Literature Update Immunology

Period: 01- 30 June 2010

IBD

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- Incidence and **risk of hospitalisation due to shingles and chickenpox** in patients with rheumatic diseases treated with TNF antagonists
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IBD

World J Gastroenterol. 2010 Jun 7;16(21):2589-90.
Prediction of disease course in inflammatory bowel diseases
Lakatos PL.

Clinical presentation at diagnosis and disease course of both Crohn's disease (CD) and ulcerative colitis are heterogeneous and variable over time. Since most patients have a relapsing course and most CD patients develop complications (e.g. stricture and/or perforation), much emphasis has been placed in the recent years on the determination of important predictive factors. The identification of these factors may eventually lead to a more personalized, tailored therapy. In this TOPIC HIGHLIGHT series, we provide an update on the available literature regarding important clinical, endoscopic, fecal, serological/routine laboratory and genetic factors. Our aim is to assist clinicians in the everyday practical decision-making when choosing the treatment strategy for their patients suffering from inflammatory bowel diseases.

World J Gastroenterol. 2010 Jun 7;16(21):2591-9.
Is the disease course predictable in inflammatory bowel diseases?
Lakatos PL, Kiss LS.

During the course of the disease, most patients with Crohn's disease (CD) may eventually develop a stricturing or a perforating complication, and a significant number of patients with both CD and ulcerative colitis will undergo surgery. In recent years, research has focused on the determination of factors important in the prediction of disease course in inflammatory bowel diseases to improve stratification of patients, identify individual patient profiles, including clinical, laboratory and molecular markers, which hopefully will allow physicians to choose the most appropriate management in terms of therapy and intensity of follow-up. This review summarizes the available evidence on clinical, endoscopic variables and biomarkers in the prediction of short and long-term outcome in patients with inflammatory bowel diseases.

World J Gastroenterol. 2010 Jun 7;16(21):2600-3.
Do clinical factors help to predict disease course in inflammatory bowel disease?
Louis E, Belaiche J, Reenaers C.

While therapeutic strategies able to change the natural history of the disease are developing, it is of major importance to have available predictive factors for aggressive disease to try and target these therapeutic strategies. Clinical predictors have probably been the most broadly studied. In both Crohn's disease (CD) and ulcerative colitis (UC), age at diagnosis, disease location and smoking habit are currently the strongest predictors of disease course. A younger age at onset is associated with more aggressive disease both in CD and UC. Disease location in CD is associated with different types of complications: surgery and recurrence in upper gastrointestinal and proximal small bowel disease; and surgery in distal small bowel disease and peri-anal lesions in rectal disease. In UC, extensive colitis is clearly been associated with more severe disease. Finally, active smoking globally increases disease severity in CD but decreases it in UC. Besides these important factors, others may predispose to some specific disease evolution and complications, and are also reviewed in the present paper.

World J Gastroenterol. 2010 Jun 7;16(21):2604-8.
Serologic and laboratory markers in prediction of the disease course in inflammatory bowel disease
Dubinsky MC.

The search for biologic markers that can assess the natural history and perhaps predict the course of individual's disease including response to treatments over time has become an important focus of inflammatory bowel disease research. The knowledge of an individual's prognosis can help physicians

and patients make important management decisions and aid communication on risk and benefits of disease and treatment.

World J Gastroenterol. 2010 Jun 7;16(21):2609-15.
Role of genetics in prediction of disease course and response to therapy
Vermeire S, Van Assche G, Rutgeerts P.

The clinical course of Crohn's disease and ulcerative colitis is highly variable between patients, and this has therapeutic implications. A number of clinical features have been identified, which predict a mild or more severe outcome. However, several of these are subjective and/or not persistent over time. With the progress in genetics research in inflammatory bowel disease (IBD), genetic markers are increasingly being proposed to improve stratification of patients. Genetics have the major advantage of being stable over time and not prone to subjective interpretation. Nevertheless, none of the genetic variants associated with particular outcomes have shown sufficient sensitivity or specificity to have been implemented in daily management. Along the same line of thinking, pharmacogenetics or the study of association between variability in drug response and genetic variation has also received more attention as part of the endeavor for personalized medicine. The ultimate goal in this area of medicine is to adapt medication to a patient's specific genetic background and therefore improve on efficacy and safety rates. Although pharmacogenetic studies have been performed for all classes of drugs applied in IBD, few have generated consistent findings or have been replicated. The only genetic test approved for clinical practice is thiopurine S-methyltransferase testing prior to starting treatment with thiopurine analogues. The other reported associations have suffered from lack of confirmation or still need replication efforts. Nevertheless, the importance and necessity of pharmacogenetic studies will increase further as more therapeutic classes are being developed.

World J Gastroenterol. 2010 Jun 7;16(21):2616-25.
Mucosal biomarkers in inflammatory bowel disease: key pathogenic players or disease predictors?
Scaldaferri F, Correale C, Gasbarrini A, Danese S.

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of the bowel, including ulcerative colitis and Crohn's disease. A single etiology has not been identified, but rather the pathogenesis of IBD is very complex and involves several major and minor contributors, employing different inflammatory pathways which have different roles in different patients. Although new and powerful medical treatments are available, many are biological drugs or immunosuppressants, which are associated with significant side effects and elevated costs. As a result, the need for predicting disease course and response to therapy is essential. Major attempts have been made at identifying clinical characteristics, concurrent medical therapy, and serological and genetic markers as predictors of response to biological agents. Only few reports exist on how mucosal/tissue markers are able to predict clinical behavior of the disease or its response to therapy. The aim of this paper therefore is to review the little information available regarding tissue markers as predictors of response to therapy, and reevaluate the role of tissue factors associated with disease severity, which can eventually be ranked as "tissue factor predictors". Five main categories are assessed, including mucosal cytokines and chemokines, adhesion molecules and markers of activation, immune and non-immune cells, and other mucosal components. Improvement in the design and specificity of clinical studies are mandatory to be able to classify tissue markers as predictors of disease course and response to specific therapy, obtain the goal of achieving "personalized pathogenesis-oriented therapy" in IBD.

World J Gastroenterol. 2010 Jun 7;16(21):2626-32.
Role of endoscopy in predicting the disease course in inflammatory bowel disease
Allez M, Lémann M.

Endoscopy provides a direct evaluation of mucosal lesions in inflammatory bowel disease (IBD), permitting the description of elementary lesions, their surface extent and severity. The severity of mucosal lesions directly reflects disease activity and may help to identify an aggressive behavior of the disease. Several studies have recently pointed out the potential role of endoscopy in the prediction of IBD outcome. Indeed, severe endoscopic lesions in Crohn's disease (CD) patients, defined by deep and extensive ulcerations on at least one part of the colon, are associated with an increased risk of

penetrating complication and surgery. Severe endoscopic lesions during severe attacks of ulcerative colitis (UC) are associated with an increased risk of colectomy in the short and long term. Severity of postoperative recurrence in CD may help to predict the risk of clinical relapse and need for further surgery. Achievement of mucosal healing, which can be obtained by administration of several types of drugs, is associated with a better outcome, less surgery and hospitalization. This review focuses on the assessment of endoscopic severity in CD and UC and on the impact of endoscopic severity on disease outcome. More specifically, we discuss how endoscopy can be used at different stages of IBD to predict the disease course and/or to adapt treatment strategies.

Can J Gastroenterol. 2010 May;24(5):297-302
Replication and meta-analysis of 13,000 cases defines the risk for interleukin-23 receptor and autophagy-related 16-like 1 variants in Crohn's disease
Cotterill L, Payne D, Levinson S, McLaughlin J, Wesley E, Feeney M, Durbin H, Lal S, Makin A, Campbell S, Roberts SA, O'Neill C, Edwards C, Newman WG.

