Literature Update Immunology

Period: 01-31 Dec 2009

IBD

Aliment Pharmacol Ther. 2009 Aug 26.
Efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF.
Allez M, Vermeire S, Mozziconacci N, Michetti P, Laharie D, Louis E, Bigard MA, Hébuterne X, Treton X, Kohn A, Marteau P, Cortot A, Nichita C, Vanassche G, Rutgeerts P, Lémann M, Colombel JF.

Adalimumab (ADA) and certolizumab pegol (CZP) have demonstrated efficacy in Crohn's disease (CD) patients previously treated with infliximab (IFX). Aim: To assess the efficacy and tolerability of a third anti-TNF in CD after failure of and/or intolerance to two different anti-TNF. Methods: CD patients who received ADA or CZP after loss of response and/or intolerance to two anti-TNF were included in this retrospective study. Data were collected using a standardized questionnaire. Clinical response, duration, safety and reasons for discontinuation were assessed. Results: Sixty-seven patients treated with CZP (n=40) or ADA (n=27) were included. A clinical response was observed in 41 (61%) at week 6 and 34 patients (51%) at week 20. The probability of remaining under treatment at 3 months, 6 months and 9 months was 68%, 60% and 45%, respectively. At the end of follow-up, the third anti-TNF had been stopped in 36 patients for intolerance (n=13), or failure (n=23). Two deaths were observed. Conclusion: Treatment, with a third anti-TNF (CZP or ADA) agent, of CD patients who have experienced loss of response and/or intolerance to two anti-TNF antibodies, has favorable short- and long-term efficacy and is an option to be considered in patients with no other therapeutic options.

Aliment Pharmacol Ther. 2009 Aug 18.
An analysis of the placebo effect in Crohn's disease over time.
Gallahan WC, Case D, Bloomfeld RS.

Abstract Background: Randomized, placebo controlled trials are used to assess the efficacy of therapies for Crohn's disease. The placebo response and remission rates vary among studies. Aim: The purpose of this study was to analyze how the placebo response and remission rates in Crohn's trials have changed over time in the era of parenteral biologic therapies. Methods: A search for randomized, placebo-controlled trials of parenteral biologic therapies for active Crohn's disease was conducted using online databases. The placebo response and remission rates and study week of evaluation were recorded for each trial. The placebo response and remission rates were analyzed as functions of publication date and study week of evaluation. Results: The odds of a placebo induced remission and response significantly increased as the week of evaluation increased. The placebo remission rate increased significantly with year of publication. Adjusted for week of evaluation, this increase in placebo remission rate over time was no longer significant. The increase in the placebo response over this time period was not statistically significant. Conclusion: The observed increase in placebo remission rates over time in trials of parenteral biologic therapies in Crohn's disease is explained by longer times to the primary endpoint in more recent trials.

Am J Gastroenterol. 2009 Dec;104(12):2973-86. Epub 2009 Sep 15.
Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas.
Ng SC, Plamondon S, Gupta A, Burling D, Swatton A, Vaizey CJ, Kamm MA.

OBJECTIVES:Anti-tumor necrosis factor (TNF) therapy heals Crohn's fistulas clinically, but the rate, extent, and duration to achieve fistula track healing are unknown.METHODS:We sought to monitor deep healing, as indicated by magnetic resonance imaging (MRI), and to use this to determine treatment duration. Clinical and MRI fistula healing (at 6, 12, and 18 months), Crohn's Disease Activity Index (CDAI), Perianal Crohn's Disease Activity Index (PDAI), and the Inflammatory Bowel Disease Questionnaire were prospectively assessed.RESULTS:Thirty-four consecutive patients with perineal fistulas were treated with infliximab (19), adalimumab (7; all infliximab failures) and thalidomide (8).

Median follow-up was 110 weeks (range, 74-161). Baseline MRI: 38% >/=2 tracks, 21% anolabial/rectovaginal. At latest follow-up, clinical fistula 'response' and 'closure' were seen in 50 and 46% of antibody-treated patients, respectively. All patients stopped thalidomide early due to side effects. Of 26 antibody-treated patients, at 6 (n=25), 12 (n=25), and 18 (n=20) months, respectively, MRI showed complete healing (20, 28, and 30%, respectively), improvement (68, 72, and 65%), no change (12, 0, and 0%) or worsening (0, 0, and 5%). MRI healing at 6 months (n=5) persisted at 12 and 18 months, including in two patients who stopped treatment at 6 months. Fistula history length and complexity did not influence the outcome. The only surgical intervention was seton insertion in one patient. The PDAI and CDAI scores decreased, and quality of life improved significantly at last follow-up.CONCLUSIONS:MRI fistula resolution was variable and slower than clinical healing. Prolonged treatment is often required for internal track resolution. Preliminary data suggest once MRI healing has occurred fistulas remain healed, while remaining on, or stopping anti-TNFalpha therapy. The use of a second antibody is clinically valuable.

Am J Gastroenterol. 2009 Dec;104(12):2990-5. Epub 2009 Sep 1.
An open-label prospective randomized multicenter study shows very rapid remission of ulcerative colitis by intensive granulocyte and monocyte adsorptive apheresis as compared with routine weekly treatment.
Sakuraba A, Motoya S, Watanabe K, Nishishita M, Kanke K, Matsui T, Suzuki Y, Oshima T, Kunisaki R, Matsumoto T, Hanai H, Fukunaga K, Yoshimura N, Chiba T, Funakoshi S, Aoyama N, Andoh A, Nakase H, Mizuta Y, Suzuki R, Akamatsu T, Iizuka M, Ashida T, Hibi T.

OBJECTIVES:Granulocyte and monocyte adsorptive apheresis (GMA) has shown efficacy in patients with active ulcerative colitis (UC). However, with routine weekly treatment, it may take several weeks to achieve remission, and to date, the efficacy of a more frequent treatment schedule remains unknown. The aim of this study was to assess the clinical efficacy and safety of intensive GMA treatment in patients with active UC.METHODS:This was an open-label, prospective, randomized multicenter study to compare an intensive, two GMA sessions per week, with the routine, one GMA session per week. A total of 163 patients with mild-to-moderately active UC were randomly assigned to routine weekly treatment or intensive treatment. The maximum number of sessions of GMA permitted was 10. However, when patients achieved remission, GMA was discontinued. Remission rate at the end of the study, time to remission, and adverse events were assessed in both groups.RESULTS:Of the 163 patients, 149 were available for efficacy analysis as per protocol, 76 were in weekly GMA, and 73 were in intensive GMA. At the end of the study period, clinical remission was achieved in 41 of 76 patients (54.0%) in weekly GMA and in 52 of 73 patients (71.2%) in intensive GMA (P=0.029). The mean time to remission was 28.1+/-16.9 days in the weekly GMA treatment group and 14.9+/-9.5 days in the intensive GMA group (P<0.0001). Intensive GMA was well tolerated without GMA-related serious adverse side effects.CONCLUSIONS:Intensive GMA in patients with active UC seems to be more efficacious than weekly treatment, and significantly reduced the patients' morbidity time without increasing the incidence of side effects.

Nat Rev Gastroenterol Hepatol. 2009 Dec 1.
Clinical implications of mucosal healing for the management of IBD.
Pineton de Chambrun G, Peyrin-Biroulet L, Lémann M, Colombel JF; Medscape.

Mucosal healing (MH) has emerged as an important treatment goal for patients with IBD. Historically, the therapeutic goals of induction and maintenance of clinical remission seemed insufficient to change the natural history of IBD. Evidence has now accumulated to show that MH can alter the course of IBD, as it is associated with sustained clinical remission, and reduced rates of hospitalization and surgical resection. In patients with ulcerative colitis, MH may represent the ultimate therapeutic goal because inflammation is limited to the mucosa. In patients with Crohn's disease, which is a transmural disease, MH could be considered as a minimum therapeutic goal. This Review focuses on the definition of MH and discusses the ability of each available IBD medication to induce and maintain MH. The importance of achieving MH is also discussed and literature that demonstrates improvement of disease course with MH is reviewed. Finally, we discuss how best to integrate the treatment end point of MH into clinical practice for the management of patients with IBD.

Gastroenterol Clin North Am. 2009 Dec;38(4):577-94.
Evolving inflammatory bowel disease treatment paradigms: top-down versus step-up.

Devlin SM, Panaccione R.
Republished in:
Med Clin North Am. 2010 Jan;94(1):1-18.

Crohn disease (CD) and ulcerative colitis (UC) comprise a group of inflammatory disorders of the gastrointestinal tract that can vary in severity of disease, anatomic extent of inflammation, presence and nature of extraintestinal manifestations, and response to therapeutic approaches. There have been attempts to classify CD based on the location and behavior of disease. Advances in understanding of genetic susceptibility to inflammatory bowel disease (IBD) suggest that CD and UC may represent a continuum of overlapping disorders. This has led to an attempt to classify IBD on clinical, molecular, and serologic grounds. Differences in clinical, genetic, and immunologic profiles may require more targeted, refined treatment approaches to help clinicians make decisions regarding recently introduced biologic agents. This article provides an overview of the current approaches to therapy for CD and UC and focuses on the evidence supporting the rationale for changing paradigms in the management of IBD, including mucosal healing as an end point and earlier use of immunosuppressive and biologic agents, particularly in CD (so-called top-down therapy).

Med Clin North Am. 2010 Jan;94(1):19-34.
Treatment of fistulizing inflammatory bowel disease.
Schwartz DA, Maltz BE.

Fistulas manifest frequently in Crohn disease and can result in significant morbidity and often lead to the need for surgical intervention. Historically, it has been more difficult to obtain complete fistula closure in patients with perianal Crohn disease. Anti-tumor necrosis factor-alpha agents and the use of more accurate imaging modalities such as magnetic resonance imaging and rectal endoscopic ultrasound have enhanced the ability to manage fistulizing Crohn disease. A combined medical and surgical approach usually presents the best option for most patients.

