Rev Gastroenterol Hepatol. 2010 Jun;4(3):285-91.

Value of mucosal assessment and biomarkers in inflammatory bowel disease

Stidham RW, Higgins PD.

Clinical remission at a single point in time provides surprisingly little predictive value for future inflammatory bowel disease (IBD) activity owing to the waxing and waning nature of the disease course. Furthermore, patients often present with complications of IBD despite apparent clinical remission, suggesting that undetected subclinical inflammation is driving these complications. This has led to research on a variety of surrogate markers of biologically significant asymptomatic inflammatory disease activity, including endoscopic healing, histologic normalization and biomarkers of inflammation in the blood and stool. If these have strong predictive value, they could be used to risk-stratify patients and justify the early use of immunomodulators and anti-TNF agents. Mucosal healing has been associated with positive outcomes in IBD, but the supporting data are largely retrospective and subject to channeling bias, and it is not clear whether complete mucosal healing produces better outcomes than partial healing. Stool and blood biomarkers correlate well with mucosal inflammation, but are imperfect surrogates for mucosal healing. Before using surrogate markers of intestinal inflammation to justify long-term, potentially toxic and costly therapy, prospective longitudinal studies are needed to identify surrogate end points with cut points that justify changes in therapy, and which therapies provide cost-effective benefits for mild, moderate or severe inflammation.

Curr Opin Gastroenterol. 2010 Jul;26(4):332-6.

Pediatric inflammatory bowel diseases: coming of age

Ruemmele FM.

PURPOSE OF REVIEW: Inflammatory bowel diseases (IBD) comprise a heterogeneous group of distinct intestinal disorders. Here, we discuss the concept of childhood-onset IBD as separate disease forms within a larger multifactorial disease category. **RECENT FINDINGS:** There are excellent epidemiological data indicating that the incidence of pediatric IBD, mainly Crohn's disease, is still increasing over the last decades, with indicators of more extensive and more severe disease presentations in children compared to adults, also reflected by higher levels of humoral immune responses. Recent genetic scans allowed to identify particular susceptibility genes for pediatric IBD forms, such as IL27 or probably DcR3. Early postnatal onset forms of IBD might reflect monogenetic causes, as suggested with the finding of IL10 signaling defects that may define a new form of IBD. **SUMMARY:** There are good epidemiological, genetic and clinical data to distinguish different forms of IBD, particularly forms starting early in life. Profound insights in the molecular basis of immune dysregulation in IBD have been gained over the last few years. These recent discoveries will nourish and substantially stimulate the future search for precise cause(s) responsible for life-long intestinal inflammation and it will help to explain the still ongoing rise in incidence in childhood IBD.

Aliment Pharmacol Ther. 2010; 32: 313-323 [Epub ahead of print]

Systematic review: steroid withdrawal in anti-TNF-treated patients with inflammatory bowel disease

Bultman E, Kuipers EJ, van der Woude CJ.

Summary Background: The increasing awareness of increased risk for opportunistic infections when combining several immunosuppressant drugs led to new treatment goals for inflammatory bowel disease (IBD) including limited use of steroids. **Aim:** We conducted a systematic review to establish steroid withdrawal in anti-TNF treated IBD-patients. **Methods:** Medline was searched using the search-terms Ulcerative Colitis (UC) [Mesh], Crohn Disease (CD) [Mesh], IBD [Mesh], crohn, colitis, IBD and steroid sparing, all combined with infliximab and adalimumab. We selected English-language publications that addressed the effect of anti-TNF on steroid withdrawal. Studies had to assess patients with luminal CD or UC. Numbers of patients able to withdraw steroids were calculated. **Results:** Six studies could be included; five reporting on infliximab and one on adalimumab. Studies were heterogeneously designed. Overall in the adult population up to 38% of the patients were able to withdraw corticosteroids during infliximab therapy. In the pediatric population up to 75% of the patients were able to withdraw corticosteroids during infliximab therapy. **Conclusions:** Although a consensus on the definition of steroid-sparing is lacking, approximately two thirds of the IBD-patients are unable to withdraw corticosteroid treatment during anti-TNF therapy.

Aliment Pharmacol Ther. 2010; 32: 384-393 [Epub ahead of print]

Clinical trial: impact of prior infliximab therapy on clinical response to certolizumab pegol maintenance therapy for Crohn's disease

Hanauer SB, Panes J, Colombel JF, Bloomfield R, Schreiber S, Sandborn WJ.

Summary Background Certolizumab pegol (CZP) is an effective therapy for Crohn's disease refractory to aminosalicylates, corticosteroids, and immunosuppressants. In PRECiSE 2 patients were also eligible for enrollment if prior infliximab therapy was terminated due to loss of response. Aims Evaluation of prior infliximab therapy on sustained response and remission to CZP for Crohn's disease. Methods PRECiSE 2 data was analyzed for predictors of sustained response and remission. Covariates included prior infliximab therapy, and baseline Crohn's Disease Activity Index (CDAI). Results Week 26 response (≥ 100 -point decrease from baseline CDAI) and remission ($\text{CDAI} \leq 150$) were greater with CZP vs. placebo in patients previously receiving infliximab (response: 44.2% vs. 25.5%, $P = 0.018$; remission: 32.7% vs. 13.7, $P = 0.008$) and infliximab-naïve patients (response: 68.7% vs. 39.6%, $P < 0.001$; remission: 52.8% vs. 33.3%, $P < 0.001$). Prior infliximab use was the only independent predictor of Week 26 response and remission in both groups (response $\text{OR}(\text{CZP vs placebo})=3.06$ [95% CI: 1.21-7.77]; remission $\text{OR}(\text{CZP vs placebo})=4.22$ [95% CI: 1.45-12.28]). Adverse events were similar for both groups. Conclusions CZP is an effective maintenance therapy in Crohn's disease regardless of prior infliximab use. Efficacy is higher in patients receiving CZP therapy as a first-line biologic, but approximately 50% of infliximab-experienced patients benefited from second-line CZP therapy.

Am J Gastroenterol. 2010 Jul;105(7):1574-82. Epub 2010 Mar 16.

Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data

Schreiber S, Colombel JF, Bloomfield R, Nikolaus S, Schölmerich J, Panés J, Sandborn WJ; PRECiSE 2 Study Investigators.

OBJECTIVES: We sought to analyze the efficacy (response and remission) and safety data from the PRECiSE 2 trial of certolizumab pegol according to duration of Crohn's disease since diagnosis at baseline. METHODS: Responders to induction treatment with certolizumab pegol at week 6 in PRECiSE 2 ($n=425$) were randomized to receive certolizumab pegol 400 mg ($n=215$) or placebo ($n=210$) until week 26. Logistic regression analysis identified factors linked to Crohn's disease history (short duration, no prior infliximab use, no corticosteroids, no operations) as prognostics of outcome. Efficacy (response, remission) and safety data were reanalyzed according to duration of Crohn's disease since diagnosis at baseline. RESULTS: The proportions of patients in response at study end were inversely related to duration of Crohn's disease. Maintenance of response with certolizumab pegol was achieved in 89.5% of patients with a diagnosis < 1 year ($P < 0.01$ vs. placebo), compared with 57.3% of patients with a diagnosis $> \text{ or } = 5$ years ($P < 0.001$ vs. placebo). Corresponding remission rates were 68.4% ($P < 0.05$ vs. placebo) and 44.3% ($P < 0.001$ vs. placebo), respectively. Response and remission rates did not differ significantly by disease duration in placebo subgroups. Incidences of adverse events were unaffected by duration of disease at baseline. CONCLUSIONS: These data suggest that patients treated with certolizumab pegol 400 mg earlier rather than later, with a confirmed Crohn's disease diagnosis, may achieve better treatment outcomes.