BACKGROUND/OBJECTIVE: Variants in the interleukin-23 receptor (IL23R) and the autophagy-related 16-like 1 (ATG16L1) genes have been associated with an increased risk of Crohn's disease (CD). Both genes were identified through genome-wide association scans and subsequent studies have validated these associations. To assess the effect size of these variants, an independent case-control association study and meta-analysis were performed. METHODS: British Caucasian subjects with inflammatory bowel disease (n=500) and 877 ethnically matched controls were genotyped for the disease-associated variants in IL23R and ATG16L1. In addition, meta-analyses of 12,991 patients and 14,598 controls, and 11,909 patients and 15,798 controls, were conducted on independently published data for the associations between IL23R and ATG16L1 variants and CD, respectively. RESULTS: In the present cohort, both susceptibility variants showed highly significant associations, including IL23R (rs11209026, P=0.0006; OR 0.37; 95% CI 0.21 to 0.67) and ATG16L1 (rs2241880, P=0.0017; OR 1.36; 95% CI 1.12 to 1.66). The meta-analysis based on the random effects model showed similar combined effects for rs11209026 (n=26, OR 0.41; 95% CI 0.37 to 0.46) and rs2241880 (n=25, OR 1.33; 95% CI 1.28 to 1.39). There was no statistically significant gene-gene interaction between caspase recruitment domain (CARD15) variants and the IL23R or ATG16L1 polymorphisms (P=0.44 and P=0.24, respectively). CONCLUSION: The present cohort and meta-analysis provides strong evidence that, in addition to CARD15, polymorphisms in both IL23R and ATG16L1 alter susceptibility to CD and that these effects are consistent across all populations of European ancestry; however, only ATG16L1 is relevant to inflammatory bowel disease in the Asian population.

Am J Gastroenterol. 2010 Jun;105(6):1430-6. Epub 2010 Jan 26.
Outcome following infliximab therapy in children with ulcerative colitis
Hyams JS, Lerer T, Griffiths A, Pfefferkorn M, Stephens M, Evans J, Otley A, Carvalho R, Mack D, Bousvaros A, Rosh J, Grossman A, Tomer G, Kay M, Crandall W, Oliva-Hemker M, Keljo D, LeLeiko N, Markowitz J; Pediatric Inflammatory Bowel Disease Collaborative Research Group.

OBJECTIVES: Infliximab is effective in treating moderate/severe ulcerative colitis (UC) in adults. The aim of this study was to determine the outcome after treatment with infliximab in pediatric UC. METHODS: We performed a multicenter cohort study of 332 pediatric patients with UC enrolled in the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. Children<or=16 years of age and newly diagnosed with UC are enrolled in the registry. Disease and medication information are collected prospectively from the treating physician at diagnosis, 30 days, and quarterly thereafter. No interventions were specified, per protocol. RESULTS: Of 332 patients, 52 (16%) received infliximab (23%<3 months from diagnosis, 38% 3-12 months, 38% >12 months). Mean age at infliximab initiation was 13.3+/-2.6 (range 6-17) years; 87% of patients had pancolitis. Median follow-up was 30 months. Continuous maintenance (CM) therapy was given in 65%, episodic in 21%, episodic converted to CM in 6%, and insufficient data in 8% of patients. Sixty-three percent of patients were corticosteroid refractory, and 35% were corticosteroid dependent. Concomitant medications at first infliximab infusion included corticosteroids (87%), thiopurines (63%), and 5-aminosalicylates (51%). Corticosteroid-free inactive disease by physician global assessment was noted in 12/44 (27%), 15/39 (38%), and 6/28 (21%) patients at 6, 12, and 24 months, respectively. Kaplan-Meier analysis showed that the likelihood of remaining colectomy free after treatment with infliximab was 75% at 6 months, 72% at 12 months, and 61% at 2 years. CONCLUSIONS: In this cohort of children with UC receiving infliximab, corticosteroid-free inactive

disease was observed in 38 and 21% of patients at 12 and 24 months, respectively. By 24 months, 61% of patients had avoided colectomy.

Am J Gastroenterol. 2010 Jun;105(6):1445-6; author reply 1446.
How deep is remission in perianal Crohn's disease and do imaging modalities matter?
Savoye G, Savoye-Collet C.

No abstract available

Gastroenterology. 2010 Jun;138(7):2282-91. Epub 2010 Feb 26.
Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response
Turner D, Mack D, Leleiko N, Walters TD, Uusoue K, Leach ST, Day AS, Crandall W, Silverberg MS, Markowitz J, Otley AR, Keljo D, Mamula P, Kugathasan S, Hyams J, Griffiths AM.

BACKGROUND & AIMS: In a prospective study of children with severe ulcerative colitis (UC), we aimed to assess outcomes and to identify predictors of nonresponse to intravenous corticosteroids. METHODS: A total of 128 children (47% males; 12.9 +/- 3.9 y) hospitalized for severe UC were enrolled from 10 pediatric centers. Clinical and laboratory data and the Pediatric UC Activity Index (PUCAI) were recorded throughout the admission. Patients were followed up for 1 year postdischarge. RESULTS: Thirty-seven (29%; 95% confidence interval [CI], 22%-37%) children failed intravenous corticosteroids and received, within 10.5 +/- 6.4 days, cyclosporine (n = 1; 3%), colectomy (n = 3; 8%), or infliximab (n = 33; 89%). Several predictors were associated with intravenous corticosteroids failure, but the best model included number of stools, amount of blood, age, and new-onset disease (odds ratio [OR], 1.9; 95% CI, 1.1-3.5; OR, 2.5; 95% CI, 1.3-4.6; OR, 1.2; 95% CI, 1.04-1.36; and OR, 0.27; 95% CI, 0.1-0.7, respectively). The PUCAI, followed closely by the Travis rule, strongly predicted response when compared with other measures (Seo and Lindgren indices, C-reactive protein level, and fecal calprotectin level) (P < .001). Aiming for sensitivity on day 3, a PUCAI greater than 45 screened for patients likely to fail intravenous corticosteroids (negative predictive value, 94%; positive predictive value, 43%; P < .001). Aiming for specificity on day 5, a PUCAI score greater than 70 optimally guided implementation of salvage therapy (positive predictive value, 100%; negative predictive value, 79%; P < .001). Twenty-five of 33 children treated with infliximab responded. The overall cumulative colectomy rate was 9% and 19% by discharge and 1-year, respectively. The day 3 PUCAI score predicted response up to 1 year postdischarge (P < .001; time to salvage therapy). CONCLUSIONS: The PUCAI, calculated on days 3 and 5 of steroid therapy, can identify patients requiring salvage therapy. Infliximab is an effective therapy in steroid-refractory pediatric UC.

Gastroenterology. 2010 Jun;138(7):2378-87. Epub 2010 Feb 23.
Interleukin-15 and its soluble receptor mediate the response to infliximab in patients with Crohn's disease
Bouchaud G, Mortier E, Flamant M, Barbieux I, Plet A, Galmiche JP, Jacques Y, Bourreille A.