Gastroenterol Clin North Am. 2009 Dec;38(4):729-52.
Novel diagnostic and prognostic modalities in inflammatory bowel disease.
Zisman TL, Rubin DT.
Republished in:
Med Clin North Am. 2010 Jan;94(1):155-78.

Inflammatory bowel disease remains a complex disease with variable clinical presentations and oftennonspecific symptoms. Physicians must rely on diagnostic tools for clarification of disease diagnosis and for guiding management of patients with established disease. Advances in radiologic imaging modalities facilitate early and accurate detection of luminal disease and extraluminal complications. The introduction and dissemination of small bowel capsule endoscopy and double-balloon enteroscopy permit detailed visualization and sampling of the mucosa throughout the entire bowel. Serologic biomarkers are evolving as a valuable tool to clarify diagnosis and stratify patients by disease phenotypes and patterns of behavior. Neutrophil-derived fecal biomarkers are emerging as useful surrogate markers of intestinal inflammation with the potential for a variety of clinical applications, but their application to clinical management has not yet been clarified.

Med Clin North Am. 2010 Jan;94(1):179-88.
Postoperative management of crohn disease.
Cho SM, Cho SW, Regueiro M.

Crohn disease often recurs after surgical resection. Despite extensive research in the prevention of postoperative Crohn disease, optimal management strategies have yet to be defined. Risk of disease recurrence needs to be carefully balanced against potential risks associated with treatment. Patients with low risk of postoperative recurrence may not require medication, whereas those at moderate risk may benefit from antibiotics or immunomodulators. Those at highest risk of recurrence may benefit from biologic therapy for maintenance of surgical remission. Postoperative colonoscopy within 1 year of resective surgery is important for identification of disease recurrence and modification of medications.

Gut. 2009 Aug 2.
Trough Serum Infliximab: A Predictive Factor Of Clinical Outcome For Infliximab Therapy In Acute Ulcerative Colitis.
Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR.

Background & AIMS: Antibodies to infliximab reduce serum infliximab with loss of clinical benefit, but undetectable trough serum concentrations of infliximab may occur without antibody formation. The relation between trough serum infliximab and clinical outcomes was evaluated in acute ulcerative colitis. METHODS: In a cohort of 115 ulcerative colitis patients treated with 3-dose induction followed by scheduled maintenance infliximab, rates of clinical remission, colectomy, antibodies to infliximab and trough serum infliximab were determined. RESULTS: Rates of remission were 32% at week 10 and 37% at week 54. Colectomy occurred in 40% of patients, at a median of 5.3 (IQR: 1.9-12.1) months. Detectable trough serum infliximab was present in 39% of patients and among patients with undetectable infliximab, 41% were antibody positive and 20% were antibody negative. For antibody positive and antibody negative patients, rates of remission (18% vs. 14%), endoscopic improvement (25% vs. 35%) and colectomy (52% vs. 59%) were not different. A detectable serum infliximab was associated with higher rates of remission (69% vs. 15%; P <0.001) and endoscopic improvement (76% vs. 28%, P <0.001). An undetectable serum infliximab predicted an increased risk for colectomy (55% vs. 7%, odds ratio 9.3; 95% confidence interval, 2.9 - 29.9; P <0.001). Concurrent immunosuppression was not associated with clinical outcomes. CONCLUSIONS: For ulcerative colitis patients treated with infliximab, a detectable trough serum infliximab predicts clinical remission, endoscopic improvement, and a lower risk for colectomy. In assessing clinical outcomes to infliximab, the presence of antibodies to infliximab is a surrogate for absent drug.

Inflamm Bowel Dis. 2009 Aug 3.
World Gastroenterology Organisation Practice Guidelines for the Diagnosis and Management of IBD in 2010.
Bernstein CN, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, Gearry R, Goh KL, Hamid S, Khan AG, Lemair AW; Malfertheiner, Ouyang Q, Rey JF, Sood A, Steinwurz F, Thomsen OO, Thomson A, Watermeyer G.

Inflammatory bowel disease (IBD) represents a group of idiopathic, chronic, inflammatory intestinal conditions. Its two main disease categories are: Crohn's disease (CD) and ulcerative colitis (UC), which feature both overlapping and distinct clinical and pathological features. While these diseases have, in the past, been most evident in the developed world, their prevalence in the developing world has been gradually increasing in recent decades. This poses unique issues in diagnosis and management which have been scarcely addressed in the literature or in extant guidelines. Depending on the nature of the complaints, investigations to diagnose either form of IBD or to assess disease activity will vary and will also be influenced by geographic variations in other conditions that might mimic IBD. Similarly, therapy varies depending on the phenotype of the disease being treated and available resources. The World Gastroenterology Organization has, accordingly, developed guidelines for diagnosing and treating IBD using a cascade approach to account for variability in resources in countries around the world.

World J Gastroenterol. 2009 Dec 14;15(46):5784-8.
Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease.
Liu ZJ, Yadav PK, Su JL, Wang JS, Fei K.

The etiopathology of inflammatory bowel disease (IBD) remains elusive. Accumulating evidence suggests that the abnormality of innate and adaptive immunity responses plays an important role in intestinal inflammation. IBD including Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract, which is implicated in an inappropriate and overactive mucosal immune response to luminal flora. Traditionally, CD is regarded as a Th1-mediated inflammatory disorder while UC is regarded as a Th2-like disease. Recently, Th17 cells were identified as a new subset of T helper cells unrelated to Th1 or Th2 cells, and several cytokines [e.g. interleukin (IL)-21, IL-23] are involved in regulating their activation and differentiation. They not only play an important role in host defense against extracellular pathogens, but are also associated with the development of autoimmunity and inflammatory response such as IBD. The identification of Th17 cells helps us to explain some of the anomalies seen in the Th1/Th2 axis and has broadened our understanding of the immunopathological effects of Th17 cells in the development of IBD.

J Gastroenterol. 2009 Dec 4.
Evolving paradigms in the pathogenesis of IBD.
Mayer L.

The pathogenesis of all immune-mediated inflammatory diseases has been carefully studied over the past several decades, but it is only recently that we have come to appreciate common pathways and genes. This is especially true for the inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis, where a keener appreciation of the contributions of genetics, environment, and immune response have been dissected. In fact, in many ways, IBD has become the model for studying such disorders. The complex nature of interactions is continuing to be defined, and novel therapies targeting defects in these interactions have been developed and are being tested in the clinic. The era of bench to bedside has finally matured, and cures for debilitating diseases are now in sight. This review describes our current state of knowledge of each component of IBD pathogenesis. What has evolved is a clearer picture and novel targets for therapy.

PLoS One. 2009 Nov 24;4(11):e7984.
Mucosal gene expression of antimicrobial peptides in inflammatory bowel disease before and after first infliximab treatment.
Arijs I, De Hertogh G, Lemaire K, Quintens R, Van Lommel L, Van Steen K, Leemans P, Cleynen I, Van Assche G, Vermeire S, Geboes K, Schuit F, Rutgeerts P.

BACKGROUND: Antimicrobial peptides (AMPs) protect the host intestinal mucosa against microorganisms. Abnormal expression of defensins was shown in inflammatory bowel disease (IBD), but it is not clear whether this is a primary defect. We investigated the impact of anti-inflammatory therapy with infliximab on the mucosal gene expression of AMPs in IBD. METHODOLOGY/PRINCIPAL FINDINGS: Mucosal gene expression of 81 AMPs was assessed in 61 IBD patients before and 4-6 weeks after their first infliximab infusion and in 12 control patients, using Affymetrix arrays. Quantitative real-time reverse-transcription PCR and immunohistochemistry were used to confirm microarray data. The dysregulation of many AMPs in colonic IBD in comparison with control colons was widely restored by infliximab therapy, and only DEFB1 expression remained significantly decreased after therapy in the colonic mucosa of IBD responders to infliximab. In ileal Crohn's disease (CD), expression of two neuropeptides with antimicrobial activity, PYY and CHGB, was significantly decreased before therapy compared to control ileums, and ileal PYY expression remained significantly decreased after therapy in CD responders. Expression of the downregulated AMPs before and after treatment (DEFB1 and PYY) correlated with villin 1 expression, a gut epithelial cell marker, indicating that the decrease is a consequence of epithelial damage. CONCLUSIONS/SIGNIFICANCE: Our study shows that the dysregulation of AMPs in IBD mucosa is the consequence of inflammation, but may be responsible for perpetuation of inflammation due to ineffective clearance of microorganisms.

Am J Gastroenterol. 2009 Dec 8.
Are Colonoscopy and Bowel Ultrasound Useful for Assessing Response to Short-Term Therapy and Predicting Disease Outcome of Moderate-to-Severe Forms of Ulcerative Colitis?: A Prospective Study.
Parente F, Molteni M, Marino B, Colli A, Ardizzone S, Greco S, Sampietro G, Foschi D, Gallus S.

OBJECTIVES:Mucosal healing has been proposed as an important sign of the efficacy of medical treatment of inflammatory bowel disease; however, direct evidence in ulcerative colitis (UC) is scarce. We evaluated the usefulness of colonoscopy and bowel ultrasound (US) as indexes of response to short-term therapy and as predictors of subsequent outcome in UC.METHODS:A total of 83 patients with moderate-to-severe UC were recruited; endoscopic and US severity was graded 0-3 at entry according to validated scores. Of the recruited patients, 74, who were clinically responsive to steroids, were followed up with repeated colonoscopy and bowel US at 3, 9, and 15 months from recruitment. Concordance between clinical, endoscopic, and US scores at various visits was determined by kappa statistics. Multiple unconditional logistic regression models were used to assess the predictivity of clinical, endoscopic, and US scores measured at 3 and 9 months on the development of endoscopic UC relapse within 15 months.RESULTS:A variable concordance was found over time between endoscopic and clinical score (weighted kappa between 0.38 and 0.95), with high and consistent concordance between endoscopic and

US scores (weighted kappa between 0.76 and 0.90). On logistic regression analysis, moderate-to-severe endoscopic and US scores at 3 months were associated with a high risk of endoscopic activity at 15 months (odds ratio (OR): 5.2; 95% confidence interval (CI): 1.6-17.6 and OR: 9.1; 95% CI: 2.5-33.5, respectively).CONCLUSIONS:Bowel US may be used as a surrogate of colonoscopy in assessing the short-term response of severe forms of UC to therapy. Both US score and endoscopic score after 3 months of steroid therapy predict outcome of disease at 15 months.Am J Gastroenterol advance online publication, 8 December 2009; doi:10.1038/ajg.2009.672.