Am J Gastroenterol. 2010 Jul;105(7):1583-5.

Editorial: improved efficacy of biological maintenance therapy in "early" compared with "late" Crohn's disease: strike while the iron is hot with anti-TNF agents?

Ananthakrishnan AN, Binion DG.

There is growing interest in the use of biologic therapy early in the course of Crohn's disease. In this issue, Schreiber et al. use data from the PRECiSE trials to demonstrate a greater response to certolizumab in patients with shorter duration of disease. This suggests that early treatment prior to the occurrence of significant tissue remodeling and irreversible cumulative bowel damage may result in better outcomes. This editorial describes the data published so far on the correlation between disease duration and treatment response and examines the potential benefits to such treatment algorithms.

Aliment Pharmacol Ther. 2010; 32: 459-465 [Epub ahead of print]

Pre-operative management is associated with low rate of post-operative morbidity in penetrating Crohn's disease

Zerbib P, Koriche D, Truant S, Bouras AF, Vernier-Massouille G, Seguy D, Pruvot F, Cortot A, Colombel J.

Abstract Background and Aim: Ileocecal resection for penetrating Crohn's disease is still challenging with a high rate of post-operative morbidity and faecal diversion. We report retrospectively the results of pre-operative management for penetrating Crohn's disease focusing on the rate of post-operative major morbidities and need for faecal diversion. Methods: Between 1997 and 2007, 78 patients with penetrating Crohn's disease underwent a first ileocecal resection after a pre-operative management consisting in bowel rest, nutritional therapy, intravenous antibiotics, weaning off steroids and immunosuppressors, and drainage of abscesses when appropriate. Results: Resection was performed for terminal ileitis associated with fistula (n = 41), abscesses (n = 37) or both (n = 5). A pre-operative nutritional therapy was performed in 50 patients (68%) for 23 days (range, 7 - 69 days) along with a weaning off steroids and immunosuppressors. A diverting stoma was performed for 6 patients (7.7%). There was no post-operative death. Post-operative complications were classified as minor in 10 patients (12.8%), and major in 4 patients (5%). Overall, the post-operative course was uneventful in 58 patients (74%). Conclusion: Pre-operative management for penetrating Crohn's disease allowed ileocecal resection with low rate of post-operative morbidity and faecal diversion.

Aliment Pharmacol Ther. 2010; 32: 510-511 [Epub ahead of print]

Cytomegalovirus affects clinical outcome of infliximab in ulcerative colitis refractory to tacrolimus

Nakase, S. Yamamoto, M. Matsuura, Y. Honzawa, T. Chiba

No abstract available

Expert Rev Clin Immunol. 2010 Jul;6(4):501-4.

Postoperative Crohn's disease: how can we prevent it?

Swoger JM, Regueiro M.

No abstract available

Expert Rev Clin Immunol. 2010 Jul;6(4):537-41.

Role of IL-21 in inflammatory bowel disease

Pallone F, Fina D, Caruso R, Monteleone G.

IL-21 was first described as a critical regulator of T- and B-cell functions. More recently, it has become apparent that IL-21 controls the activity of both immune and nonimmune cells and, depending on the timing and context analyzed, it can promote either inflammatory or counter-regulatory effects. IL-21 participates in the immune responses against tumor cells and chronic viral infections, but excessive production of IL-21 has been associated with the development of immune-inflammatory diseases in various organs. In this article, we focus on data supporting the pathogenic role of IL-21 in human inflammatory bowel diseases and discuss preclinical studies that suggest that neutralization of IL-21 in vivo could be a new strategy to counteract the inflammatory bowel disease-related, tissue damaging immune response.

Expert Rev Clin Immunol. 2010 Jul;6(4):543-50.

Drug targeting strategies for the treatment of inflammatory bowel disease: a mechanistic update

Dahan A, Amidon GL, Zimmermann EM.

The therapeutic management of inflammatory bowel disease (IBD) represents the perfect scenario for drug targeting to the site(s) of action. While existing formulation-based targeting strategies include rectal dosage forms and oral systems that target the colon by pH-, time-, microflora- and pressure-triggered drug release, novel approaches for site-specific delivery in IBD therapy will target the inflamed intestine per se rather than intestinal region. The purpose of this article is to present a mechanistic update on the strategies employed to achieve minimal systemic exposure accompanied by maximal drug levels in the

inflamed intestinal tissue. The introduction of biological agents, micro/nanoparticulate carriers including liposomes, transgenic bacteria, and gene therapy opportunities are discussed, as well as the challenges remaining to be achieved in the targeted treatment of IBD.

Expert Rev Clin Immunol. 2010 Jul;6(4):567-72.

Leukocyte traffic control: a novel therapeutic strategy for inflammatory bowel disease

Fiorino G, Correale C, Fries W, Repici A, Malesci A, Danese S.

Inflammatory bowel diseases share common pathogenetic mechanisms that are not yet completely understood. It is clear, however, that the expression and production of cytokines in response to inflammation plays a key role in mediating the migration of activated leukocytes. The process of angiogenesis and the expression of adhesion molecules on the intestinal microvasculature act as gateways, facilitating the recruitment of leukocytes into the gut mucosa. New agents specifically blocking adhesion molecules, in particular integrins, have been developed in order to limit the passage of activated leukocytes into the mucosa. Non-gut-specific anti-integrin agents, such as natalizumab, have been shown to be effective in the treatment of IBD, but the risk of serious adverse events has limited their further development. The development of a new specific molecule, vedolizumab, is currently under investigation in a large clinical trial. This novel specific anti-integrin drug seems to hold promise in the treatment of gut inflammation.

Expert Rev Clin Immunol. 2010 Jul;6(4):597-605.

Stem cell treatment for Crohn's disease

Panés J, Ordás I, Ricart E.

While stem cell-based treatments have been established as a clinical standard of care for some conditions, such as hematopoietic stem cell transplants for cancer, the scope of potential stem cell-based therapies has expanded in recent years due to advances in stem cell research, paving the way for the increasing utilization of stem cell therapies in severe immune-mediated diseases including inflammatory bowel diseases (IBDs) and, in particular, Crohn's disease. Both hematopoietic stem cells and mesenchymal (stromal) stem cells are considered to be of potential therapeutic benefit in immune-mediated conditions. A growing body of experimental and clinical evidence shows that hematopoietic stem cell transplant induces long-lasting remission in a majority of patients with active severe Crohn's disease refractory to drug treatments, and the differential effect of potent immunosuppression and immune reconstitution in this setting is under evaluation. Mesenchymal stem cells have been shown to exert immunomodulatory action on various types of immune-mediated diseases, and in experimental models of IBD, but evaluation of the potential efficacy of this therapy in IBD is still in the early stages.