BACKGROUND & AIMS: Infliximab is a monoclonal antibody against tumor necrosis factor that is used to treat patients with inflammatory bowel disease. We investigated serum levels and cellular expression of interleukin (IL)-15 and its receptor (sIL-15Ralpha) in patients with Crohn's disease (CD) treated with infliximab; and the effect on sIL-15Ralpha secretion by epithelial cells. METHODS: CD patients were given infliximab (n = 40; 3 infusions); 37 healthy controls were studied. Serum levels of IL-15, sIL-15Ralpha, and complex were determined by radioimmunoassay and cytokine levels by enzyme-linked immunosorbent assay. IL-15Ralpha and A Desintegrin and Metalloproteinase 17 levels were assessed by immunohistochemistry. Epithelial cell lines (HT-29 and Caco-2) were cultured with infliximab, adalimumab, or etanercept. Patients were classified as responders and nonresponders according to their Crohn's Disease Activity Index and clinical observations. RESULTS: Before infliximab, IL-15 was higher in responders than in controls and nonresponders. After infliximab, IL-15 decreased in responders while remaining stable in nonresponders. sIL-15Ralpha and IL-15/sIL-15Ralpha complex levels were higher in CD than in controls and increased only in responders after infliximab. IL-15Ralpha and A Desintegrin and Metalloproteinase 17 colocalized in epithelial cells and were higher in CD patients. In vitro, infliximab but not adalimumab and etanercept induced sIL-15Ralpha secretion by epithelial cells. CONCLUSIONS: Serum level of sIL-15Ralpha and the IL-15/sIL-15Ralpha complex increased in responder patients and

the response was associated with a decrease of IL-15. Infliximab induced the release of the IL-15 receptor alpha, suggesting a specific modulation of IL-15 and its soluble receptor by reverse signaling through transmembrane tumor necrosis factor alpha.

Inflamm Bowel Dis. 2009 Oct 15;16(7):1091-1092. [Epub ahead of print]
Fecal calprotectin variability in Crohn's disease
Moum B, Jahnsen J, Bernklev T.

No abstract available.

Inflamm Bowel Dis. 2009 Nov 18;16(7):1173-1179. [Epub ahead of print]
Impact of prior irregular infliximab dosing on performance of long-term infliximab maintenance therapy in Crohn's disease
Stein DJ, Ananthakrishnan AN, Issa M, Williams JB, Beaulieu DB, Zadvornova Y, Ward A, Johnson K, Knox JF, Skaros S, Binion DG.

BACKGROUND:: Infliximab is efficacious in the management of moderate to severe Crohn's disease (CD). There are limited data regarding performance of infliximab in patients who require reinitiation of maintenance dosing following previous irregular exposure. METHODS:: This was a retrospective, observational study of CD patients treated with maintenance infliximab beyond 3 years. Maintenance infliximab infusion regimens were categorized as scheduled maintenance (SM) (maintenance infusions q </=8 weeks after loading) or prior irregular (PI) (no loading, gap in therapy >8 weeks prior to or during maintenance therapy). We examined differences in need for medical and surgical hospitalizations as well as associated healthcare costs between the 2 groups. RESULTS:: In all, 104 CD patients met criteria for 3-year maintenance infliximab treatment (SM n = 64; PI n = 40). The rates of CD-related surgeries (60.9% and 55.0%, P = not significant [N.S.]) and medical hospitalizations (35.9% and 37.5%, P = N.S.) prior to infliximab initiation was similar between the 2 groups. However, the rate of medical (26.5% versus 47.5%, P = 0.035) and surgical hospitalizations (21.8% versus 48.7%, P = 0.009) were significantly lower in the SM compared to the PI group. During the third year of treatment the excess costs per patient for the PI group compared to the SM group amounted to $11,464 in spite of both cohorts being on SM therapy. CONCLUSIONS:: Patients who begin and continue an uninterrupted maintenance dosing regimen had a lower incidence of hospitalization and surgery than those who received an irregular or interrupted regimen prior to beginning an SM regimen. (Inflamm Bowel Dis 2010).

Inflamm Bowel Dis. 2009 Nov 2;16(7):1180-1186. [Epub ahead of print]
Exogenous alkaline phosphatase for the treatment of patients with moderate to severe ulcerative colitis
Lukas M, Drastich P, Konecny M, Gionchetti P, Urban O, Cantoni F, Bortlik M, Duricova D, Bulitta M.

BACKGROUND:: Increased activity of intestinal alkaline phosphatase (AP) occurs locally in patients with ulcerative colitis (UC), aimed at repairing inflammatory tissue damage. We evaluated the safety and preliminary efficacy of exogenous AP administered to patients with UC in an open-label, first-in-patient exploratory trial, conducted in the Internal Medicine and Gastroenterology hospital departments in the Czech Republic and Italy. METHODS:: Twenty-one patients were enrolled (13 females), age 23-54 years, with steroid- and/or immunosuppressant-refractory, moderate/severe UC (Mayo score 6-11). Oral AP enzyme 30,000 U was administered daily for 7 days, intraduodenally. Efficacy outcomes were changes in Mayo score at Day 21 posttreatment; changes in Modified Truelove-Witts Severity index (MTWSI) at Days 21, 63; C-reactive protein and stool calprotectin levels at Days 7, 21, 63. Safety evaluations were adverse events and laboratory abnormalities reported up to Day 63 posttreatment. RESULTS:: No clinically relevant adverse events causing withdrawal or considered serious, or laboratory abnormalities or antibody formation against AP were observed. Mayo scores were significantly decreased at Day 21, and MTWSI at Days 21 and 63. C-reactive protein and stool calprotectin levels were decreased at Days 21 and 63. Clinical response on the Mayo score after a single 7-day AP course was 48% at Day 21. CONCLUSIONS:: In this uncontrolled trial, administration of exogenous AP enzyme daily over a 7-day course to patients with UC was associated with short-term improvement in disease activity scores, with clinical effects being observed within 21 days and associated with reductions in C-reactive protein and stool calprotectin. AP enzyme treatment was well tolerated and nonimmunogenic. (Inflamm Bowel Dis 2009;).

Inflamm Bowel Dis. 2009 Nov 18;16(7):1195-1202. [Epub ahead of print]
Methotrexate for maintenance of remission in chronic active Crohn's disease: Long-term single-center experience and meta-analysis of observational studies
Hausmann J, Zabel K, Herrmann E, Schröder O.

BACKGROUND: According to current guidelines methotrexate (MTX) should be considered as a second-line immunomodulator in patients with chronic active Crohn's disease (CD) if purine analogs are not tolerated or there is a lack of efficacy. However, its therapeutic role remains controversial to the present day. METHODS: Medical records of all eligible patients treated in the outpatient clinic of the Johann Wolfgang Goethe-University Hospital between December 2000 and January 2009 were reviewed. RESULTS: Sixty-three patients were identified. The mean duration of treatment was 100 weeks (range, 2-364 weeks) with a mean cumulative dose of MTX of 2130 mg (range, 40-9005 mg). In 50 (79%) patients started on MTX clinical remission could be achieved within 3 months of treatment. The cumulative probability of these patients to maintain remission was 95.3%, 89.5%, 70.6%, and 62.8% at 6 months, 1, 2, and 3 years of treatment, respectively. The respective figures of the meta-analysis were 94%, 86%, 75%, 53%, and 43. Drug-related side effects were reported in 50 patients (79%), leading to withdrawal of MTX in 21 cases (33%). CONCLUSIONS:: Along with previous observations our data demonstrate the efficacy of MTX as a second-line immunomodulator in chronic active CD. However, its use is limited due to intolerable side effects in a large proportion of patients. The results should encourage further research in order to establish the definite significance of MTX in chronic active CD. (Inflamm Bowel Dis 2010).

Inflamm Bowel Dis. 2010 Jan 5;16(7):1203-1208. [Epub ahead of print]
Phase I trial of sargramostim in pediatric Crohn's disease
Kelsen JR, Rosh J, Heyman M, Winter HS, Ferry G, Cohen S, Mamula P, Baldassano RN.