Radiographics. 2009 Oct;29(6):1847-67.
Utility of high-resolution MR imaging in demonstrating transmural pathologic changes in Crohn disease.
Sinha R, Rajiah P, Murphy P, Hawker P, Sanders S.

Magnetic resonance (MR) imaging has emerged as an imaging modality that can be used to help diagnose and evaluate Crohn disease of the small and large bowel. MR imaging has high diagnostic accuracy in the detection of Crohn disease, and high-resolution thin-section MR images can demonstrate transmural pathologic changes of Crohn disease from the level of the mucosa to that of the mesentery. High-resolution MR image data also may be used to construct high-quality multiplanar and endoluminal views that may provide additional diagnostic information. Knowledge of the MR imaging findings of Crohn disease and how they correlate with the pathologic features of the disease is important to facilitate accurate diagnosis and detect complications.

J Clin Gastroenterol. 2010 Jan;44(1):34-7.
Infliximab reintroduction is not associated to a higher rate of immune-related adverse effects in patients with inflammatory bowel disease initially treated with a three-infusion induction regimen.
Domènech E, Zabana Y, Mañosa M, Garcia-Planella E, Cabré E, Gassull MA.

BACKGROUND: Episodic infliximab (IFX) treatment is associated with a higher risk for acute infusion reactions (AIR) and secondary loss of response (SLR), but this has not been evaluated in patients initially treated with an induction regimen with 3 IFX infusions. AIMS: To evaluate whether IFX reintroduction after > or = 4 months in patients treated with a 3-infusion induction regimen is associated with a higher incidence of AIR or SLR. METHODS: Incidence of immunogenic adverse effects was assessed in patients with inflammatory bowel disease who received > or = 4 consecutive IFX infusions (3 infusions at weeks 0, 2, and 6, plus > or = 1 maintenance infusion) (Continuous, n=47) and patients who were treated with a successful initial 3-infusion induction scheme and in whom IFX was then discontinued because of a complete response but reintroduced > or = 4 months later (Reintro, n=29). RESULTS: AIR rate was 17% in both groups, and SLR rate was 26% in the Continuous group and 15% in the Reintro group (not significant). The lack of concomitant immunomodulators and/or pretreatment with hydrocortisone were associated with AIR development (P=0.002). CONCLUSIONS: In patients who completed a 3-infusion induction regimen, IFX can be safely reintroduced even after a long time from discontinuation.

Aliment Pharmacol Ther. 2009 Oct 14.
Clinical outcome of newly diagnosed Crohn's disease: comparative, retrospective, study before and after infliximab availability.
Domènech E, Zabana Y, Garcia-Planella E, López San Román A, Nos P, Ginard D, Gordillo J, Martínez-Silva F, Beltrán B, Mañosa M, Cabré E, Gassull MA.

Summary Background: Infliximab (IFX) could change the course of Crohn's disease (CD) by reducing steroid use, surgery, or prompting earlier introduction of immunomodulators (IMM). Aim: To evaluate the impact of IFX availability on the course of early CD. Patients and methods: Two cohorts of newly diagnosed CD patients were identified: The first cohort included patients diagnosed from January 1994 to December 1997, and the second from January 2000 to December 2003. All patients were diagnosed, treated and followed in a same centre until December 1999 (first cohort) or December 2005 (second cohort). Development of disease-related complications, steroid, IMM or IFX requirements, and intestinal resections during follow-up were registered. Results: A total of 328 patients were included (146 first cohort, 182 second cohort). A similar proportion of patients in both cohorts received steroids, but steroid exposure resulted significantly more intense in the first cohort (P= 0,001). In the second cohort, 14% of patients received IFX. Thiopurines were used more (P=0,001) and earlier (P=0,012) in the second cohort.

No differences in surgical requirements or the development of disease-related complications were found. Conclusions: Following a step-up therapeutic algorithm, IFX availability did not reduce surgical requirements or the development of disease-related complications.

Aliment Pharmacol Ther. 2009 Oct 10.
A new rapid home test for faecal calprotectin in ulcerative colitis.
Elkjaer M, Burisch J, Voxen Hansen V, Deibjerg Kristensen B, Slott Jensen JK, Munkholm P.

Abstract Background: Enzyme-linked immunosorbent assay (ELISA) is a time consuming method for faecal calprotectin (FC). Two new quantitative rapid tests (RT) have been developed. Aim: To compare the new rapid tests with ELISA as 'Gold Standard'. Methods: Quantitative analysis involved application of a sample onto the 'Lateral Flow Device' (LFD). The colour intensity of a test line was read using a laptop computer linked to a scanner (RT scanning). A picture taken with a mobile phone (HT photo) of the same LFD was sent to a server via Mobile Internet and the result appearing on the phone screen after 15 seconds. Results: Four hundred and four faecal samples were analysed. Mean differences of 1.7 mg/kg (range -23.4-20.1) ELISA versus RT scanning, 6.8 mg/kg (-28-14.5) ELISA versus HT photo and 2.9 mg/kg (-10.3-4.5) RT scanning versus HT photo were found with good agreement calculated by kappa statistic (86%, 87% and 95%, respectively). The Coefficients of Variation for HT photo < 10% with a sensitivity of 96.2% and a specificity of 90.1%. Conclusion: The new rapid tests are accurate, and are of utility in clinical settings. Feasibility of the home test as part of disease control and self-management are currently being investigated.

J Am Acad Dermatol. 2010,62,162
Infliximab treatment of severe genital ulcers associated with Behçet disease.
Chikatoshi Kasugai, Daisuke Watanabe, Kimihiko Mizutani, Yuko Masuda, Masahiro Zako, Tomoyuki Mukai, Yasuhiko Tamada, Yoshinari Matsumoto

No abstract available.

J Pediatr Gastroenterol Nutr. 2010 Jan;50(1):27-31.
Rising incidence of inflammatory bowel disease among children: a 12-year study.
Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD.

OBJECTIVE: Data suggest an increase in the incidence of pediatric inflammatory bowel disease (IBD). We examined the trend of the incidence of IBD in children. PATIENTS AND METHODS: A retrospective investigation was conducted on a cohort of children diagnosed with IBD between 1991 and 2002 who were registered in the IBD center at Texas Children's Hospital. The diagnosis of IBD was based on clinical, radiological, endoscopic, and histological examinations. RESULTS: There were 272 children eligible for the analysis; 56% diagnosed with Crohn disease (CD), 22% with ulcerative colitis (UC), and 22% with indeterminate colitis. The male-to-female ratio was 1.2:1 in CD, 0.6:1 in UC, and 0.8:1 in indeterminate colitis. From 1991 to 2002, the incidence rate has doubled from 1.1/100,000/year (95% confidence interval [CI] 0.85-1.36) to 2.4/1001,000/year (95% CI 2.10-2.77). This trend was valid for CD but not for UC. Whites had higher incidence rate of IBD than African Americans or Hispanics: 4.15/100,000/year (95% CI 3.48-4.82) versus 1.83/100,000/year (95% CI 1.14-2.51), and 0.61/100,000/year (95% CI 0.33-0.89), respectively. African Americans were predominantly diagnosed with CD. CONCLUSIONS: The results demonstrate the rising incidence of IBD among children with evidence of more CD than UC. Recognition of these results will have important implications for diagnosis and management of IBD in children.

World J Gastroenterol. 2010 Jan 7;16(1):15-20.
Limitations in assessment of mucosal healing in inflammatory bowel disease.
Freeman HJ.

An emerging parameter to define the effectiveness of new therapeutic agents in clinical trials, and by extension, for use in day-to-day clinical practice has been labeled mucosal healing. It has been hypothesized that complete healing of the intestinal mucosa in inflammatory bowel diseases should result in reduced disease complications, reduced hospitalization and reduced surgical treatment. By implication,

the natural history of inflammatory bowel disease might then be altered. Measurement of mucosal healing, however, is largely observational, requiring repeated invasive endoscopic examinations, sometimes with mucosal biopsies. Other indirect imaging methods may play a role in this assessment along with other surrogate markers, including intestinal permeability. These measurements may have significant limitations that prohibit precise correlation with symptom-based disease activity indices in clinical trials. This likely reflects the dynamic nature of this evolving and individualized inflammatory process that tends to be focused, but not limited, to the mucosa of the intestinal tract.

Scand J Gastroenterol. 2009;44(12):1435-42.
A systematic review and meta-analysis of anti-adhesion molecule therapy in patients with active Crohn's disease.
Li Y, Tian Y, Yu C, Zhu W, Li J.