Expert Rev Clin Immunol. 2010 Jul;6(4):607-20.

Current status of monoclonal antibody therapy for the treatment of inflammatory bowel disease

Shah B, Mayer L.

Crohn's disease and ulcerative colitis are complex diseases that have required the use of multiple modalities to aid in treatment. With an increasing understanding of the underlying pathogenetic mechanisms and identification of specific therapeutic targets, monoclonal antibody treatment has been an ideal strategy for inducing and maintaining remission in these patients. This article addresses approved agents and the supporting data justifying their use in Crohn's disease and ulcerative colitis, the safety of and immunologic reactions to these agents, as well as newer agents for treatment.

Expert Rev Clin Immunol. 2010 Jul;6(4):659-66.

Use of immunomodulators and biologic therapies in children with inflammatory bowel disease

Bousvaros A.

The immunomodulators (6-mercaptopurine, azathioprine and methotrexate) and biologics (infliximab, adalimumab, certolizumab and natalizumab) are medications essential in the management of pediatric inflammatory bowel disease. If properly utilized, these medications can control active disease, reduce corticosteroid exposure, induce remission, and promote normal growth and development. However, these medications also have significant toxicity and increase the risk of infections and lymphoma. This article

provides information about the safety and efficacy of these medications in the treatment of children with Crohn's disease and ulcerative colitis.

Aliment Pharmacol Ther. 2010 Aug;32(4):522-8. Epub 2010 May 25.

Treatment of ulcerative colitis with adalimumab or infliximab: long-term follow-up of a single-centre cohort

Gies N, Kroeker KI, Wong K, Fedorak RN.

Background Randomized, controlled trials have demonstrated that anti-TNF agents are efficacious in inducing remission in cases of Crohn's disease and ulcerative colitis. However, response rates for anti-TNF agents in 'real life' clinical practice are less well-defined. **Aims** To examine the response rates and long-term outcomes of infliximab and adalimumab treatment for out-patients with ulcerative colitis and to study the variables associated with response rates. **Methods** In a prospective study, a single-centre out-patient cohort was treated and followed up according to a structured protocol of clinical care. Response to treatment was assessed using a physician's global assessment that focused on normalization of bowel frequency, absence of blood with defecation and tapering of corticosteroids to zero. **Results** Fifty-three ulcerative colitis patients were included in the study. Responses to induction therapy were 96.4% (27/28) for infliximab and 80% (20/25) for adalimumab ($P = 0.0889$). Responses to maintenance therapy were similar: infliximab 77.8% (14/18) and adalimumab 70.0% (14/20) ($P = 0.7190$). Multivariate analyses of the induction and maintenance responses did not reveal confounding elements. No new safety signals were identified. **Conclusions** This long-term follow-up of a single-centre cohort of ulcerative colitis patients demonstrates that 'real-life' out-patient treatment with infliximab and adalimumab is effective in induction and maintenance of response.

Inflamm Bowel Dis. 2010 Aug;16(8):1367-75.

Serum anti-glycan antibodies predict complicated Crohn's disease behavior: a cohort study

Rieder F, Schleder S, Wolf A, Dirmeier A, Strauch U, Obermeier F, Lopez R, Spector L, Fire E, Yarden J, Rogler G, Dotan N, Klebl F.

BACKGROUND: A high proportion of patients with Crohn's disease (CD) over time develop complications like fistulae and strictures, requiring surgery. We tested a panel of antiglycan antibodies for predicting the occurrence of complications and CD-related surgery in an adult patient cohort. **METHODS:** Serum samples of 149 CD patients of the German inflammatory bowel disease (IBD) network were tested for the presence of anti-laminarin IgA (Anti-L), anti-chitin IgA (Anti-C), anti-chitobioside IgA (ACCA), anti-laminaribioside IgG (ALCA), anti-mannobioside IgG (AMCA), and anti-Saccaromyces cerevisiae IgG (gASCA) carbohydrate antibodies by enzyme-linked immunosorbent assay (ELISA) (IBDX(R) panel, Glycominds, Lod, Israel) in a blinded fashion. Clinical data were available on occurrence of complicated disease or CD-related surgery as well as disease activity, onset, and location. **RESULTS:** The median follow-up of the patients without any previous complication or surgery at time of sample procurement was 53.7 months. Overall, 26.3% developed a complication and 17.1% underwent CD-related surgery, respectively. Positivity for gASCA, AMCA, ACCA, and Anti-L alone or an increasing frequency of positive serum antibodies independently predicted a faster progression toward a more severe disease course. Once a complication or surgery had occurred only positivity for Anti-L or more than 3 markers out of the whole panel indicated progression to an additional surgery or complication. The antibody status of most patients remained stable over time. **CONCLUSIONS:** This is the first study showing the clinical value of serum antiglycan antibodies for prediction of a more complicated disease course in adult patients with CD.

Inflamm Bowel Dis. 2010 Aug;16(8):1421-30.

Efficacy of methotrexate in ulcerative colitis: failure or promise

Herfarth HH, Osterman MT, Isaacs KL, Lewis JD, Sands BE.

BACKGROUND: Low-dose methotrexate is a widely used and efficacious therapy in chronic inflammatory disorders such as psoriasis and rheumatoid arthritis. Prospective randomized controlled trials have demonstrated the efficacy of parenteral methotrexate in Crohn's disease (CD). We performed a systematic review of the efficacy of methotrexate in ulcerative colitis (UC) and discuss the results in the context of the known pharmacokinetics and adverse events of methotrexate therapy in inflammatory bowel diseases and other inflammatory conditions. **MATERIALS AND METHODS:** We performed a

systematic review of the literature in Medline, Embase, and Web of Science. All publications describing patients with UC treated with methotrexate were included. **RESULTS:** We identified 12 studies or retrospective case series and 5 meeting abstracts that met the inclusion criteria. Only 1 study reported a prospective randomized placebo-controlled trial using methotrexate at a dose of 12.5 mg orally with no significant clinical benefit. However, the majority of uncontrolled retrospective analyses suggest a clinical response to methotrexate therapy in a range of 30%-80% when the drug is applied by parenteral route in doses between 20-25 mg. **CONCLUSIONS:** The only randomized controlled trial of methotrexate in UC employed oral dosing and doses lower than those shown to be effective in CD and did not demonstrate efficacy, whereas uncontrolled, retrospective studies using doses and routes of administration similar to those employed in CD suggest benefit. Well-designed, prospective, placebo-controlled trials of methotrexate in UC are needed.

Inflamm Bowel Dis. 2010 Aug;16(8):1431-42.

Nonfistulizing perianal Crohn's disease: clinical features, epidemiology, and treatment

Bouguen G, Siproudhis L, Bretagne JF, Bigard MA, Peyrin-Biroulet L.