BACKGROUND:: Improving granulocyte function may represent an effective therapy for Crohn's disease (CD). We performed a Phase I-2 trial of sargramostim (SRG) in children with CD. METHODS:: This was multicenter, open-label study in 6-16-year-old patients with moderate to severely active CD. Patients received either 4 or 6 mug/kg SRG subcutaneously daily for 8 weeks, with and without concomitant corticosteroids (CS). The primary endpoint was identification of a safe and tolerable dose in children. The secondary endpoint was establishment of the pharmacokinetics (PK). Efficacy, a tertiary endpoint, was measured by the Pediatric CD Activity Index (PCDAI). Response was defined as a decrease from baseline of >/=12.5 points and remission as absolute PCDAI of </=10. RESULTS:: In all, 22 patients were enrolled: 12 and 10 received 4 and 6 mg/kg, respectively; 19 completed the course. Both doses were found to be safe and well tolerated. Mild injection-site reactions occurred in 90% of patients. Three patients required dose reductions due to elevated absolute neutrophil counts. Following 4 mug/kg the mean area under the curve (AUC) was 2.64 and 2.80 ngh/mL for the 6-11- and 12-16-year-old groups, respectively. The mean half-life (t(1/2)) was 1.22 and 1.59 hours, respectively. Following 6 mug/kg, the mean AUC was 5.01 ngh/mL for the 12-16-year-old group, a 1.8-fold increase. A total of 16/18 patients (88%) achieved remission or response. CONCLUSIONS:: Sargramostim at both 4 and 6 mg/kg was well tolerated. PK analysis suggested dose proportionality unaffected by CS exposure. Remission and response data are encouraging, but further trials are needed to assess efficacy. (Inflamm Bowel Dis 2010).

Inflamm Bowel Dis. 2009 Nov 16;16(7):1209-1218. [Epub ahead of print]
Randomized, double-blind, placebo-controlled trial of the oral interleukin-12/23 inhibitor apilimod mesylate for treatment of active Crohn's disease
Sands BE, Jacobson EW, Sylwestrowicz T, Younes Z, Dryden G, Fedorak R, Greenbloom S.

BACKGROUND:: Interleukin-12 (IL-12) and interleukin-23 (IL-23) are inflammatory cytokines linked to the Th-1 and Th-17 phenotypes associated with Crohn's disease (CD). We investigated the activity and safety of apilimod mesylate (formerly STA-5326), an oral IL-12 and IL-23 inhibitor, in patients with active CD. METHODS:: We performed a multicenter, Phase 2, randomized, double-blinded, placebo-controlled study to evaluate the efficacy of apilimod mesylate in treating 220 adult patients with moderate-to-severe CD (Crohn's Disease Activity Index [CDAI] score 220-450). Patients were stratified according to C-reactive protein (CRP) levels and corticosteroid use and were randomly assigned to receive placebo or apilimod mesylate 50 mg daily or 100 mg daily. The study was divided into an induction phase (43 days)

and a maintenance phase (125 days). The primary analysis involved a comparison of the proportion of patients experiencing clinical response, defined as at least a 100-point decrease in CDAI score from baseline at day 29. Data on adverse events were also collected. RESULTS:: In all, 220 of the planned 282 patients were enrolled when the Data Monitoring Committee determined that the drug was not efficacious as a treatment and closed enrollment. A clinical response was experienced by 18 patients (24.7%) in the 50-mg daily (QD) group (n = 73) and 19 patients (25.7%) in the 100 mg QD group (n = 74), as compared with 21 patients (28.8%) in the placebo group (n = 73) on day 29 (P = 0.71 for each comparison). No significant adverse safety signal was observed. CONCLUSIONS:: Apilimod was well-tolerated but did not demonstrate efficacy over placebo in patients with active CD. (Inflamm Bowel Dis 2009).

Inflamm Bowel Dis. 2009 Nov 18;16(7):1219-1226. [Epub ahead of print]
Magnetic resonance follow-through imaging for evaluation of disease activity in ileal Crohn's disease: An observational, retrospective cohort study
Parisinos CA, McIntyre VE, Heron T, Subedi D, Arnott ID, Mowat C, Wilson DC, McGurk S, Glancy S, Zealley IA, Satsangi J, Lees CW.

BACKGROUND: Magnetic resonance follow-through (MRFT) is a new cross-sectional imaging modality with the potential to accurately stage ileal Crohn's disease (CD), while avoiding ionizing radiation and the discomfort associated with enteroclysis. We aimed to assess the reliability of this technique in assessing the extent and activity of ileal CD, and to assess its influence on subsequent management. METHODS:: Out of a total of 342 patients undergoing MRFT between 2004 and 2008, 221 were performed in 191 patients with confirmed CD. Case notes were reviewed in detail with documentation of all investigations pre- and post-MRFT. Agreement between inflammatory markers, histopathology, and MRFT findings was determined. RESULTS:: Overall, 116/221 (52.5%) of MRFTs showed active ileal CD, and 76/221 (34.4%) quiescent CD, while 29/221 (13.1%) were suboptimal. Overall, 66 strictures and 18 fistulae were identified. There was substantial agreement between active ileal CD on MRFT and histopathology (n = 59; kappa = 0.66; P = 0.0006; sensitivity 85.1%, specificity 85.7%) and fecal calprotectin (n = 14; kappa = 0.72; P = 0.047), while C-reactive protein (CRP) showed moderate agreement (n = 107; kappa = 0.402; P = 0.00028). Management was influenced by MRFT reports following active (52/84, 62% treated medically) or quiescent (48/62, 77.4% managed conservatively) disease. Fibrotic strictures were predominantly treated surgically (7/14, 50%). In all, 13/32 (40.6%) patients with inflammatory ileal strictures required surgery, mostly due to steroid-resistant disease. Overall, 75 MR findings were documented in 221 MRFTs, including 1 renal cancer. CONCLUSIONS:: MRFT provides accurate information on ileal CD activity, with close agreement to inflammatory markers and histopathology. It represents a substantial advance in the staging of CD, while avoiding painful enteroclysis and radiation exposure in young patients. (Inflamm Bowel Dis 2010).

Inflamm Bowel Dis. 2009 Oct 15;16(7):1263-1264. [Epub ahead of print]
Magnetic resonance imaging for Crohn's disease: Is this really the end of colonoscopy?
Peyrin-Biroulet L.

No abstract available

Expert Opin Drug Saf. 2010 Jul;9(4):573-92.
Efficacy and safety of drugs for ulcerative colitis
Rosenberg LN, Peppercorn MA.

IMPORTANCE OF THE FIELD: Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon that carries considerable burden and morbidity for patients and presents a constant challenge in management for gastroenterologists. Continued advances in medical therapies provide a range of treatment options for patients, but with this is the need to balance the potential benefits of a particular medication with its side effect profile in both the short and the long term. AREAS COVERED IN THIS REVIEW: This article will review the current drugs used in the treatment of UC, including 5-amninosalicylates, antibiotics, steroids, immunomodulators and biologics, with particular attention to their indications, efficacy and toxicity profile. WHAT THE READER WILL GAIN: The reader will gain a comprehensive understanding of the various medical therapies used in the treatment of UC with focus on efficacy and toxicity profiles, allowing providers to choose appropriate medical therapies for their patients. TAKE HOME MESSAGE: The

particular agent used depends upon the extent and severity of disease, with mild-to-moderate disease treated with conventional therapy including 5-amninosalicylates. Steroids are used in the short term to bring active disease into remission, and the more aggressive immunomodulators and biologics are reserved for more severe disease given their toxicity profiles.