OBJECTIVE: Due to the crucial role played by adhesion molecules in the pathogenesis of Crohn's disease (CD), targeting of these molecules has recently been proposed as a new direction for the development of anti-inflammatory strategies for CD. The aim of this study was to provide up-to-date evidence on the effectiveness and safety of anti-adhesion molecule therapy in treating active CD. MATERIAL AND METHODS: We studied articles retrieved by PubMed, EMBASE, the Cochrane Library and the Science Citation Index for randomized controlled trials (RCTs) relevant to CD and anti-adhesion molecule therapy. RESULTS: Seven RCTs comparing anti-adhesion molecule therapy with placebo were included in a meta-analysis to evaluate the efficacy and safety of anti-adhesion molecule strategies in active CD. On the basis of pooled results of the seven RCTs (n = 2228), we found a significant difference in clinical remission rates between groups [relative risk (RR) 1.31, 95% confidence interval (CI) 1.12-1.52, fixed-effect model]. Five RCTs (n = 2178) compared the response rates of anti-adhesion molecule therapy and placebo; in overall analysis, anti-adhesion molecule therapy was effective for active CD (RR 1.28, 95% CI 1.16-1.42, random-effect model). In five studies enrolling 1867 individuals, anti-adhesion molecule therapy did not increase adverse events (RR 1.03, 95% CI 0.98-1.08, fixed-effect model). CONCLUSIONS: Anti-adhesion molecule therapy, which could prevent leukocyte recruitment, was effective and safe for treating active CD. Because of the small number of studies included in this meta-analysis, the results should be interpreted with caution.

Scand J Gastroenterol. 2010;45(1):46-50.
Reproductive wish represents an important factor influencing therapeutic strategy in inflammatory bowel diseases.
Zelinkova Z, Mensink PB, Dees J, Kuipers EJ, van der Woude CJ.

OBJECTIVE: Inflammatory bowel disease (IBD) affects patients in reproductive age but little is known about the peri-conceptional use of medication for IBD. The aim of this study was to assess the type of medication used by IBD patients with the desire to reproduce and changes in medication in the peri-conceptional period. MATERIAL AND METHODS: IBD patients with active conception plans and pregnant patients were prospectively recruited from the outpatient clinic of a single academic medical center. IBD-related medication and changes in this medication for reasons of a desire to conceive or pregnancy were analyzed. RESULTS: In total, 61 patients (51 females; 40 with Crohn's disease, 21 with ulcerative colitis) were included. Thirteen patients (21%) used no medication, 44 (72%) used monotherapy and four (7%) used combination treatment. Of patients on monotherapy, 11 (19%) used 5-aminosalicylates, five (9%) used steroids, 11 (19%) used thiopurines, five (9%) used methotrexate and 11 (19%) used anti-tumor necrosis factor agents. Thirty-seven patients (61%) consulted a physician prior to conception. About one-third of these patients required a change in their medication due to their conception plans. CONCLUSIONS: In a referral center, the majority of IBD patients with conception plans require medication for which limited information on the safety of peri-conceptional use is available. In addition, the desire to reproduce leads to medication changes in about one-third of these patients.

- The **efficacy** and **safety** of a **third anti-TNF monoclonal antibody** in **Crohn's disease after failure** of **two other anti-TNF antibodies.**
- An **analysis** of the **placebo effect** in **Crohn's disease** over time.
- **Prospective evaluation** of **anti-tumor necrosis factor therapy** guided by magnetic resonance imaging for **Crohn's perineal fistulas**.

- An Open-Label Prospective Randomized Multicenter Study Shows Very **Rapid Remission** of **Ulcerative Colitis by Intensive Granulocyte** and **Monocyte Adsorptive Apheresis** as Compared With **Routine Weekly Treatment**.
- Clinical implications of **mucosal healing** for the **management of IBD**.
- **Evolving Inflammatory Bowel Disease Treatment Paradigms**: Top-Down Versus Step-Up.
- **Treatment** of **Fistulizing Inflammatory Bowel Disease**.
- **Novel diagnostic** and **prognostic modalities** in **inflammatory bowel disease.**
- **Postoperative management** of **crohn disease**.
- **Trough serum infliximab**: a predictive factor of clinical outcome for infliximab treatment in **acute ulcerative colitis.**
- **World Gastroenterology Organization Practice Guidelines** for the **Diagnosis** and **Management** of **IBD** in 2010.
- Potential role of **Th17** cells in the **pathogenesis** of **inflammatory bowel disease**.
- Evolving paradigms in the **pathogenesis** of **IBD.**
- **Mucosal gene expression** of **antimicrobial peptides** in **inflammatory bowel disease** before and after first infliximab treatment.
- Are **Colonoscopy** and **Bowel Ultrasound** Useful for **Assessing Response to Short-Term Therapy** and **Predicting Disease Outcome** of **Moderate-to-Severe Forms** of **Ulcerative Colitis**?: A Prospective Study.
- **Utility** of **high-resolution MR imaging** in **demonstrating transmural pathologic changes** in **Crohn disease.**
- **Infliximab Reintroduction** is **Not Associated** to a **Higher Rate of Immune-related Adverse Effects** in Patients With **Inflammatory Bowel Disease** Initially Treated With a Three-infusion Induction Regimen.
- **Clinical outcome of newly diagnosed Crohn's disease**: a comparative, retrospective study before and after infliximab availability.
- A new **rapid home test** for **faecal calprotectin** in **ulcerative colitis**.
- **Infliximab** treatment of **severe genital ulcers** associated with **Behçet disease**.
- **Rising Incidence** of **Inflammatory Bowel Disease Among Children**: A 12-year Study.
- **Limitations** in **assessment** of **mucosal healing** in **inflammatory bowel disease**.
- A systematic review and meta-analysis of **anti-adhesion molecule therapy** in patients with **active Crohn's disease.**
- **Reproductive wish** represents an important factor influencing **therapeutic strategy in inflammatory bowel diseases**.

Safety

Arthritis Rheum. 2009 Nov 30;60(12):3572-3581.
MLN3897 plus methotrexate in patients with rheumatoid arthritis: Safety, efficacy, pharmacokinetics, and pharmacodynamics of an oral CCR1 antagonist in a phase IIa, double-blind, placebo-controlled, randomized, proof-of-concept study.
Vergunst CE, Gerlag DM, von Moltke L, Karol M, Wyant T, Chi X, Matzkin E, Leach T, Tak PP.

OBJECTIVE: To assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of the CC chemokine receptor CCR1 antagonist MLN3897 in patients with rheumatoid arthritis (RA) receiving methotrexate (MTX). METHODS: In this phase IIa, proof-of-concept study, patients meeting the American College of Rheumatology (ACR) criteria for RA who had been taking MTX for >/=6 months with evidence of active disease were randomly assigned to receive either 10 mg oral MLN3897 or matching placebo

once daily for 12 weeks (days 1-83) while continuing to receive MTX once a week. Clinical assessments, safety monitoring, and sampling for pharmacokinetic and pharmacodynamic analyses were performed throughout the study. The primary efficacy end point was the difference in the percentage of patients meeting the ACR 20% improvement criteria (achieving an ACR20 response) on day 84 in the MLN3897-treated group compared with that in the placebo-treated group. RESULTS: MLN3897 was well tolerated, with no evidence of systemic immunosuppression. In the intent-to-treat population, there was no significant difference in day 84 ACR20 response rates between MLN3897-treated patients and placebo-treated patients (35% versus 33%, respectively; P = 0.72). Results were similar for the per-protocol population. Pharmacokinetic analyses demonstrated no interactions between MLN3897 and MTX. MLN3897 was associated with a high degree of CCR1 occupancy (>/=90% on days 28, 56, and 84 in 82% of patients, by macrophage inflammatory protein 1alpha internalization assay). CONCLUSION: MLN3897 at a concentration of 10 mg once daily had no discernible activity in patients with RA who were also receiving MTX. The results suggest that CCR1 antagonism is unlikely to be a viable strategy for the treatment of RA when used in isolation at the receptor occupancy levels reached in this study.

Am J Gastroenterol. 2009 Dec;104(12):3042-9. Epub 2009 Sep 1.
Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in Pediatric Crohn's Disease.
Rosh JR, Lerer T, Markowitz J, Goli SR, Mamula P, Noe JD, Pfefferkorn MD, Kelleher KT, Griffiths AM, Kugathasan S, Keljo D, Oliva-Hemker M, Crandall W, Carvalho RS, Mack DR, Hyams JS.

OBJECTIVES:Adalimumab, an anti-tumor necrosis factor immunoglobulin-1 antibody, is increasingly being reported as a potential treatment option for children with moderate-to-severe Crohn's disease (CD). The aim of this study was to characterize common indications, safety, tolerability, and clinical response to adalimumab in pediatric CD in a large, multicenter, patient cohort.METHODS:Data were obtained using a retrospective, uncontrolled chart review at 12 sites of the Pediatric Inflammatory Bowel Disease Collaborative Research Group. Clinical, laboratory, and demographic data were obtained for CD patients who received at least one dose of adalimumab. Indication for adalimumab, concomitant medications, and clinical outcome at 3, 6, and 12 months for each patient were recorded using physician global assessment (PGA) and Pediatric CD Activity Index scores. Serious adverse events were identified.RESULTS:A total of 115 patients (54% female) received at least one dose of adalimumab. The mean age at the diagnosis of CD was 11.1+/-3.1 years, with the first adalimumab dose administered at 4.7+/-2.8 years after diagnosis. The most common dosing frequency was every other week with induction doses of 160/80 mg in 19%, 80/40 mg in 44%, and 40/40 mg in 15% of patients. Maintenance dosing was 40 mg every other week in 88% of patients. Mean follow-up after initial adalimumab dose was 10+/-8.6 months. Infliximab treatment preceded adalimumab in 95% of patients, with a mean of 12 infliximab infusions (range: 1-44). Infliximab discontinuation was due to loss of response (47%), infusion reaction or infliximab intolerance (45%), or preference for a subcutaneous medication (9%). Concomitant medications at the commencement of adalimumab were corticosteroids (38%), azathioprine/6-mercaptopurine (41%), and methotrexate (23%). Clinical response measured by PGA at 3, 6, and 12 months was 65, 71, and 70%, respectively, with steroid-free remission at 3, 6, and 12 months of 22, 33, and 42%, respectively. There were no malignancies, serious infections, or deaths in the study subjects.CONCLUSIONS:Adalimumab was a well-tolerated and effective rescue therapy for moderate-to-severe pediatric CD patients previously treated with infliximab. Adalimumab demonstrated a steroid-sparing effect, and >70% of patients achieved rapid response that was sustained through 12 months.