Nonfistulizing perianal lesions, including ulcerations, strictures, and anal carcinoma, are frequently observed in Crohn's disease. Their clinical course remains poorly known. The management of these lesions is difficult because none of the treatments used is evidence-based. Ulcerations may be symptomatic in up to 85% of patients. Most ulcerations heal spontaneously but may also progress to anal stenosis or fistula/abscess. Topical treatments only improve symptoms, while complete healing can occur in patients with perianal ulcerations receiving infliximab therapy. Half of all patients with anal strictures will require permanent fecal diversion. Dilatation for symptomatic strictures should be performed on a highly selective basis in the absence of active rectal disease in order to avoid infectious complications. Anorectal strictures associated with rectal lesions should first be managed with medical therapy. Skin tags are usually painless and may hide other perianal lesions. Anal cancer is uncommon. Its treatment is similar to that recommended for anal cancer occurring in non-Crohn's disease patients. After reviewing the classification, clinical features, and epidemiology of each type of nonfistulizing perianal lesion (ulceration, stricture, skin tags, and anal cancer), we discuss the efficacy of medical treatment and surgery. This review article may help physicians in decision-making when managing potentially disabling lesions.

J Gastrointestin Liver Dis. 2010 Jun;19(2):147-53.

Ultrastructural evidence of mucosal healing after infliximab in patients with ulcerative colitis

Fratila OC, Craciun C.

BACKGROUND: Infliximab is a monoclonal anti-TNF-alpha antibody that has been shown to be effective in Crohn's disease therapy. However, data are scarce about the mechanism of action and its efficacy in ulcerative colitis (UC). **AIM:** To assess intracellular changes of the colonic mucosa in patients with UC before and after infliximab treatment. **METHODS:** 7 patients (18-65 years, 4 men) with active, refractory, moderate to severe UC (Lichtiger's Clinical Activity Index > 6, Endoscopic Index > 4) underwent colonoscopy before and 4 weeks after the initial infusion of infliximab 5mg/kg of body weight. Endoscopically obtained biopsy specimens were processed specifically, stained with uranyl-acetate and lead citrate and examined with a JEOL-1010 transmission electron microscope. **RESULTS:** Before treatment we noticed severe alterations of the epithelium: microvilli depletion, shattering of the epithelial junctions, cytoplasmic vacuolization, dilatation of the endoplasmic reticulum, pycnotic nuclei, altered structure of mitochondria and Golgi complexes. Rarefaction of the goblet cells, and abnormal mucus formation and secretion were also observed. The corresponding chorion showed structural alteration of component cells, obstructed capillaries, erythrocyte extravasation, and many plasmocytes and neutrophils. After infliximab, improvement in morphology and function of the epithelial organelles, rich mucus secretion and recovery of the chorionic components were noticed. **CONCLUSIONS:** Our study revealed important intracellular alterations of the UC mucosa that were restored after infliximab therapy. These features may contribute to a better understanding of UC pathogenesis and mechanism of action of the anti-TNF-alpha therapies.

Dig Dis Sci. 2010 Jun;55(6):1674-80. Epub 2009 Aug 20.

Response to medical treatment in patients with Crohn's disease: the role of NOD2/CRAD15, disease phenotype, and age of diagnosis

Weiss B, Lebowitz O, Fidler HH, Maza I, Levine A, Shaoul R, Reif S, Bujanover Y, Karban A.

PURPOSE: Factors influencing response to medications in Crohn's disease (CD) patients are not fully understood. We aimed to evaluate the relationships between NOD2/CARD15 mutations, disease phenotype and age of CD diagnosis and response to medical treatment with systemic steroids, azathioprine (AZA) or 6-mercaptopurine (6-MP), and infliximab. **METHODS:** A retrospective medical records analysis was made of patients previously tested for the CD-associated NOD2/CARD15 mutations. Harvey-Bradshaw score was used to assess remission or response to therapy. **RESULTS:** CD-associated NOD2/CARD15 mutations were not related to the rate of steroids dependency or clinical response to AZA/6-MP and infliximab. Steroid dependency was associated with colonic involvement. Thirty-three of 127 (26%) patients with colonic disease were steroid dependent, compared with 7/72 (9.7%) patients with isolated small bowel disease (ISBD), ($p = 0.009$). ISBD was mildly associated with a better remission/response to AZA/6-MP treatment. Disease behavior and age of diagnosis were not related to response to therapy. **CONCLUSIONS:** Response to treatment with systemic steroids, AZA/6-MP and infliximab are not related to NOD2/CARD15 mutations, age of diagnosis and disease behavior. Patients with colonic disease have higher rates of steroid dependency.

Eur Rev Med Pharmacol Sci. 2010 Apr;14(4):342-6.

New biological agents for the treatment of the "high risk" IBD patients

Guidi L, Marzo M, Felice C, Mocci G, Sparano L, Pugliese D, De Vitis I, Papa A, Armuzzi A.

BACKGROUND: Several new biological drugs have been introduced in the last decade or are under investigation for the treatment of IBD. They include anti TNF α agents, anti adhesion molecules, anti IL-12/23, anti IL-6R and others. Their role in IBD therapy will be discussed in regard of the association of chronic inflammation and cancer in the gut. The risk of colorectal cancer is increased in ulcerative colitis (UC) and, to some extent, in Crohn's disease (CD). This association is well known from many years. However, the mechanisms linking chronic inflammation and carcinogenesis are beginning to be elucidated only recently. **RESULTS AND CONCLUSIONS:** Experimental data indicate that several cytokines could play a role in promoting tumour development. In this perspective, the anti cytokine agents could be not only powerful tools in treating inflammation but also efficacious in preventing the onset of inflammation associated colorectal cancer.

J Pediatr Gastroenterol Nutr. 2010 Aug;51(2):140-145.

Extraintestinal Manifestations of Pediatric Inflammatory Bowel Disease and Their Relation to Disease Type and Severity

Dotson JL, Hyams JS, Markowitz J, Leleiko NS, Mack DR, Evans JS, Pfefferkorn MD, Griffiths AM, Otley AR, Bousvaros A, Kugathasan S, Rosh JR, Keljo D, Carvalho RS, Tomer G, Mamula P, Kay MH, Kerzner B, Oliva-Hemker M, Langton CR, Crandall W.

OBJECTIVES: Although it is known that extraintestinal manifestations (EIMs) commonly occur in pediatric inflammatory bowel disease (IBD), little research has examined rates of EIMs and their relation to other disease-related factors in this population. The purpose of this study was to determine the rates of EIMs in pediatric IBD and examine correlations with age, sex, diagnosis, disease severity, and distribution. **PATIENTS AND METHODS:** Data were prospectively collected as part of the Pediatric IBD Collaborative Research Group Registry, an observational database enrolling newly diagnosed IBD patients <16 years old since 2002. Rates of EIM (occurring anytime during the period of enrollment) and the aforementioned variables (at baseline) were examined. Patients with indeterminate colitis were excluded from the analysis given the relatively small number of patients. **RESULTS:** One thousand nine patients were enrolled (mean age 11.6 \pm 3.1 years, 57.5% boys, mean follow-up 26.2 \pm 18.2 months). Two hundred eighty-five (28.2%) patients experienced 1 or more EIMs. Eighty-seven percent of EIM occurred within the first year. Increased disease severity at baseline (mild vs moderate/severe) was associated with the occurrence of any EIM ($P < 0.001$), arthralgia ($P = 0.024$), aphthous stomatitis ($P = 0.001$), and erythema nodosum ($P = 0.009$) for both Crohn disease (CD) and ulcerative colitis (UC) during the period of follow-up. Statistically significant differences in the rates of EIMs between CD and UC were seen for aphthous stomatitis, erythema nodosum, and sclerosing cholangitis. **CONCLUSIONS:** EIMs as defined in this study occur in approximately one quarter of pediatric patients with IBD. Disease type and disease severity were commonly associated with the occurrence of EIMs.