Eur J Gastroenterol Hepatol. 2010 Jul;22(7):872-9.
Early azathioprine/biological therapy is associated with decreased risk for first surgery and delays time to surgery but not reoperation in both smokers and nonsmokers with Crohn's disease, while smoking decreases the risk of colectomy in ulcerative colitis
Szamosi T, Banai J, Lakatos L, Czegledi Z, David G, Zsigmond F, Pandur T, Erdelyi Z, Gemela O, Papp M, Papp J, Lakatos PL.

BACKGROUND/AIMS: Smoking may alter the natural course of Crohn's disease (CD). Smokers are more likely to develop complications, relapses and have a greater risk for surgery. In contrast, in ulcerative colitis (UC), smoking might improve the disease course. Our aim was to assess the combined effect of disease phenotype, smoking, and immunomodulator [azathioprine (AZA), AZA/biological] treatment on the risk of intestinal resection/reoperation in CD and colectomy in UC. PATIENTS/METHODS: Six hundred and eighty-one inflammatory bowel disease patients were analyzed (CD: 340, male/female: 155/185, duration: 9.4+/-7.5 years; UC: 341, male/female: 174/164, duration: 11.5+/-9.7 years). Patients were interviewed on their smoking habits at the time of diagnosis and during the regular follow-up visits. Medical records were retrospectively analyzed. RESULTS: Smoking was present in 45.5% in CD and 15.8% in UC. CD patients who underwent at least one bowel resection comprised 46.5%. In an univariate analysis, disease location, behavior, AZA, or AZA/biological use before surgery [odds ratio (OR): 0.26 and 0.22, P<0.001] and smoking (OR: 1.61, P = 0.03) were associated with risk for first surgery. Smoking, AZA, or AZA/biological (P<0.001) use before first surgery and disease behavior were independently associated with risk for surgery in a proportional Cox-regression analysis. Perianal disease (OR: 3.2, P = 0.001) and frequent relapses (OR: 4.8, P<0.001) but not smoking, AZA, or AZA/biological use after first surgery were predictive for reoperation. In UC, the rate of colectomy was 5.6%. Disease location (P = 0.001) and smoking status (P = 0.02) were independently associated with risk for colectomy in a proportional Cox-regression analysis. CONCLUSION: Our data suggest that early AZA/biological therapy reduces the risk for first operation but not reoperation in CD, in both smokers and nonsmokers. In contrast, smoking was associated with a decreased need for colectomy in UC.

Front Biosci (Schol Ed). 2010 Jun 1;2:993-1008.
Stem cells as potential therapeutic targets for inflammatory bowel disease
Singh UP, Singh NP, Singh B, Mishra MK, Nagarkatti M, Nagarkatti PS, Singh SR.

The incidence and prevalence of Crohn's disease and ulcerative colitis, the two major forms of inflammatory bowel disease (IBD), are rising. According to some estimates >1 million new cases of IBD arise in the United States annually. The conventional therapies available for IBD range from anti-inflammatory drugs to immunosuppressive agents, but these therapies generally fail to achieve satisfactory results due to their side effects. Interest in a new therapeutic option, that is, biological therapy, has gained much momentum recently due to its focus on different stages of the inflammatory process. Stem cell (SC) research has become a new direction for IBD therapy due to our recent understanding of cell populations involved in the pathogenic process. To this end, hematopoietic and mesenchymal stem cells are receiving more attention from IBD investigators. The intestinal environment, with its crypts and niches, supports incoming embryonic and hematopoietic stem cells and allows them to engraft and differentiate. The above findings suggest that, in the future, SC-based therapy will be a promising alternative to conventional therapy for IBD. In this review, we discuss SCs as potential therapeutic targets for future treatment of IBD.

Clin Gastroenterol Hepatol. 2010 Feb 4. [Epub ahead of print]
Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease
Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D.

BACKGROUND & AIMS: Infliximab might prevent postsurgical recurrence of Crohn's disease. However, it is unclear whether long-term therapy is necessary and whether alternative strategies could be applied to

minimize potential side effects and reduce the costs of treatment. METHODS: We performed a prospective cohort study in 12 consecutive patients, treated immediately after surgery with maintenance infliximab (5 mg/kg), who did not have clinical or endoscopic evidence of disease recurrence after 24 months; they were followed up for an additional year. Infliximab treatment was then discontinued; patients with disease recurrence, based on endoscopy (Rutgeerts score, >/=2), were given lower doses of infliximab (starting with 1 mg/kg) to re-establish mucosal integrity. Surrogate markers of disease activity (fecal calprotectin [FC], C-reactive protein, and erythrocyte sedimentation rate) were assessed after each infliximab dose. RESULTS: None of the patients had clinical or endoscopic recurrence of Crohn's disease 3 years after surgery. However, discontinuation of infliximab caused endoscopic recurrence after 4 months in 10 of 12 patients (83%). All 10 patients then were treated again with infliximab, which, at a dose of 3 mg/kg every 8 weeks, restored and maintained mucosal integrity for 1 year. Among the surrogate markers, FC levels correlated with endoscopic scores (Wald test, P < .0001). CONCLUSIONS: Long-term maintenance therapy with infliximab is required to maintain mucosal integrity in patients after surgery for Crohn's disease. However, a dose of 3 mg/kg (a 40% reduction from the standard dose) was sufficient to avoid disease recurrence, determined by endoscopy, in all patients at 1 year. FC levels correlate with mucosal status at different infliximab doses.

Clin Gastroenterol Hepatol. 2010 Apr 24. [Epub ahead of print]
Anti-tumor necrosis factor therapy in Crohn's disease: more information and more questions about the long term
Bernstein CN.

No abstract available

Clin Gastroenterol Hepatol. 2010 Feb 1. [Epub ahead of print]
Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months
Lichtenstein GR, Thomsen OO, Schreiber S, Lawrance IC, Hanauer SB, Bloomfield R, Sandborn WJ; Precise 3 Study Investigators.

BACKGROUND & AIMS: The safety and efficacy of maintenance therapy with the anti-tumor necrosis factor certolizumab pegol has not been reported beyond 6 months. We assessed the long-term efficacy, safety, and immunogenicity of continuous versus interrupted maintenance therapy with subcutaneous certolizumab pegol in patients with Crohn's disease. METHODS: Patients who responded to induction therapy at week 6 of the PEGylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy (PRECiSE) 2 trial were assigned randomly to groups given certolizumab pegol (continuous) or placebo (drug-interruption) during weeks 6 to 26. Patients who completed PRECiSE 2 were eligible to enter PRECiSE 3, an ongoing, prospective, open-label extension trial in which patients have received certolizumab pegol (400 mg) every 4 weeks for 54 weeks to date, and were not offered the option to increase their dose. Disease activity was measured by the Harvey-Bradshaw Index. RESULTS: Harvey-Bradshaw Index responses at week 26 for the continuous and drug-interruption groups were 56.3% and 37.6%, respectively; corresponding remission rates were 47.9% and 32.4%, respectively. Of patients responding at week 26, response rates at week 80 after the start of PRECiSE 2 in the continuous and drug-interruption groups were 66.1% and 63.3%, respectively; among patients in remission at week 26, week 80 remission rates were 62.1% and 63.2%, respectively. More patients in the drug-interruption group developed antibodies against certolizumab pegol (and had lower plasma concentrations of certolizumab pegol) than the continuously treated group. CONCLUSIONS: Certolizumab pegol effectively maintains remission of Crohn's disease for up to 18 months. Continuous therapy is more effective than interrupted therapy.

Safety

Arthritis Care Res (Hoboken). 2010 Jun;62(6):747-8.
Introduction to special section: Drug safety in the rheumatic diseases
Lovell D.