Arthritis Res Ther. 2009 Nov 26;11(6):R179.
Safety of TNF blocking agents in rheumatic patients with serology suggesting past-hepatitis B state: results from a cohort of 21 patients.
Charpin C, Guis S, Colson P, Borentain P, Mattei JP, Alcaraz P, Balandraud N, Thomachot B, Roudier J, Gerolami R.

ABSTRACT: INTRODUCTION: Reactivation of hepatitis B virus (HBV) infection in patients with past infection has been described in 5-10% of individuals undergoing immunosuppressive therapies. No data are available to date on the outcome of patients treated by TNFalpha inhibitors for chronic arthritis with a serological pattern of past HBV infection. The aim of our study was to monitor HBV markers in HBsAg-negative/anti-HBc antibodies positive patients treated by a TNFalpha inhibitor for inflammatory arthritides. METHODS: 21 HBsAg-negative/anti-HBc Ab-positive patients were included. HBV serological patterns were compared with those determined before starting TNFalpha inhibitors. Serum HBV DNA testing by

polymerase chain reaction (PCR) was additionally performed. Spearman correlation analysis was used and P<0.05 was chosen as the significant threshold. RESULTS: Before starting therapy, mean anti-HBsAb titre was 725 IU/L, no patient had anti-HBsAb titre <10 IU/L, 18 patients had anti-HBsAb>100 IU/L. At a mean time of 27.2 months following therapy introduction, mean anti-HBsAb titre was 675 IU/L, anti-HBsAb titre remained >100 IU/L in 17 patients. There was a strong correlation between the first and second anti-HBsAb titres (r=0.98, P=0.013). Moreover, no patient had anti-HBsAb titre below 10 IU/L nor HBV reactivation (HBsAg seroreversion or positive HBV DNA detection). However, the anti-HBsAb titre decreased by more than 30% in 6 patients. The mean anti-HBsAb titre at baseline was significantly lower (P=0.006) and the mean duration of anti-TNFalpha therapy, although non significant (P=0.09), was longer in these six patients as compared to patients without decrease in anti-HBsAb titre. CONCLUSIONS: Anti-TNFalpha are likely to be safe in patients with past hepatitis B serological pattern. However, the significant decrease of anti-HBsAb titre observed in a proportion of patients deserves HBV virological follow-up in these patients, especially in those with a low anti-HBsAb titre at baseline.

Med Clin North Am. 2010 Jan;94(1):53-73.
Pregnancy and inflammatory bowel disease.
Mahadevan U.

This review covers important questions that arise for physicians caring for women with inflammatory bowel disease. Fertility, pregnancy outcomes and the safety of medications in pregnancy and lactation are discussed.

Gastroenterol Clin North Am. 2009 Dec;38(4):669-89.
Safety profile of IBD: lymphoma risks.
Bewtra M, Lewis JD.
Republished in:
Med Clin North Am. 2010 Jan;94(1):93-113.

This article describes the cancer risks of commonly used inflammatory bowel disease (IBD) medications, with an emphasis on hematologic malignancy risks. The increasing use of immunosuppressant therapies in the treatment of IBD has raised this question to an even greater importance. Studies evaluating these medications are complicated due to varying disease severity and concomitant use of other immunosuppressant medication. The potential risks of all therapies must be weighed against the benefits these therapies can offer these patients.

Gastroenterol Clin North Am. 2009 Dec;38(4):691-709.
Safety profile of IBD therapeutics: infectious risks.
Afif W, Loftus EV Jr.
Republished in:
Med Clin North Am. 2010 Jan;94(1):115-33.

Over the last decade, the medical treatment of inflammatory bowel disease (IBD) has been revolutionized, with increasing use of both immunomodulatory and biologic medications. Corticosteroids have increasingly been associated with an elevated risk of serious and opportunistic infections, both independently and in combination with immunomodulator and biologic agents. There are limited data on the infectious risk of immunomodulators. It is unclear if anti-tumor necrosis factor agents increase overall infectious risk in patients with IBD, but the available literature has demonstrated an increased risk of opportunistic infections, particularly in terms of tuberculosis and histoplasmosis. Combination therapy likely increases the risk of opportunistic infections in patients with IBD but this has not yet been conclusively proved.

J Rheumatol. 2009 Nov 16.
Agreement Between Quantiferon-TB Gold Test and Tuberculin Skin Test in the Identification of Latent Tuberculosis Infection in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis.
Inanc N, Aydin SZ, Karakurt S, Atagunduz P, Yavuz S, Direskeneli H.

OBJECTIVE: To compare the Quantiferon-TB Gold test (QTF-G) with the tuberculin skin test (TST) for the detection of latent tuberculosis infection (LTBI) among patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), with reevaluation of the patients treated with tumor necrosis factor-alpha (TNF-alpha) antagonists in the followup. METHODS: The study involved 140 consecutive patients, 82 with RA and 58 with AS. Thirty patients were evaluated with QTF-G for detection of LTBI before and after 6 months of TNF-alpha antagonist treatment. QTF-G was also performed on 49 healthy controls. QTF-G results were recorded as positive, negative, or indeterminate. A positive TST was defined as >/= 5 mm for RA and AS. RESULTS: The percentages of positive QTF-G were comparable in RA and AS (37% vs 32%). The rate of positive QTF-G in healthy controls (29%) was also similar to RA and AS. In contrast to QTF-G results, a high rate of TST positivity was observed in AS compared to RA (82% vs 55%; p = 0.02). The total agreement between QTF-G and TST was observed to be 61% (kappa = 0.29) in the whole group, 70% (kappa = 0.42) in RA, and 49% (kappa = 0.14) in AS. After 6 months of treatment with TNF-alpha antagonists, a high rate of QTF-G change was observed in patients with indeterminate results (23% vs 3%; p = 0.03). CONCLUSION: The comparable prevalence of LTBI among the study groups according to QTF-G supports the view that QTF-G is less susceptible to external factors than TST. Sequential testing for QTF-G in patients with indeterminate or negative results may also be helpful in discriminating LTBI better.

Rheumatology (Oxford). 2010 Jan;49(1):82-90. Epub 2009 Nov 11.
Initiation of rheumatoid arthritis treatments and the risk of serious infections.
Grijalva CG, Kaltenbach L, Arbogast PG, Mitchel EF Jr, Griffin MR.

OBJECTIVE: In clinical trials of RA patients on traditional DMARDs, the addition of TNF-alpha antagonists increased infections compared with addition of placebo. Our objective was to compare serious infections following initiation of different RA regimens. Prior comparative studies of DMARD initiation have yielded conflicting results. METHODS: We estimated hospitalization rates for infections following initiation of TNF-alpha antagonists, other DMARDs and oral glucocorticoids in Tennessee Medicaid-enrolled RA patients (1995-2005). Exposure time was measured using pharmacy information and infections were identified using validated definitions. Initiation of RA regimens was compared using Cox regression models with MTX as the reference. Sensitivity analyses excluded glucocorticoid users, applied a first exposure carried forward approach, restricted observations to 2002-05 and first episodes of use and explored effects of unmeasured confounders. RESULTS: We identified 28 906 new episodes of medication use, including TNF-alpha antagonists (8%), MTX alone (15%) and glucocorticoids alone (57%). Compared with MTX initiation, TNF-alpha antagonist initiation did not significantly increase the risk of hospitalizations for pneumonia [adjusted hazard ratio (aHR) 1.61; 95% CI 0.85, 3.03] or any infection (aHR 1.31; 95% CI 0.78, 2.19). Initiation of LEF, SSZ or HCQ did not increase serious infections, compared with MTX. Both initiation and concurrent glucocorticoid use were associated with a dose-dependent increase in serious infections. Sensitivity analyses showed consistent results. CONCLUSIONS: Compared with initiation of MTX alone, initiation of TNF-alpha antagonists was not associated with a large increase in the risk of serious infections. Glucocorticoid use was associated with a dose-dependent increase in the risk of these infections.

Rheumatology (Oxford). 2010 Jan;49(1):42. Epub 2009 Sep 4.
Intramedullary tuberculoma during infliximab therapy.
Ottaviani S, Meyer O, Dieudé

No abstract available.

Ann Rheum Dis 2010 69: i61-i64.
Heart disease and rheumatoid arthritis: understanding the risks
S E Gabriel

No abstract available.

Allergy. 2009 Nov 27.
Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions.

Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, Romagnani S, Maggi E.

Background: Infliximab is a chimeric monoclonal antibody against TNF-alpha useful in the treatment of many chronic inflammatory diseases. Severe anaphylaxis has been reported during therapy, although the exact mechanism has not been fully defined. The reactions have been related to the infliximab immunogenicity and development of specific antibodies. Aims of the study: Evaluation of the development of IgE and non-IgE antibodies to infliximab and their relationship with infusion reaction. Methods: Seventy-one patients (11 reactives, 11 therapeutically nonresponders, and 49 unreactive therapeutically responders) and 20 non-infliximab-exposed control subjects (ten rheumatoid arthritis, five spondyloarthropathies, five vasculitis) were evaluated for the presence of IgE (ImmunoCAP assay), IgM, and non-isotype-specific (ELISA assays) anti-infliximab antibodies. Sera were obtained at baseline and during the course of treatment, before each infliximab infusion. Results: Eleven out of 71 patients had a hypersensitivity reaction to infliximab. Non-isotype-specific anti-infliximab antibodies were detected in eight reactive and two nonresponder patients. Three patients with severe reactions displayed anti-infliximab IgE antibodies and positive skin testing. Detectable levels of anti-infliximab IgM antibodies were shown in three additional IgE- and skin testing-negative patients. IgE and IgM antibodies to infliximab were not detectable in the two nonresponder patients. Antibodies developed before the 2nd and the 3rd infusion, and their appearance was strictly related to the timing of the reaction. Conclusions: This report indicates that in some patients with infliximab-related severe reactions, IgE or IgM antibodies against infliximab were detectable. The majority of reactions could be predicted by the appearance of anti-infliximab antibodies.