J Pediatr Gastroenterol Nutr. 2010 Aug;51(2):151-4.

Postoperative outcome of colectomy for pediatric patients with ulcerative colitis

Patton D, Gupta N, Wojcicki JM, Garnett EA, Nobuhara K, Heyman MB.

BACKGROUND:: Few studies have reported on the surgical outcomes of colectomy in pediatric patients with ulcerative colitis (UC). **PATIENTS AND METHODS::** We conducted a retrospective chart review of all pediatric patients diagnosed with UC who underwent colectomy at UCSF between 1980 and 2005 to identify early (within 30 days) and later complications of surgery. **RESULTS::** Complete medical records were available for 31 patients [12.4 +/- 3.3 (range 6-19) years] with UC who underwent colectomy at UCSF Children's Hospital. Total colectomy with ileal pouch anal anastomosis (IPAA) was performed in 21 of the 31 patients (12 without diverting ileostomy). Five of the 31 patients had an initial colectomy with IPAA and J-pouch performed later; 4 had an initial subtotal colectomy for urgent indications. Only one of 31 had IPAA with S-pouch. The median number of early postoperative complications was 1.0; 4 required additional surgery to treat complications. The most common early complications were small intestinal obstruction in 6 (19%) and wound infection in 4 (13%). Preoperative medications included corticosteroids in 25 (81%), 6-mercaptopurine/azathioprine in 10 (32%), and 5-aminosalicylates in 19 (61%). Medication exposure was not related to postoperative complications. Late complications included pouchitis in 12 (39%), anastomotic, anal, or rectal strictures in 5 (16%), and fistulas in 5 (16%); 1 (3%) was subsequently diagnosed as having Crohn disease. **CONCLUSIONS::** Postcolectomy morbidity is common among pediatric patients with UC. Preoperative medications were not associated with postoperative complications. Investigations to determine preoperative factors affecting surgical outcomes and long-term satisfaction following this surgery in a large pediatric cohort are needed.

J Pediatr Gastroenterol Nutr. 2010 Jul;51(1):35-40.

Quality of life in children with crohn disease

Hill R, Lewindon P, Muir R, Grangé I, Connor F, Ee L, Withers G, Cleghorn G, Davies P.

OBJECTIVES:: Quality of life (QOL) is reportedly poor in children with Crohn disease (CD) but improves with increasing disease duration. This article aims to detail QOL in a cohort of Australian children with CD in relation to disease duration, disease activity, and treatment. **MATERIALS AND METHODS::** QOL, assessed using the IMPACT-III questionnaire, and disease activity measures, assessed using the Pediatric Crohn's Disease Activity Index (PCDAI), were available in 41 children with CD. For this cohort, a total of 186 measurements of both parameters were available. **RESULTS::** QOL was found to be significantly lower, and disease activity significantly higher ($F = 31.1$, $P = 0.00$), in patients within 6 months of their diagnosis compared with those up to 2.5 years, up to 5 years, and beyond 5 years since diagnosis. Higher disease activity was associated with poorer QOL ($r = -0.51$, $P = 0.00$). Total QOL was highest in children on nil medications and lowest in children on enteral nutrition. The PCDAI ($t = -6.0$, $P = 0.00$) was a significant predictor of QOL, with the clinical history ($t = -6.9$, $P = 0.00$) and examination ($t = -2.9$, $P = 0.01$) sections of the PCDAI significantly predicting QOL. Disease duration, age, or sex was neither related to nor significant predictors of QOL, but height z score and type of treatment approached significance. **CONCLUSIONS::** Children with CD within 6 months of their diagnosis have impaired QOL compared with those diagnosed beyond 6 months. These patients, along with those with growth impairment, ongoing elevated disease activity with abdominal pain, diarrhoea and/or perirectal and extraintestinal complications, may benefit from regular assessments of QOL as part of their clinical treatment.

Safety

J Rheumatol. 2010 Jul;37(7):1542; author reply 1543.

Tumor necrosis factor-alpha blocker induced tuberculosis

Kharbanda P, Dagaonkar R, Balakrishnan C, Udwadia ZF.

No abstract available

J Rheumatol. 2010 Jul;37(7):1549-50.

Dermatomyositis during adalimumab therapy for rheumatoid arthritis

Brunasso AM, Scocco GL, Massone C.

No abstract available

J Rheumatol. 2010 Jul;37(7):1551.

Measuring multiple etanercept levels in the breast milk of a nursing mother with rheumatoid arthritis

Keeling S, Wolbink GJ.

No abstract available

Aliment Pharmacol Ther. 2010 Apr 16. [Epub ahead of print]

Review article: malignancy on thiopurine treatment with special reference to inflammatory bowel disease

Smith MA, Irving PM, Marinaki AM, Sanderson JD.

Abstract Background: Immunosuppression is a risk factor for carcinogenesis. Thiopurines specifically contribute to this. As thiopurines are used more aggressively in the treatment of IBD, it is likely that we will see more thiopurine-related malignancy. Aim: To review the literature, exploring how immunosuppression, thiopurines specifically, might cause cancer and which malignancies occur in practice, placing specific emphasis on IBD cohorts. Methods: Search terms included "malignancy""cancer""azathioprine""mercaptopurine""thioguanine""thiopurine" and "inflammatory bowel disease""crohn's disease""ulcerative colitis". We also searched for specific cancers (lymphoma, colorectal cancer, skin cancer, cervical cancer) and reviewed the reference lists of the articles detected. Results: Immunosuppression is associated with an increased risk of cancer. Thiopurines are associated with specific additional risks. In IBD cohorts very few thiopurine-related malignancies have been reported. However, studies suggest a relative risk of 4-5 for lymphoma. This still translates to a low actual risk, (one extra lymphoma in every 300-1400 years of thiopurine treatment). Conclusion: Whilst we must be aware of this risk and counsel our patients appropriately, thiopurines remain a mainstay of IBD therapy. We present practical advice aimed at minimising our patients' risk of developing malignancy, whilst optimising the benefits that thiopurines can provide.

Journal of Crohn's and Colitis, Published online: 28 June 2010

Hepatosplenic T-cell lymphoma and inflammatory bowel disease

Thai A, Prindiville T

No abstract available

J Cell Physiol. 2010 Aug;224(2):316-26.

Early years of biological agents therapy in Crohn's disease and risk of the human polyomavirus JC reactivation

Bellizzi A, Barucca V, Fioriti D, Colosimo MT, Mischitelli M, Anzivino E, Chiarini F, Pietropaolo V.