No abstract available

Arthritis Care Res (Hoboken). 2010 Jun;62(6):749-54.
Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases.
Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, Montecucco C, Sarzi-Puttini P.

OBJECTIVE: To assess the safety of anti-tumor necrosis factor alpha (anti-TNFalpha) therapy on the course of hepatitis B virus (HBV) infection in carriers of antibodies to hepatitis B core antigen (anti-HBc) affected by chronic inflammatory arthropathies. METHODS: From January 2001 to December 2008, HBV markers were determined before the first administration of anti-TNFalpha agents in all 732 patients affected by inflammatory arthropathies treated with anti-TNFalpha at 2 outpatient rheumatologic clinics in Northern Italy. Anti-HBc-positive patients were prospectively evaluated and HBV markers and HBV DNA were assessed every 6 months, in case of aminotransferase elevation, and at the end of the study. RESULTS: At the time of recruitment, 72 patients were anti-HBc carriers, 5 of whom were positive for hepatitis B surface antigen (HBsAg) and not included in the study. The ratio of men:women was 26:41 and the mean +/- SD followup was 42.52 +/- 21.33 months. Of the patients, 25 were treated with infliximab, 23 with etanercept, and 19 with adalimumab. Fifty-one patients were treated also with methotrexate, 52 with nonsteroidal antiinflammatory drugs, and 43 with prednisone (3 with a dosage >7.5 mg/day). All anti-HBc patients were HBV DNA negative at the first observation. During followup, no patient presented HBV reactivation with viral load increase and no patient became HBsAg positive. CONCLUSION: Anti-HBc positivity in HBsAg-negative patients is a sign of previous HBV infection and does not indicate chronic hepatitis. In these patients, anti-TNFalpha therapy appears to be quite safe, as no HBV reactivation was found in our study. Nevertheless, careful monitoring is necessary.

Arthritis Care Res (Hoboken). 2010 Jun;62(6):755-63.
Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register.
Dixon WG, Watson KD, Lunt M, Mercer LK, Hyrich KL, Symmons DP; British Society For Rheumatology Biologics Register Control Centre Consortium; British Society for Rheumatology Biologics Register.

OBJECTIVE: To explore the influence of anti-tumor necrosis factor (anti-TNF) therapy upon the incidence of cancer in patients with rheumatoid arthritis (RA) and prior malignancy. METHODS: Using data from the British Society for Rheumatology Biologics Register, a national prospective observational study established in 2001, we identified 293 patients with a prior malignancy from over 14,000 patients with RA. We compared rates of incident malignancy in 177 anti-TNF-treated patients and 117 patients with active RA treated with traditional disease-modifying antirheumatic drugs (DMARDs), all with prior malignancy. One patient switched therapy and contributed to both cohorts. RESULTS: The rates of incident malignancy were 25.3 events/1,000 person-years in the anti-TNF cohort and 38.3/1,000 person-years in the DMARD cohort, generating an age- and sex-adjusted incidence rate ratio of 0.58 (95% confidence interval 0.23-1.43) for the anti-TNF-treated cohort compared with the DMARD cohort. Of the patients with prior melanomas, 3 (18%) of 17 in the anti-TNF cohort developed an incident malignancy, compared with 0 of 10 in the DMARD cohort. CONCLUSION: The way in which UK rheumatologists are selecting patients with RA and prior malignancy to receive anti-TNF therapy is not leading to an increased risk of

incident malignancy. Although reassuring, these results should not be interpreted as indicating that it is safe to treat all RA patients with prior malignancy with anti-TNF therapy.

Arthritis Care Res (Hoboken). 2010 Jun;62(6):764-9.
Neutropenia in patients receiving anti-tumor necrosis factor therapy.
Hastings R, Ding T, Butt S, Gadsby K, Zhang W, Moots RJ, Deighton C.

OBJECTIVE: To examine the rates of and risk factors for neutropenia together with the dynamics of neutrophil and other white cell subset counts in a cohort of patients treated with a tumor necrosis factor (TNF) inhibitor for inflammatory arthritis. METHODS: We performed a retrospective cohort study examining the association between baseline demographics, clinical features, medications used, and development of neutropenia, and behavior of neutrophil and other white cell subset counts during TNF inhibitor therapy. RESULTS: In 367 patients (298 [81.2%] with rheumatoid arthritis, 38 [10.4%] with ankylosing spondylitis, and 31 [8.4%] with psoriatic arthritis), 69 (18.8%) had at least one episode of neutropenia (<2.0 x 10(9)/liter) during TNF inhibitor therapy, and of these, 6% developed serious infections secondary to neutropenia. There was no significant difference in disease, demographic, or drug variables between patients with and without neutropenia. However, patients with neutropenia had significantly lower baseline neutrophil counts (4.2 x 10(9)/liter; 95% confidence interval [95% CI] 3.8, 4.6 versus 6.2 x 10(9)/liter; 95% CI 6.0, 6.5), and a previous history of neutropenia while receiving disease-modifying antirheumatic drugs increased the risk while receiving TNF inhibitors (hazard ratio 2.97; 95% CI 1.69, 5.25). A significant drop in mean neutrophil count (1.12 x 10(9)/liter; 95% CI 0.92, 1.32) was observed after 2 weeks of TNF inhibitor therapy. Other white cell subsets tended to significantly increase. CONCLUSION: TNF inhibitor therapy is associated with a significant reduction in peripheral blood neutrophil count, leading to 19% of patients becoming neutropenic. Risk of neutropenia is significantly higher in patients with a low baseline neutrophil count or previous history of neutropenia. We suggest that patients receiving TNF inhibitor therapy would benefit from regular complete blood cell count monitoring.

Arthritis Care Res (Hoboken). 2010 Jun;62(6):770-4.
Trouble with tumor necrosis factor alpha inhibitors, not just tuberculosis.
Racunica T, Cassidy D, Cicuttini F, Hall A.

No abstract available

Arthritis Care Res (Hoboken). 2010 Jun;62(6):785-90.
Prevention of acute adverse events related to infliximab infusions in pediatric patients.
Lahdenne P, Wikström AM, Aalto K, Kolho KL.

OBJECTIVE: To study whether premedication with an oral antifebrile agent (acetaminophen) and antihistamine (cetirizine) could decrease the frequency of acute infusion reactions in pediatric patients. METHODS: All pediatric patients scheduled for infliximab infusions at the Helsinki University Central Hospital, a tertiary care center, were prospectively introduced to a standard oral premedication of acetaminophen (20 mg/kg) and cetirizine (10 mg) prior to infliximab infusions for a period of 1 year. All acute adverse events related to infliximab infusions given according to the guidelines of pediatric rheumatologists or gastroenterologists were registered for this time period and retrospectively during the preceding year. RESULTS: During the study period, infliximab infusions with premedication were given to 64 pediatric patients (48 with rheumatic disease and l6 with inflammatory bowel disease, mean age 13 years, n = 34 boys, and n = 30 girls). Infliximab was introduced to 14 children; the rest were on maintenance therapy. Twelve infusion reactions, 4 mild and 8 severe, were observed in 8 (12.5%) of the 64 subjects, and in 1 subject 4 times. During the preceding year, 60 pediatric patients had received infliximab infusions without premedication. In this latter group, infusion reactions occurred in 5 children (8.3%; P > 0.05). The presentation of an acute infusion reaction was not related to the sex or diagnosis of the patient. CONCLUSION: In pediatric patients, acute infusion reactions related to infliximab could not be prevented with premedication with oral acetaminophen and cetirizine.