Radiographics. 2009 Oct;29(6):1811-25.
MR imaging of the small bowel.
Fidler JL, Guimaraes L, Einstein DM.

Cross-sectional imaging techniques are playing an increasing role in the evaluation of suspected small-bowel disorders, and a growing awareness of the risks of ionizing radiation exposure has prompted the exploration of alternative imaging techniques. Advantages of magnetic resonance (MR) imaging include a lack of ionizing radiation, the ability to provide dynamic information regarding bowel distention and motility, improved soft-tissue contrast, and a relatively safe intravenous contrast agent profile. Limitations of MR imaging include cost, imager access, variability in examination quality, and lower spatial and temporal resolution compared with those of computed tomography (CT). MR imaging of the small bowel is indicated for patients with Crohn disease, those for whom exposure to radiation is a concern, those with contraindications to CT, and those with low-grade small-bowel obstruction. MR imaging may be performed with enterography or enteroclysis. In enterography, large volumes of fluid are ingested. Several different contrast agents may be used. These agents are classified according to their signal intensity on T1- and T2-weighted images. In enteroclysis, enteric contrast material is administered through a nasoenteric tube. Crohn disease is the primary indication for MR imaging of the small bowel because many patients require multiple follow-up examinations. Findings suggestive of active inflammation include bowel wall thickening and hyperenhancement, ulcerations, increased mesenteric vascularity, and perienteric inflammation. Complications are well depicted and may include penetrating disease and small-bowel obstruction.

Ann Rheum Dis 2010;69:i61-i64 doi:10.1136/ard.2009.
Heart disease and rheumatoid arthritis: understanding the risks.
S E Gabriel

No abstract available.

Clin Gastroenterol Hepatol. 2009 Nov;7(11):1257. Epub 2009 Sep 22.
Reply to de Vries HE, Van Oijen MGH, de Jong DJ. Safety of infliximab in inflammatory bowel disease needs to be debated. Clin Gastroenterol Hepatol 2009;7:603-604.
Caspersen S, Mortensen C, Riis L, Jess T, Bendtsen F.

Comment on:

Clin Gastroenterol Hepatol. 2009 May;7(5):603-4.

No abstract available.

J Clin Gastroenterol. 2010 Jan;44(1):e20-2.
Adalimumab-induced autoimmune hepatitis.
Adar T, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O.

Antitumor necrosis factor antibodies are widely used in the treatment of autoimmune diseases. We describe the occurrence of autoimmune hepatitis in a patient treated with adalimumab, a fully human IgG antibody against tumor necrosis factor, for psoriatic arthritis. The patient made a full recovery after discontinuation of adalimumab and treatment with steroids. This is the first reported case of adalimumab-induced autoimmune hepatitis.

Inflamm Bowel Dis. 2009 Dec 21.
Safety of adalimumab in Crohn's disease during pregnancy: Case report and review of the literature.
Jürgens M, Brand S, Filik L, Hübener C, Hasbargen U, Beigel F, Tillack C, Göke B, Ochsenkühn T, Seiderer J.

No abstract available.

J Rheumatol..
Can Tumor Necrosis Factor Inhibitors Be Safely Used in Pregnancy?
Ali YM, Kuriya B, Orozco C, Cush JJ, Keystone EC.

OBJECTIVE: We review available safety data for use of currently approved tumor necrosis factor (TNF) inhibitors during pregnancy and lactation and suggest guidelines for use of these agents among women of reproductive age. METHODS: Although regulatory agencies encourage the inclusion of pregnant women and those of child-bearing age in randomized controlled trials, pregnant and lactating women have universally been excluded from studies because of unknown or potential risks to the fetus. Thus, strong evidence-based treatment recommendations during pregnancy are usually lacking and safety information is derived from voluntary reports of adverse events during postmarketing surveillance or via uncontrolled, observational studies, reviewed here. RESULTS: Uncommon adverse pregnancy outcomes observed with TNF inhibitor therapy appear to approximate those seen in women not receiving such therapy and may include premature birth, miscarriage, low birthweight, hypertension, and preeclampsia. There are rare reports of fetal malformations or congenital anomalies in patients exposed to TNF inhibitors during conception or pregnancy. However, the incidence of these events appears to be far below the 3% rate of congenital anomalies in the general population. CONCLUSION: If the activity or disease severity precludes the cessation of a TNF inhibitor and/or DMARD, uncontrolled observations suggest that conception and early pregnancy are not adversely affected by use of TNF inhibitors. Nearly 70% of pregnant patients can discontinue their TNF inhibitor early in the pregnancy (or with determination of pregnancy) without augmenting maternal or fetal risks.

J Rheumatol..
Possible Reactivation of Potential Hepatitis B Virus Occult Infection by Tumor Necrosis Factor-{alpha} Blocker in the Treatment of Rheumatic Diseases.
Kim YJ, Bae SC, Sung YK, Kim TH, Jun JB, Yoo DH, Kim TY, Sohn JH, Lee HS.

OBJECTIVE: To assess the safety of anti-tumor necrosis factor (TNF-alpha) therapy in patients with rheumatic diseases in terms of the reactivation of potential hepatitis B virus (HBV) occult infection. METHODS: Patients who had taken anti-TNF-alpha for the treatment of rheumatic diseases from January 2002 to May 2008 were included in the study. In this patient group, we retrospectively investigated a series of serum aminotransferase levels, HBV serologic status, the type of anti-TNF-alpha therapy, duration of the anti-TNF-alpha treatment, and concurrent use of hepatotoxic drugs. RESULTS: A total of 266 cases were documented using 3 serologic markers for HBV infection: HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), and HBV core IgG Ab (HBcAb). Of these, 8 cases had chronic hepatitis B (HBsAg+), 170 cases were HBcAb-negative, and 88 cases were identified as having potential HBV occult

infections represented by HBsAg-negative and HBcAb-positive, irrespective of the status of the HBsAb. The frequency of clinically significant (> 2 times normal value) and persistent increase (> 2 consecutive tests) of aminotransferase levels was significantly higher in the group with a potential HBV occult infection compared to the HBcAb-negative group. In the multiple logistic regression analysis controlling for various potential confounding factors such as prophylactic anti-tuberculosis medication, methotrexate, nonsteroidal antiinflammatory drugs, and the type of anti-TNF-alpha therapy, only potential HBV occult infection was a significant risk factor for abnormal liver function test (LFT). CONCLUSION: All rheumatic patients who plan to take anti-TNF-alpha treatment should undergo a test for HBV serology, including HBcAb, and have a close followup with an LFT test during therapy. Further prospective studies for hepatitis B viral load using HBV-polymerase chain reaction in patients who are HbcAb positive are needed to identify whether the abnormal LFT comes from the reactivation of occult HBV infection.

Ocul Immunol Inflamm. 2009 Nov-Dec;17(6):403-14.
Clinical review: Anti-TNFalpha therapies in uveitis: perspective on 5 years of clinical experience.
Sharma SM, Nestel AR, Lee RW, Dick AD.

No abstract available.

N Engl J Med. 2009 Dec 17;361(25):2487-8; author reply 2489-90.
Asymptomatic reactivation of JC virus in patients treated with natalizumab.
Gorelik L, Goelz S, Sandrock AW.

Comment on:
N Engl J Med. 2009 Sep 10;361(11):1067-74.
No abstract available.

- **MLN3897** plus **methotrexate** in patients with **rheumatoid arthritis**: Safety, efficacy, pharmacokinetics, and pharmacodynamics of an **oral CCR1 antagonist** in a phase IIa, double-blind, placebo-controlled, randomized, proof-of-concept study.
- Retrospective Evaluation of the **Safety** and **Effect** of **Adalimumab Therapy** (RESEAT) in **Pediatric Crohn's Disease.**
- **Safety** of **TNF blocking agents** in **rheumatic patients** with **serology suggesting past-hepatitis B state:** results from a cohort of **21 patients**.
- **Pregnancy** and **Inflammatory Bowel Disease**.
- **Safety Profile of IBD: Lymphoma Risks.**
- **Safety Profile of IBD Therapeutics: Infectious Risks.**
- Agreement Between **Quantiferon-TB Gold Test** and **Tuberculin Skin Test** in the Identification of Latent **Tuberculosis Infection** in Patients with **Rheumatoid Arthritis and Ankylosing Spondylitis.**
- **Initiation** of **rheumatoid arthritis treatments** and the **risk** of **serious infections**.
- **Intramedullary tuberculoma** during **infliximab therapy**.
- **Heart disease** and **rheumatoid arthritis:** understanding the **risks.**
- **Anti-infliximab** IgE and non-IgE antibodies and induction of **infusion-related severe anaphylactic reactions.**
- **MR imaging** of the **small bowel.**
- **Heart disease** and **rheumatoid arthritis**: **understanding** the **risks**.
- Reply to the letter: **Safety** of **infliximab** in **inflammatory bowel disease** need to be **debated**.
- **Adalimumab-induced Autoimmune Hepatitis.**
- **Safety** of **adalimumab** in **Crohn's disease during pregnancy**: Case report and review of the literature.
- Can **Tumor Necrosis Factor Inhibitors** Be **Safely** Used in **Pregnancy**?
- **Possible Reactivation** of **Potential Hepatitis B Virus Occult Infection** by **Tumor Necrosis Factor-{alpha} Blocker** in the Treatment of **Rheumatic Diseases.**
- **Safety** of **biologic agents** after **rituximab therapy** in patients with **rheumatoid arthritis.**
- **Asymptomatic Reactivation** of **JC Virus** in Patients Treated with **Natalizumab.**

IBD

Aliment Pharmacol Ther. 2009 Aug 26.
Efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF.
Allez M, Vermeire S, Mozziconacci N, Michetti P, Laharie D, Louis E, Bigard MA, Hébuterne X, Treton X, Kohn A, Marteau P, Cortot A, Nichita C, Vanassche G, Rutgeerts P, Lémann M, Colombel JF.