Although the remarkable efficacy of biological therapy has resulted in significant success in inflammatory bowel disease (IBD) management, susceptibility to infections remains a concern. The biological agents include the tumor necrosis factor-alpha (TNF-alpha) inhibitors, for instance infliximab, and other immunomodulating agents, such as natalizumab. Progressive multifocal leukoencephalopathy (PML), a rare but mostly fatal opportunistic brain infection caused by reactivation of the human polyomavirus JC virus (JCV), has been found in two patients with multiple sclerosis and one patient with Crohn's disease (CD), linked to treatment with natalizumab. After these cases of PML, the commercial and investigational use of natalizumab was suspended in February 2005 but was subsequently resumed for multiple sclerosis and for CD, only through a special restricted distribution program. This review, starting from an extensive literature search by the PubMed database, resumes the clinical aspects and pathophysiology of CD and focuses on the biologics in current use in CD (infliximab, adalimumab, and natalizumab), in order to provide a reference and gateway to prevention, recognition, and management of JCV, in the early

years of biological agents therapy. It also proposed to provide an overview on the hypothetical mechanism of reactivation of JC virus related to the use of these drugs.

Ann Rheum Dis. 2010 Jun 28. [Epub ahead of print]

Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis

Solomon DH, Love TJ, Canning C, Schneeweiss S.

OBJECTIVE: To examine the risk of diabetes mellitus (DM) among subjects with rheumatoid arthritis (RA), psoriatic arthritis or psoriasis (PsA/PsO), compared with non-rheumatic controls. **METHODS:** Study cohorts were assembled using linked healthcare utilisation data from British Columbia. All people with at least two diagnoses of RA or PsA/PsO were included and compared with a cohort of people without any known rheumatic disease. The outcome of interest was a diagnosis of new-onset DM, as defined by initiation of an antidiabetic drug. Incidence rates (IRs) per 1000 person-years and IR ratios were calculated and Cox regression models were constructed to determine the hazard ratio (HR) for diabetes by age, gender, systemic immunosuppressive drug and glucocorticoid use. **RESULTS:** The study cohort comprised 48 718 subjects with RA, 40 346 with PsA/PsO and 442 033 without any rheumatic disease. The IR for DM among subjects with RA was 8.6 per 1000 person-years (95% CI 8.5 to 8.7), PsA/PsO 8.2 (95% CI 8.1 to 8.3) and for non-rheumatic controls 5.8 (95% CI 5.8 to 5.8). The adjusted HR for RA compared with non-rheumatic controls was 1.5 (95% CI 1.4 to 1.5) and 1.4 (95% CI 1.3 to 1.5) for PsA/PsO. **CONCLUSIONS:** RA and PsA/PsO appear to be associated with an increased risk of DM. The ability of potent antirheumatic treatments to reverse this trend warrants study.

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

Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis

Collamer AN, Battafarano DF.

OBJECTIVE: The induction or exacerbation of psoriasis in patients treated with tumor necrosis factor (TNF) antagonists is a well-established phenomenon. The goals of this comprehensive literature analysis were to update currently available data regarding this adverse event, to identify any clinical patterns in the cohort of reported patients, and to review the possible immunopathogenesis. **METHODS:** A systematic literature review was performed utilizing PubMed and Medline databases (1996 to August 2009) searching the index terms "tumor necrosis factor alpha inhibitor," "TNF," "infliximab," "etanercept," "adalimumab," combined with the terms "psoriasis," "pustular," "skin," "rash," "palmoplantar," and "paradoxical." All relevant articles were reviewed. Patients who did not appear to meet accepted classification criteria for their treated disease, who had a more probable explanation or other likely diagnosis for their skin findings or known possible triggering factor for the skin eruption, including infection, were excluded from this analysis. **RESULTS:** Two hundred seven cases met inclusion criteria for review. Of these, 43% were diagnosed with rheumatoid arthritis, 26% with seronegative spondyloarthritis, and 20% with inflammatory bowel disease. Mean patient age was 45 years and 65% were female. Fifty-nine percent were being treated with infliximab, 22% with adalimumab, and 19% with etanercept. Lesion morphology included pustular psoriasis in 56%, plaque psoriasis in 50%, and guttate lesions in 12%; 15% experienced lesions of more than 1 type. No statistically significant predisposing factors for the development of new-onset psoriasis were found. Sixty-six percent of patients were able to continue TNF antagonist therapy with psoriasis treatments. The pathogenesis appears to involve disruption of the cytokine milieu with production of unopposed interferon-alpha production by plasmacytoid dendritic cells in genetically predisposed individuals. Genetic polymorphisms may play a role in this paradoxical reaction to TNF blockade. **CONCLUSIONS:** TNF antagonist induced psoriasis is a well-described adverse event without any known predisposing risk factors. Most patients can be managed conservatively without drug withdrawal. Registry data reporting is necessary to define the true incidence and prevalence of this condition. Genomic studies of affected patients may assist with identification of predisposed patients and elucidation of the molecular trigger of this perplexing response.

Ann Rheum Dis. 2010 Jul 5. [Epub ahead of print]

Common vaccinations among adults do not increase the risk of developing rheumatoid arthritis: results from the Swedish EIRA study

Bengtsson C, Kapetanovic MC, Källberg H, Sverdrup B, Nordmark B, Klareskog L, Alfredsson L; EIRA Study Group.

OBJECTIVE: To investigate the association between vaccinations in adults and the risk of developing rheumatoid arthritis (RA). **METHODS:** Data from the Swedish population-based Epidemiological Investigation of RA case-control study encompassing 1998 incident cases of RA aged 18-70 years and 2252 randomly selected controls matched for age, sex and residency were analysed. Those vaccinated within 5 years before disease onset were compared with those not vaccinated by calculating OR with 95% CI. **RESULTS:** Vaccinations neither increased the risk of RA overall (OR 1.0, 95% CI 0.9 to 1.1) nor the risk of two major subgroups of RA (antibodies to citrullinated peptide-positive (ACPA-positive) and ACPA-negative disease). Furthermore, vaccinations did not increase the risk of RA in smokers or carriers of HLA-DRB1 shared epitope alleles, two groups with established risk factors for RA. **CONCLUSIONS:** In this case-control study of incident cases of newly diagnosed RA, no increased risk of RA following immunisation was observed for vaccinations overall or for any specific vaccination. This indicates that immunological provocation of adults with commonly used vaccines in their present form carries no risk of RA. These findings should be implemented among public healthcare providers in order to encourage vaccinations according to recommended national vaccination schedules.

Am J Gastroenterol. 2010 Jul;105(7):1604-9. Epub 2010 Jan 26.

Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study

Armstrong RG, West J, Card TR.