Arthritis Care Res (Hoboken). 2010 Jun;62(6):791-9.
Prediction of nonspecific side effects in rheumatoid arthritis patients by beliefs about medicines.
Nestoriuc Y, Orav EJ, Liang MH, Horne R, Barsky AJ.

OBJECTIVE: This study examines the determinants of patients' side effects from arthritis medication. Proposed predictors were patients' beliefs about medications, objective disease activity, treatment regimen, and psychiatric and rheumatoid arthritis symptoms. METHODS: In a longitudinal design, 100 rheumatoid arthritis outpatients were investigated at baseline and again at 6 months after receiving both pharmacologic and psychosocial treatment. RESULTS: Multivariate analyses showed no influence of disease status, type of treatment, or psychiatric or arthritis symptoms on side effects. Heightened concerns about arthritis medication at baseline predicted side effects at baseline (partial correlation $r = 0.37$, $P < 0.001$) and at 6 months (partial correlation $r = 0.25$, $P < 0.001$) after controlling for relevant disease- and treatment-related variables. In a cross-lagged panel analysis, prior experience with side effects from arthritis medication was ruled out as a cause of heightened concerns, indicating that negative beliefs genuinely contribute to side effects. A comparison of patients who did and did not start new medications showed no difference in side effects in patients with positive beliefs about medications, but led to significantly more side effects in patients with negative beliefs. CONCLUSION: Patients' beliefs about arthritis medications were stable and consistently associated with side effects. Patients with greater concerns about their arthritis medications are at higher risk for developing side effects, especially when starting new drugs. Identifying those patients is important to avoid premature drug discontinuation. Research into cause and preventability of negative attitudes to prescribed medicines is needed.

Arthritis Care Res (Hoboken). 2010 Jun;62(6):896-8.
Yellow fever revaccination during infliximab therapy.
Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, Lima RA.

No abstract available

Semin Cutan Med Surg. 2010 Mar;29(1):16-9.
Assessing long-term drug safety: lessons (re) learned from raptiva.
Seminara NM, Gelfand JM.

Efalizumab was approved for moderate to severe psoriasis in 2003 based on studies in approximately 2700 patients, of whom only 218 were exposed to the drug for more than 1 year. In 2009, after more than 46,000 patients were exposed to efalizumab, the drug was withdrawn from the market after 3 confirmed and 1 suspected case of progressive multifocal leukoencephalopathy (PML) were spontaneously reported. As PML is very rare, it is extremely unlikely that the 4 reported cases were due to chance and given that PML occurs primarily in patients who are immunosuppressed, the association is likely causal. The identification of PML as a serious, but statistically rare risk of efalizumab demonstrates the strengths and weaknesses of the current drug approval and pharmacovigilance processes for fully measuring the safety of a drug. Patients and clinicians need to be aware of the relative completeness and limitations of existing safety data of a drug when selecting a treatment.

Can J Gastroenterol. 2010 May;24(5):307-11.
The safety of infliximab infusions in the community setting
Ducharme J, Pelletier C, Zacharias R.

BACKGROUND: Tumour necrosis factor-alpha (TNFalpha) has an important role in the pathogenesis of inflammatory conditions such as rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis. Infliximab, a chimeric anti-TNFalpha monoclonal antibody, has been shown to reduce the severity of symptoms or induces remission of active disease. Infusions have generally been limited to the hospital setting due to cost and concerns for patient safety. Studies defining its efficacy and safety have, therefore, originated almost exclusively from hospital settings. OBJECTIVE: To evaluate the safety of infliximab in a community clinic environment, across all types of patients. METHODS: A retrospective chart review of 3161 patients who received a combined 20,976 infusions at a network of community clinics over 16.5 months was conducted. Adverse drug reaction (ADR) information was retrieved and coded for time of onset, severity and outcome. Only ADRs that occurred during or within the first 24 h of the infusion were included. RESULTS: A total of 524 (2.5% of all infusions) acute ADRs in 353 patients (11.2%) were recorded. Most reactions (ie, ADRs) were mild (n=263 [50.2%, 1.3% of all infusions]) or moderate (n=233 [44.5%, 1.1% of all infusions]). Twenty-eight reactions (5.3%, 0.1% of all infusions) were severe. Emergency medical services were called to transport patients to hospital for seven of the

severe reactions, of which none required admission. As per pre-established medical directives, adrenaline was administered three times. CONCLUSIONS: Infliximab infusions are safe in the community setting. Severe ADRs were rare. None required active physician intervention; nurses were able to treat all reactions by following standardized medical directives.

International Journal of Dermatology 2010; 49(6):631-635
Progressive multifocal leukoencephalopathy and antipsoriatic drugs: Assessing the risk of immunosuppressive treatments
Vito Di Lernia

No abstract available

Clin Gastroenterol Hepatol. 2010 Jun;8(6):509-15. Epub 2010 Mar 2.
Crohn's disease is a risk factor for preterm birth.
Stephansson O, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, Falconer H, Ekbom A, Sørensen HT, Nørgaard M.

BACKGROUND & AIMS: Women with Crohn's disease (CD) are considered to be at increased risk for adverse outcomes of pregnancy. However, the few studies assessing this risk have had small sample sizes and limitations. We examined outcomes of pregnancy among a large cohort of primiparous women with CD. METHODS: Our population-based prevalence study utilized data from medical birth registries in Sweden and Denmark between 1994 and 2006. Linking birth registry data with national patient registries, we identified 2377 women with a hospital diagnosis of CD prior to delivery and 869,202 women with no diagnosis of CD. Using logistic regression analysis, we estimated relative risks with 95% confidence intervals (CI) for pre-eclampsia, preterm birth, 5-minute Apgar scores below 7, cesarean section, small for gestational age (SGA), stillbirth, and congenital malformations. RESULTS: Maternal CD was associated with increased risk of moderately and very preterm birth (prevalence odds ratio [POR], 1.76; 95% CI, 1.51-2.05; and POR, 1.86; 95% CI, 1.38-2.52, respectively). Maternal CD was also associated with increased risk for cesarean section (POR, 1.93; 95% CI, 1.76-2.12). The strongest associations with CD were observed for prelabor cesarean section and induced preterm delivery. Risk of small size for gestational age birth was slightly increased among women with CD, especially during the time period of 2002-2006 (POR, 1.43; 95% CI, 1.09-1.89). We found no increased risks for pre-eclampsia, low 5-minute Apgar score, stillbirth, or congenital malformations. CONCLUSIONS: Maternal CD is a risk factor for preterm birth, but not birth defects.

Arthritis Care Res (Hoboken). 2010 Jun;62(6):785-90.
Prevention of acute adverse events related to infliximab infusions in pediatric patients
Wikström AM, Aalto K, Kolho KL, Lahdenne P

OBJECTIVE: To study whether premedication with an oral antifebrile agent (acetaminophen) and antihistamine (cetirizine) could decrease the frequency of acute infusion reactions in pediatric patients. METHODS: All pediatric patients scheduled for infliximab infusions at the Helsinki University Central Hospital, a tertiary care center, were prospectively introduced to a standard oral premedication of acetaminophen (20 mg/kg) and cetirizine (10 mg) prior to infliximab infusions for a period of 1 year. All acute adverse events related to infliximab infusions given according to the guidelines of pediatric rheumatologists or gastroenterologists were registered for this time period and retrospectively during the preceding year. RESULTS: During the study period, infliximab infusions with premedication were given to 64 pediatric patients (48 with rheumatic disease and l6 with inflammatory bowel disease, mean age 13 years, n = 34 boys, and n = 30 girls). Infliximab was introduced to 14 children; the rest were on maintenance therapy. Twelve infusion reactions, 4 mild and 8 severe, were observed in 8 (12.5%) of the 64 subjects, and in 1 subject 4 times. During the preceding year, 60 pediatric patients had received infliximab infusions without premedication. In this latter group, infusion reactions occurred in 5 children (8.3%; $P > 0.05$). The presentation of an acute infusion reaction was not related to the sex or diagnosis of the patient. CONCLUSION: In pediatric patients, acute infusion reactions related to infliximab could not be prevented with premedication with oral acetaminophen and cetirizine.