Adalimumab (ADA) and certolizumab pegol (CZP) have demonstrated efficacy in Crohn's disease (CD) patients previously treated with infliximab (IFX). Aim: To assess the efficacy and tolerability of a third anti-TNF in CD after failure of and/or intolerance to two different anti-TNF. Methods: CD patients who received ADA or CZP after loss of response and/or intolerance to two anti-TNF were included in this retrospective study. Data were collected using a standardized questionnaire. Clinical response, duration, safety and reasons for discontinuation were assessed. Results: Sixty-seven patients treated with CZP (n=40) or ADA (n=27) were included. A clinical response was observed in 41 (61%) at week 6 and 34 patients (51%) at week 20. The probability of remaining under treatment at 3 months, 6 months and 9 months was 68%, 60% and 45%, respectively. At the end of follow-up, the third anti-TNF had been stopped in 36 patients for intolerance (n=13), or failure (n=23). Two deaths were observed. Conclusion: Treatment, with a third anti-TNF (CZP or ADA) agent, of CD patients who have experienced loss of response and/or intolerance to two anti-TNF antibodies, has favorable short- and long-term efficacy and is an option to be considered in patients with no other therapeutic options.

Aliment Pharmacol Ther. 2009 Aug 18.
An analysis of the placebo effect in Crohn's disease over time.
Gallahan WC, Case D, Bloomfeld RS.

Abstract Background: Randomized, placebo controlled trials are used to assess the efficacy of therapies for Crohn's disease. The placebo response and remission rates vary among studies. Aim: The purpose of this study was to analyze how the placebo response and remission rates in Crohn's trials have changed over time in the era of parenteral biologic therapies. Methods: A search for randomized, placebo-controlled trials of parenteral biologic therapies for active Crohn's disease was conducted using online databases. The placebo response and remission rates and study week of evaluation were recorded for each trial. The placebo response and remission rates were analyzed as functions of publication date and study week of evaluation. Results: The odds of a placebo induced remission and response significantly increased as the week of evaluation increased. The placebo remission rate increased significantly with year of publication. Adjusted for week of evaluation, this increase in placebo remission rate over time was no longer significant. The increase in the placebo response over this time period was not statistically significant. Conclusion: The observed increase in placebo remission rates over time in trials of parenteral biologic therapies in Crohn's disease is explained by longer times to the primary endpoint in more recent trials.

Am J Gastroenterol. 2009 Dec;104(12):2973-86. Epub 2009 Sep 15.
Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas.
Ng SC, Plamondon S, Gupta A, Burling D, Swatton A, Vaizey CJ, Kamm MA.

OBJECTIVES:Anti-tumor necrosis factor (TNF) therapy heals Crohn's fistulas clinically, but the rate, extent, and duration to achieve fistula track healing are unknown.METHODS:We sought to monitor deep healing, as indicated by magnetic resonance imaging (MRI), and to use this to determine treatment duration. Clinical and MRI fistula healing (at 6, 12, and 18 months), Crohn's Disease Activity Index (CDAI), Perianal Crohn's Disease Activity Index (PDAI), and the Inflammatory Bowel Disease Questionnaire were prospectively assessed.RESULTS:Thirty-four consecutive patients with perineal fistulas were treated with infliximab (19), adalimumab (7; all infliximab failures) and thalidomide (8). Median follow-up was 110 weeks (range, 74-161). Baseline MRI: 38% >/=2 tracks, 21% anolabial/rectovaginal. At latest follow-up, clinical fistula 'response' and 'closure' were seen in 50 and 46% of antibody-treated patients, respectively. All patients stopped thalidomide early due to side effects. Of 26 antibody-treated patients, at 6 (n=25), 12 (n=25), and 18 (n=20) months, respectively, MRI showed

complete healing (20, 28, and 30%, respectively), improvement (68, 72, and 65%), no change (12, 0, and 0%) or worsening (0, 0, and 5%). MRI healing at 6 months (n=5) persisted at 12 and 18 months, including in two patients who stopped treatment at 6 months. Fistula history length and complexity did not influence the outcome. The only surgical intervention was seton insertion in one patient. The PDAI and CDAI scores decreased, and quality of life improved significantly at last follow-up.CONCLUSIONS:MRI fistula resolution was variable and slower than clinical healing. Prolonged treatment is often required for internal track resolution. Preliminary data suggest once MRI healing has occurred fistulas remain healed, while remaining on, or stopping anti-TNFalpha therapy. The use of a second antibody is clinically valuable.

Am J Gastroenterol. 2009 Dec;104(12):2990-5. Epub 2009 Sep 1.
An open-label prospective randomized multicenter study shows very rapid remission of ulcerative colitis by intensive granulocyte and monocyte adsorptive apheresis as compared with routine weekly treatment.
Sakuraba A, Motoya S, Watanabe K, Nishishita M, Kanke K, Matsui T, Suzuki Y, Oshima T, Kunisaki R, Matsumoto T, Hanai H, Fukunaga K, Yoshimura N, Chiba T, Funakoshi S, Aoyama N, Andoh A, Nakase H, Mizuta Y, Suzuki R, Akamatsu T, Iizuka M, Ashida T, Hibi T.

OBJECTIVES:Granulocyte and monocyte adsorptive apheresis (GMA) has shown efficacy in patients with active ulcerative colitis (UC). However, with routine weekly treatment, it may take several weeks to achieve remission, and to date, the efficacy of a more frequent treatment schedule remains unknown. The aim of this study was to assess the clinical efficacy and safety of intensive GMA treatment in patients with active UC.METHODS:This was an open-label, prospective, randomized multicenter study to compare an intensive, two GMA sessions per week, with the routine, one GMA session per week. A total of 163 patients with mild-to-moderately active UC were randomly assigned to routine weekly treatment or intensive treatment. The maximum number of sessions of GMA permitted was 10. However, when patients achieved remission, GMA was discontinued. Remission rate at the end of the study, time to remission, and adverse events were assessed in both groups.RESULTS:Of the 163 patients, 149 were available for efficacy analysis as per protocol, 76 were in weekly GMA, and 73 were in intensive GMA. At the end of the study period, clinical remission was achieved in 41 of 76 patients (54.0%) in weekly GMA and in 52 of 73 patients (71.2%) in intensive GMA (P=0.029). The mean time to remission was 28.1+/-16.9 days in the weekly GMA treatment group and 14.9+/-9.5 days in the intensive GMA group (P<0.0001). Intensive GMA was well tolerated without GMA-related serious adverse side effects.CONCLUSIONS:Intensive GMA in patients with active UC seems to be more efficacious than weekly treatment, and significantly reduced the patients' morbidity time without increasing the incidence of side effects.

Nat Rev Gastroenterol Hepatol. 2009 Dec 1.
Clinical implications of mucosal healing for the management of IBD.
Pineton de Chambrun G, Peyrin-Biroulet L, Lémann M, Colombel JF; Medscape.

Mucosal healing (MH) has emerged as an important treatment goal for patients with IBD. Historically, the therapeutic goals of induction and maintenance of clinical remission seemed insufficient to change the natural history of IBD. Evidence has now accumulated to show that MH can alter the course of IBD, as it is associated with sustained clinical remission, and reduced rates of hospitalization and surgical resection. In patients with ulcerative colitis, MH may represent the ultimate therapeutic goal because inflammation is limited to the mucosa. In patients with Crohn's disease, which is a transmural disease, MH could be considered as a minimum therapeutic goal. This Review focuses on the definition of MH and discusses the ability of each available IBD medication to induce and maintain MH. The importance of achieving MH is also discussed and literature that demonstrates improvement of disease course with MH is reviewed. Finally, we discuss how best to integrate the treatment end point of MH into clinical practice for the management of patients with IBD.

Gastroenterol Clin North Am. 2009 Dec;38(4):577-94.
Evolving inflammatory bowel disease treatment paradigms: top-down versus step-up.
Devlin SM, Panaccione R.
Republished in:
Med Clin North Am. 2010 Jan;94(1):1-18.

Crohn disease (CD) and ulcerative colitis (UC) comprise a group of inflammatory disorders of the gastrointestinal tract that can vary in severity of disease, anatomic extent of inflammation, presence and nature of extraintestinal manifestations, and response to therapeutic approaches. There have been attempts to classify CD based on the location and behavior of disease. Advances in understanding of genetic susceptibility to inflammatory bowel disease (IBD) suggest that CD and UC may represent a continuum of overlapping disorders. This has led to an attempt to classify IBD on clinical, molecular, and serologic grounds. Differences in clinical, genetic, and immunologic profiles may require more targeted, refined treatment approaches to help clinicians make decisions regarding recently introduced biologic agents. This article provides an overview of the current approaches to therapy for CD and UC and focuses on the evidence supporting the rationale for changing paradigms in the management of IBD, including mucosal healing as an end point and earlier use of immunosuppressive and biologic agents, particularly in CD (so-called top-down therapy).

Med Clin North Am. 2010 Jan;94(1):19-34.
Treatment of fistulizing inflammatory bowel disease.
Schwartz DA, Maltz BE.

Fistulas manifest frequently in Crohn disease and can result in significant morbidity and often lead to the need for surgical intervention. Historically, it has been more difficult to obtain complete fistula closure in patients with perianal Crohn disease. Anti-tumor necrosis factor-alpha agents and the use of more accurate imaging modalities such as magnetic resonance imaging and rectal endoscopic ultrasound have enhanced the ability to manage fistulizing Crohn disease. A combined medical and surgical approach usually presents the best option for most patients.

Gastroenterol Clin North Am. 2009 Dec;38(4):729-52.
Novel diagnostic and prognostic modalities in inflammatory bowel disease.
Zisman TL, Rubin DT.
Republished in:
Med Clin North Am. 2010 Jan;94(1):155-78.