OBJECTIVES: Azathioprine is an accepted treatment of inflammatory bowel disease (IBD), but concerns exist regarding its carcinogenic potential. Studies in renal transplant and rheumatology patients have reported an increased cancer risk. In IBD, studies suggest a small increased risk of lymphoma and protection against colorectal cancer, but the overall risk of malignancy has not been established. **METHODS:** We conducted a nested case-control study using the General Practice Research Database. Records of IBD patients were examined for azathioprine prescriptions and cancers. Prescriptions per year of follow-up were grouped for analysis. Azathioprine use was compared between IBD cases (with a diagnosed cancer) and IBD controls (without). **RESULTS:** Overall, 15,471 patients with IBD and over 1 year of appropriate data were identified. Among these, 392 developed cancer, of whom 10.5% received at least one prescription for azathioprine, compared with 1,914 (12.7%) of the controls. Analyzing the occurrence of any cancer against azathioprine prescription showed a nonsignificant protective effect (odds ratio (OR)=0.92, 95% confidence interval (CI)=0.79-1.06). Correction for the effects of age and smoking removed this effect (OR=1.04, 95% CI=0.89-1.21). Diagnosis of lymphoma was associated with ever use of azathioprine with OR of 3.22, CI=1.01-10.18. **CONCLUSIONS:** We found evidence of an increased risk of lymphoma, which is consistent with previous studies. We found no overall increase in risk of cancer in individuals with IBD who had taken azathioprine. Our study does not show a need for azathioprine cessation in the medium term in IBD because of the risk of malignancy.

Expert Rev Clin Immunol. 2010 Jul;6(4):621-31.

Update on the risk of lymphoma following immunosuppressive therapy for inflammatory bowel disease

Bewtra M, Lewis JD.

The care of inflammatory bowel disease has changed considerably with the introduction of a number of immunosuppressants including anti-metabolite and anti-TNF therapies. While efficacious, these medications also carry important risks, notably the potential risk of lymphoma. This risk is one of the most worrisome for both patients and physicians. Our current knowledge is still evolving; however, our understanding of what risks these drugs carry, both individually and synergistically, is critical in allowing informed decision making. In this article, we will describe the known lymphoma risks of commonly used immunosuppressant medications in inflammatory bowel disease, with an emphasis on non-Hodgkin's lymphoma and hepatosplenic T-cell lymphoma.

Inflamm Bowel Dis. 2010 Aug;16(8):1271-2.

Should patients under long-term anti-TNF therapies be followed for tuberculosis contamination?

Reenaers C, Belaiche J, Louis E.

No abstract available

Inflamm Bowel Dis. 2010 Aug;16(8):1443-4.

The good, the bad, and the ugly: adverse events and Crohn's therapies

Siao D, Velayos FS.

No abstract available

Rheumatology (Oxford). 2010 Jul 7. [Epub ahead of print]

Safety and retention rate of off-label uses of TNF antagonists in rheumatic conditions: data from the Spanish registry BIOBADASER 2.0.

Carmona L, Descalzo MA, Ruiz-Montesinos D, Manero-Ruiz FJ, Perez-Pampin E, Gomez-Reino JJ; on behalf of the BIOBADASER 2.0 Study Group.

Objective. To compare the safety and retention rate of TNF antagonists used in approved indications (AIs) and non-AIs. **Methods.** Analysis of the Spanish registry BIOBADASER 2.0 (February 2000 to October 2009). Patients were classified into AIs and off-label uses (OUs), according to the European Medicines Agency approval. Retention rates, incidence rates (IRs) and IR ratios (IRRs) of adverse events (AEs) with 95% CI were compared between uses, by log-rank test, cause-specific Cox regression models and generalized linear models with Poisson's distribution. **Results.** First treatment with TNF antagonist was available in 5150 patients, of whom 4594 (89%) were AIs (2854 RA, 882 AS and 858 PsA) and 556 (11%) were OUs [437 chronic arthropathies in the spectrum of SpAs (CA) and 119 chronic immune-mediated diseases (CIDs)]. The IR of AE was largest in CID (649 events per 1000 patient-years) and lowest in PsA (250 events per 1000 patient-years). The occurrence of AEs was significantly associated with OU [IRR of CA vs RA 1.33 (95% CI 1.19, 1.49); IRR of CID vs RA 1.94 (95% CI 1.62, 2.31)]. The largest hazard ratio for discontinuation was for CID vs RA (1.33; 95% CI 1.02, 1.71) and especially vs AS (2.18; 95% CI 1.63, 2.90). **Conclusions.** OUs of TNF antagonists need a very close ascertainment of risk/benefit. The safety and retention pattern for CID is similar to that for RA and the pattern for CA resembles that of AS. This study shows an additional value of a national registry.

Rheumatology (Oxford). 2010 Aug;49(8):1600-2. Epub 2010 Apr 5.

Whipple's endocarditis as a complication of tumour necrosis factor-alpha antagonist treatment in a man with ankylosing spondylitis

Daïen CI, Cohen JD, Makinson A, Battistella P, Bilak EJ, Jorgensen C, Reynes J, Raoult D.

No abstract available

J Am Acad Dermatol. 2010 Aug;63(2):e43-4.

Autoimmune hepatitis in two psoriasis patients treated with infliximab

Goujon C, Dahel K, Bérard F, Guillot I, Gunera-Saad N, Nicolas JF.

No abstract available

Arch Dermatol. 2010 Jul;146(7):780-4.

Tumor necrosis factor inhibitor-associated dermatomyositis

Klein R, Rosenbach M, Kim EJ, Kim B, Werth VP, Dunham J.

BACKGROUND: Dermatomyositis is an autoimmune disease of unknown etiology characterized by inflammation of the skin and muscles. Several medications have been implicated in the development of dermatomyositis; however, the disease has rarely been linked to the use of tumor necrosis factor (TNF) inhibitors. We report 4 cases of dermatomyositis that developed or were exacerbated by exposure to the TNF inhibitors etanercept and adalimumab. **Observation** Four patients with symptoms of inflammatory arthritis were treated with TNF inhibitors for a duration ranging from 2 months to 2 years. All 4 patients developed symptoms consistent with dermatomyositis, including inflammatory rash and muscle weakness. Their symptoms persisted after discontinuation of the treatment with the TNF inhibitors but responded to treatment with corticosteroids and immunosuppressive medications. **CONCLUSIONS:** Tumor necrosis factor inhibitors have been associated with the onset of a number of autoimmune

disorders, most commonly vasculitis and a lupuslike syndrome. Rarely have they been associated with dermatomyositis. The 4 cases reported herein indicate that TNF inhibitor use can be associated with either induction or exacerbation of dermatomyositis.

Br J Dermatol 2010; 163(2): 235

Management of psoriasis in pregnancy: time to deliver?

C.E.M. Griffiths

No abstract available

Br J Dermatol. 2010; 163: 334-339

Potentially modifiable risk factors for adverse pregnancy outcomes in women with psoriasis

Bandoli G, Johnson DL, Jones KL, Lopez Jiminez J, Salas E, Mirrasoul N, Van Voorhees AS, Chambers CD.