Gastroenterol Clin Biol. 2010 Feb;34(2):140-1. Epub 2010 Feb 6.

Development of diffuse psoriasis with alopecia during treatment of Crohn's disease with infliximab
Medkour F, Babai S, Chanteloup E, Buffard V, Delchier JC, Le-Louet H.

No abstract available

Arch Dermatol. 2010 Jun;146(6):651-4.
Fatal influenza A(H1N1) respiratory tract infection in a patient having psoriasis treated with infliximab
Kling MC, Larian AA, Scordi-Bello I, Emer J, Lebwohl MG.

BACKGROUND: The use of biologic agents represents a remarkable advance for patients with psoriasis and psoriatic arthritis who have experienced an incomplete response to other therapeutic modalities. Decreased mortality and improved quality of life have been reported in patients undergoing treatment with these agents. Increased risk of bacterial, viral, granulomatous, and opportunistic infections also has been associated with the use of these medications. Enhanced patient education, watchful monitoring to promote early detection of infections, discontinuation of the medication when clinical symptoms are identified, and immediate availability of supportive care are advised to balance the benefit of treatment with biologic agents against the potential risk of infection. Herein, we discuss the risk of infection and the monitoring and vaccination guidelines in patients having psoriasis treated with biologic agents. OBSERVATIONS: A woman with obesity and psoriasis that had previously been successfully treated with efalizumab (Raptiva) for 3 years was started on a regimen of infliximab (Remicade) to treat a flare. She died 1 week after her first infusion of infliximab and was found to have had influenza A(H1N1). CONCLUSIONS: We report the first case to date of a patient with psoriasis who died of influenza A(H1N1) respiratory tract infection while undergoing treatment with infliximab. Further observations are needed to make a causal association.

Ann Rheum Dis. 2010 Jun 15. [Epub ahead of print]
Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists
García-Doval I, Pérez-Zafrilla B, Descalzo MA, Roselló R, Hernández MV, Gómez-Reino JJ, Carmona L; BIOBADASER 2.0 Study Group.

OBJECTIVE: /st> To estimate the incidence of hospitalisation due to varicella zoster virus (VZV) infection in patients treated with tumour necrosis factor (TNF) antagonists for inflammatory rheumatic conditions and to compare it with the expected rate in the general population. METHODS: /st> Secondary data analysis was performed of two large databases: (1) the national registry of rheumatic diseases patients treated with biological agents (BIOBADASER); and (2) the national hospital discharge database Conjunto Mínimo Básico de Datos al Alta Hospitalaria. Hospitalisations due to shingles or chickenpox were analysed. For each condition the incidence rate (IR) and the age and gender standardised IR per 100 000 person-years plus the standardised incidence ratio (SIR) and the standardised incidence difference (SID) were estimated. RESULTS: /st> In patients exposed to TNF antagonists, the estimated IR of hospitalisation due to shingles was 32 cases per 100 000 patient-years (95% CI 14 to 78), the expected rate in the general population was 3.4 (95% CI 3.2 to 3.5), the SIR was 9 (95% CI 3 to 20) and the SID was 26 (95% CI 14 to 37). The estimated IR of hospitalisation due to chickenpox was 26 cases per 100 000 (95% CI 10 to 69), the expected rate was 1.9 (95% CI 1.8 to 2.0), the SIR was 19 (95% CI 5 to 47) and the SID 33 (95% CI 21 to 45). CONCLUSIONS: /st> Patients suffering rheumatic diseases exposed to TNF antagonists are hospitalised due to VZV infections significantly more frequently than expected in the general population. Since the absolute IR of hospitalisations due to chickenpox and shingles is low in these patients, the implementation of risky preventive measures may not be justified at present.

Joint Bone Spine. 2010 Jun 7. [Epub ahead of print]
TNFalpha antagonist therapy does not increase the Epstein-Barr virus burden in patients with rheumatoid arthritis or ankylosing spondylitis
Couderc M, Payet S, Henquell C, Dubost JJ, Soubrier M.

OBJECTIVE: The risk of non-Hodgkin lymphoma is increased in rheumatoid arthritis (RA) but not in ankylosing spondylitis (AS). In RA, the degree of inflammation is closely associated with the lymphoma

risk. Whether immunosuppressants such as methotrexate and TNFalpha antagonists affect the lymphoma risk in RA is unclear. The Epstein-Barr virus (EBV) may contribute to the pathogenesis of RA and may be involved in the development of lymphoma in patients taking methotrexate and/or TNFalpha antagonists, although these points remain debated. EBV load monitoring during immunosuppressive treatment may predict the occurrence of EBV-related lymphoma. Here, our objective was to prospectively measure the EBV load in patients receiving TNFalpha antagonists for RA or AS. METHODS: We prospectively studied patients with RA or AS before and after TNFalpha antagonist therapy initiation. The EBV load was measured in blood samples using the EBV R-gene Quantification Kit. Disease activity at the time of blood sampling was evaluated by determining the Disease Activity Score 28 (DAS28) in RA patients and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in AS patients. RESULTS: We included 46 patients with RA (82.6% women; mean age, 52.7+/-11.3 years) and 27 with AS (men, 81.5%; mean age, 45.1+/-12.7 years). In the RA group, the EBV load was measured at baseline and 9.72+/-5.7 months later. The baseline EBV load was undetectable in 33 (70.2%) patients; mean EBV load in the 13 remaining patients was 9389copies/ml (3.47 log(10)+/-0.45). Baseline EBV load did not correlate with disease activity (DAS28). At the follow-up assay, the EBV load became positive in five patients and increased significantly in one patient (four patients on etanercept, one on adalimumab, and one on infliximab); it became negative in six patients (five on adalimumab and one on etanercept) and showed non-significant changes in six patients. Mean EBV load in patients positive at follow-up was 3.63+/-0.52 log(10) copies/ml. Mean DAS28 was 4.78+/-1.1 at baseline and 2.94+/-1.24 at follow-up. At follow-up, a good EULAR response was noted in 33 (71.7%) patients and a moderate EULAR response in seven (15.2%) patients. In the AS group, the baseline EBV load measurement occurred after 12.9+/-10.6 months. Baseline EBV load was undetectable in 25 (92.6%) patients; mean load in the remaining two patients was 4.15+/-0.46 log(10) copies/ml. At follow-up, the EBV load became positive in two patients (one on adalimumab and one on infliximab) and became negative in one patient (on adalimumab). Mean load in positive patients was 3.33+/-0.24 log(10) copies/ml. Mean BASDAI was 55.1+/-16.2 at baseline and 17.88+/-18.62 at follow-up. A positive EBV load was significantly more common in the RA group than in the AS group (P=0.039). EBV load changes did not differ significantly between the RA and AS groups or across TNFalpha antagonists. No cases of lymphoma were recorded. CONCLUSION: Introducing TNFalpha antagonist therapy does not affect the EBV load in patients with RA or AS. EBV load monitoring is probably unnecessary in patients given TNFalpha antagonists for RA or AS.

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Anti-tumor necrosis factor therapy and cancer risk in patients with autoimmune disorders
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