Abstract Background: Data on pregnancy outcomes among women with psoriasis are lacking. However, there are several known comorbidities of psoriasis, including obesity, smoking, and depression each of which increases the risk for negative birth outcomes. Objectives: The purpose of this study was to determine if pregnant women with psoriasis have an excess of potentially modifiable risk factors for adverse pregnancy outcomes. Patients/Methods: Prospectively collected data from the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project were analyzed to compare the prevalence of selected risk factors between 170 pregnant women with psoriasis and 158 non-diseased controls. Results: Women with psoriasis were more likely to be overweight/obese prior to pregnancy ($p < 0.0001$), smoke ($p < 0.0001$), or have a diagnosis of depression ($p = 0.03$), and were less likely to have been taking pre-conceptional vitamin supplements ($p = 0.004$). After controlling for race/ethnicity and socio-economic status, women with psoriasis were 2.37 (95% CI, 1.45, 3.87) times more likely to be overweight/obese as women without psoriasis. Duration of disease, age at onset, measures of disease impact during pregnancy, or use of biologics in pregnancy were not significant predictors of overweight/obesity in the subset of psoriatic women. Conclusions: Pregnant women with psoriasis may be at increased risk for adverse pregnancy outcomes due to comorbidities or other health behaviors associated with the disease. These should be taken into consideration during clinical treatment of women with psoriasis who are in their childbearing years.

J Eur Acad Dermatol Venereol. 2010 Jun 21. [Epub ahead of print]

Pregnancy during adalimumab use for psoriasis

Dessinioti C, Stefanaki I, Stratigos A, Kostaki M, Katsambas A, Antoniou C.

No abstract available

Ann Rheum Dis. 2010 Aug;69(8):1571. Epub 2010 Apr 13.

Impact of anti-tumour necrosis factor therapy on the weight of patients with rheumatoid arthritis

Alcorn N, Tierney A, Wu O, Gilmour H, Madhok R.

No abstract available

Clin Rheumatol. 2010 Sep;29(9):947-55. Epub 2010 Apr 10.

A systematic review of the effect of TNF-alpha antagonists on lipid profiles in patients with rheumatoid arthritis

Pollono EN, Lopez-Olivo MA, Lopez JA, Suarez-Almazor ME.

Atherosclerosis plays a key role in cardiovascular disease in patients with rheumatoid arthritis (RA). Although therapy with TNF-alpha antagonists has resulted in dramatic improvement in the prognosis of RA, its effects on circulatory lipids are unclear. We conducted a systematic review of the literature to summarize the available evidence on lipid profile modification in patients with RA treated with TNF-alpha antagonists, with extensive searches in PubMed, the Cochrane Collaboration database (Central), and SCOPUS. Twenty-four observational studies met the inclusion criteria; 12 included only patients with RA

treated with infliximab and three, patients with RA treated with adalimumab. The other nine included a mix of patients with various rheumatic diseases, or receiving one of several TNF-alpha antagonists. Eleven studies found a statistically significant increase in total cholesterol (TC) and high-density lipoprotein (HDL); six of 20 found significant increases in triglycerides (TG). Four of 13 studies found a statistical increase in low-density lipoprotein. No major changes were observed for ApoB/ApoA1 ratios. A small trend to increased TC was observed in patients receiving TNF-alpha antagonists, mostly due to an increase in HDL. There was a small trend to increased TG, and no changes in ApoB/ApoA1 ratio. The clinical impact of these findings is unclear, and further studies are needed to clarify the role of these lipid changes on cardiovascular morbidity in RA.

Clin Rheumatol. 2010 Sep;29(9):1021-9. Epub 2010 Jun 16.

Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action

Carroll MB, Forgiione MA.

As a class, tumor necrosis factor (TNF)-alpha inhibitors have provided clinicians significant control over chronic inflammatory diseases. With their widespread use has come the emergence of new side effects such as the reactivation of latent infections. One such infection that may reactivate is the hepatitis B virus (HBV). It is currently unknown if HBV reactivation is a class effect or attributable to a particular TNF-alpha inhibitor. To answer this question, a comprehensive literature review to identify trends in related cases was performed. A systemic literature review was performed using the PubMed and Medline databases (1996 to January 2010) searching for the index term "Hepatitis B" combined with the terms "tumor necrosis factor," "TNF-alpha inhibitors," "etanercept," "adalimumab," "certolizumab," and "golimumab." All relevant articles in English were reviewed, and secondary references of interest were also retrieved. Thirty-five cases with hepatitis B surface antigen (HBsAg) positivity known prior to initiation of TNF-alpha inhibitors were identified. Infliximab was used in 17 cases, etanercept in 12 cases, and adalimumab in 6 cases. All six cases of clinically symptomatic hepatitis were associated with infliximab therapy. Infliximab was associated with the most cases of greater than 2-fold increase in alanine aminotransferase (six of nine cases) and greater than 1,000-fold increase in HBV DNA load (three of four). The two deaths reported occurred with infliximab therapy. Potential mechanisms of action for the reported observations include differences in molecular design, route of administration, and potency in clearing TNF-alpha. In patients with a positive HBsAg prior to starting a TNF-alpha inhibitor, infliximab has the most reported cases associated with HBV reactivation. While such reactivation may be due to a variety of reasons, clinicians prescribing TNF-alpha inhibitors to HBsAg-positive patients should consider prophylactic antiviral therapy and close monitoring for any clinical or serological evidence of hepatitis.

J Pediatr Gastroenterol Nutr. 2010 Aug;51(2):223-5.

Angioedema occurring in pediatric patients with crohn disease treated with adalimumab

Adamiak T, Stephens M, Werlin SL.

No abstract available

J Pediatr Gastroenterol Nutr. 2010 Aug;51(2):226-8.

Infliximab-related vasculitis in patients affected by ulcerative colitis

Pastore S, Londero M, Gortani G, Abate MV, Marchetti F, Di Leo G, Ventura A.

No abstract available

Arch Dermatol. 2010 Jul;146(7):721-6

Obesity in early adulthood as a risk factor for psoriatic arthritis

Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG.

OBJECTIVE: To study whether obesity increases the risk of psoriatic arthritis (PsA), given that obesity is a risk factor for psoriasis and is associated with more severe disease. **DESIGN:** Case series. We used Cox regression analysis to study the relationship between obesity and PsA while controlling for age at psoriasis onset, current body mass index (BMI), sex, family history of psoriasis, worst-ever body surface area (BSA) involvement, Koebner phenomenon, and nail involvement. **SETTING:** Dermatology clinics at

the University of Utah School of Medicine. Patients Volunteer sample of patients with dermatologist-diagnosed psoriasis enrolled in the Utah Psoriasis Initiative from November 2002 to October 2008 (943 subjects; 50.2% women, 49.8% men). MAIN OUTCOME MEASURES: Physician diagnosis of PsA from self-report questionnaire. RESULTS: In our subjects, we found that BMI at age 18 years was predictive of PsA (odds ratio [OR], 1.06) ($P < .01$) over and above control variables. Other variables that were predictors of PsA included younger age at psoriasis onset (odds ratio [OR], 0.98) ($P < .01$), female sex (OR, 1.45) ($P = .01$), higher worst-ever BSA involvement with psoriasis (OR, 1.01) ($P = .04$), Koebner phenomenon (OR, 1.59) ($P < .01$), and nail involvement (OR, 1.76) ($P < .01$). Current BMI and family history of psoriasis were not significant predictors of PsA. CONCLUSIONS: This study suggests that obesity at age 18 years increases the risk of developing PsA. Adiposity is associated with higher levels of inflammatory cytokines known to be associated with psoriasis. This inflammatory milieu could increase the risk of PsA in predisposed subjects. Prevention and early treatment of obesity may decrease the risk of PsA.