Inflammatory bowel disease remains a complex disease with variable clinical presentations and oftennonspecific symptoms. Physicians must rely on diagnostic tools for clarification of disease diagnosis and for guiding management of patients with established disease. Advances in radiologic imaging modalities facilitate early and accurate detection of luminal disease and extraluminal complications. The introduction and dissemination of small bowel capsule endoscopy and double-balloon enteroscopy permit detailed visualization and sampling of the mucosa throughout the entire bowel. Serologic biomarkers are evolving as a valuable tool to clarify diagnosis and stratify patients by disease phenotypes and patterns of behavior. Neutrophil-derived fecal biomarkers are emerging as useful surrogate markers of intestinal inflammation with the potential for a variety of clinical applications, but their application to clinical management has not yet been clarified.

Med Clin North Am. 2010 Jan;94(1):179-88.
Postoperative management of crohn disease.
Cho SM, Cho SW, Regueiro M.

Crohn disease often recurs after surgical resection. Despite extensive research in the prevention of postoperative Crohn disease, optimal management strategies have yet to be defined. Risk of disease recurrence needs to be carefully balanced against potential risks associated with treatment. Patients with low risk of postoperative recurrence may not require medication, whereas those at moderate risk may benefit from antibiotics or immunomodulators. Those at highest risk of recurrence may benefit from biologic therapy for maintenance of surgical remission. Postoperative colonoscopy within 1 year of resective surgery is important for identification of disease recurrence and modification of medications.

Gut. 2009 Aug 2.
Trough Serum Infliximab: A Predictive Factor Of Clinical Outcome For Infliximab Therapy In Acute Ulcerative Colitis.
Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR.

Background & AIMS: Antibodies to infliximab reduce serum infliximab with loss of clinical benefit, but undetectable trough serum concentrations of infliximab may occur without antibody formation. The relation between trough serum infliximab and clinical outcomes was evaluated in acute ulcerative colitis. METHODS: In a cohort of 115 ulcerative colitis patients treated with 3-dose induction followed by scheduled maintenance infliximab, rates of clinical remission, colectomy, antibodies to infliximab and trough serum infliximab were determined. RESULTS: Rates of remission were 32% at week 10 and 37% at week 54. Colectomy occurred in 40% of patients, at a median of 5.3 (IQR: 1.9-12.1) months. Detectable trough serum infliximab was present in 39% of patients and among patients with undetectable infliximab, 41% were antibody positive and 20% were antibody negative. For antibody positive and antibody negative patients, rates of remission (18% vs. 14%), endoscopic improvement (25% vs. 35%) and colectomy (52% vs. 59%) were not different. A detectable serum infliximab was associated with higher rates of remission (69% vs. 15%; P <0.001) and endoscopic improvement (76% vs. 28%, P <0.001). An undetectable serum infliximab predicted an increased risk for colectomy (55% vs. 7%, odds ratio 9.3; 95% confidence interval, 2.9 - 29.9; P <0.001). Concurrent immunosuppression was not associated with clinical outcomes. CONCLUSIONS: For ulcerative colitis patients treated with infliximab, a detectable trough serum infliximab predicts clinical remission, endoscopic improvement, and a lower risk for colectomy. In assessing clinical outcomes to infliximab, the presence of antibodies to infliximab is a surrogate for absent drug.

Inflamm Bowel Dis. 2009 Aug 3.
World Gastroenterology Organisation Practice Guidelines for the Diagnosis and Management of IBD in 2010.
Bernstein CN, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, Gearry R, Goh KL, Hamid S, Khan AG, Lemair AW; Malfertheiner, Ouyang Q, Rey JF, Sood A, Steinwurz F, Thomsen OO, Thomson A, Watermeyer G.

Inflammatory bowel disease (IBD) represents a group of idiopathic, chronic, inflammatory intestinal conditions. Its two main disease categories are: Crohn's disease (CD) and ulcerative colitis (UC), which feature both overlapping and distinct clinical and pathological features. While these diseases have, in the past, been most evident in the developed world, their prevalence in the developing world has been gradually increasing in recent decades. This poses unique issues in diagnosis and management which have been scarcely addressed in the literature or in extant guidelines. Depending on the nature of the complaints, investigations to diagnose either form of IBD or to assess disease activity will vary and will also be influenced by geographic variations in other conditions that might mimic IBD. Similarly, therapy varies depending on the phenotype of the disease being treated and available resources. The World Gastroenterology Organization has, accordingly, developed guidelines for diagnosing and treating IBD using a cascade approach to account for variability in resources in countries around the world.

World J Gastroenterol. 2009 Dec 14;15(46):5784-8.
Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease.
Liu ZJ, Yadav PK, Su JL, Wang JS, Fei K.

The etiopathology of inflammatory bowel disease (IBD) remains elusive. Accumulating evidence suggests that the abnormality of innate and adaptive immunity responses plays an important role in intestinal inflammation. IBD including Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract, which is implicated in an inappropriate and overactive mucosal immune response to luminal flora. Traditionally, CD is regarded as a Th1-mediated inflammatory disorder while UC is regarded as a Th2-like disease. Recently, Th17 cells were identified as a new subset of T helper cells unrelated to Th1 or Th2 cells, and several cytokines [e.g. interleukin (IL)-21, IL-23] are involved in regulating their activation and differentiation. They not only play an important role in host defense against extracellular pathogens, but are also associated with the development of autoimmunity and inflammatory response such as IBD. The identification of Th17 cells helps us to explain some of the anomalies seen in the Th1/Th2 axis and has broadened our understanding of the immunopathological effects of Th17 cells in the development of IBD.

J Gastroenterol. 2009 Dec 4.
Evolving paradigms in the pathogenesis of IBD.

Mayer L.

The pathogenesis of all immune-mediated inflammatory diseases has been carefully studied over the past several decades, but it is only recently that we have come to appreciate common pathways and genes. This is especially true for the inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis, where a keener appreciation of the contributions of genetics, environment, and immune response have been dissected. In fact, in many ways, IBD has become the model for studying such disorders. The complex nature of interactions is continuing to be defined, and novel therapies targeting defects in these interactions have been developed and are being tested in the clinic. The era of bench to bedside has finally matured, and cures for debilitating diseases are now in sight. This review describes our current state of knowledge of each component of IBD pathogenesis. What has evolved is a clearer picture and novel targets for therapy.

PLoS One. 2009 Nov 24;4(11):e7984.
Mucosal gene expression of antimicrobial peptides in inflammatory bowel disease before and after first infliximab treatment.
Arijs I, De Hertogh G, Lemaire K, Quintens R, Van Lommel L, Van Steen K, Leemans P, Cleynen I, Van Assche G, Vermeire S, Geboes K, Schuit F, Rutgeerts P.

BACKGROUND: Antimicrobial peptides (AMPs) protect the host intestinal mucosa against microorganisms. Abnormal expression of defensins was shown in inflammatory bowel disease (IBD), but it is not clear whether this is a primary defect. We investigated the impact of anti-inflammatory therapy with infliximab on the mucosal gene expression of AMPs in IBD. METHODOLOGY/PRINCIPAL FINDINGS: Mucosal gene expression of 81 AMPs was assessed in 61 IBD patients before and 4-6 weeks after their first infliximab infusion and in 12 control patients, using Affymetrix arrays. Quantitative real-time reverse-transcription PCR and immunohistochemistry were used to confirm microarray data. The dysregulation of many AMPs in colonic IBD in comparison with control colons was widely restored by infliximab therapy, and only DEFB1 expression remained significantly decreased after therapy in the colonic mucosa of IBD responders to infliximab. In ileal Crohn's disease (CD), expression of two neuropeptides with antimicrobial activity, PYY and CHGB, was significantly decreased before therapy compared to control ileums, and ileal PYY expression remained significantly decreased after therapy in CD responders. Expression of the downregulated AMPs before and after treatment (DEFB1 and PYY) correlated with villin 1 expression, a gut epithelial cell marker, indicating that the decrease is a consequence of epithelial damage. CONCLUSIONS/SIGNIFICANCE: Our study shows that the dysregulation of AMPs in IBD mucosa is the consequence of inflammation, but may be responsible for perpetuation of inflammation due to ineffective clearance of microorganisms.

Am J Gastroenterol. 2009 Dec 8.
Are Colonoscopy and Bowel Ultrasound Useful for Assessing Response to Short-Term Therapy and Predicting Disease Outcome of Moderate-to-Severe Forms of Ulcerative Colitis?: A Prospective Study.
Parente F, Molteni M, Marino B, Colli A, Ardizzone S, Greco S, Sampietro G, Foschi D, Gallus S.

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

short-term response of severe forms of UC to therapy. Both US score and endoscopic score after 3 months of steroid therapy predict outcome of disease at 15 months.Am J Gastroenterol advance online publication, 8 December 2009; doi:10.1038/ajg.2009.672.

Radiographics. 2009 Oct;29(6):1847-67.
Utility of high-resolution MR imaging in demonstrating transmural pathologic changes in Crohn disease.
Sinha R, Rajiah P, Murphy P, Hawker P, Sanders S.

Magnetic resonance (MR) imaging has emerged as an imaging modality that can be used to help diagnose and evaluate Crohn disease of the small and large bowel. MR imaging has high diagnostic accuracy in the detection of Crohn disease, and high-resolution thin-section MR images can demonstrate transmural pathologic changes of Crohn disease from the level of the mucosa to that of the mesentery. High-resolution MR image data also may be used to construct high-quality multiplanar and endoluminal views that may provide additional diagnostic information. Knowledge of the MR imaging findings of Crohn disease and how they correlate with the pathologic features of the disease is important to facilitate accurate diagnosis and detect complications.

J Clin Gastroenterol. 2010 Jan;44(1):34-7.
Infliximab reintroduction is not associated to a higher rate of immune-related adverse effects in patients with inflammatory bowel disease initially treated with a three-infusion induction regimen.
Domènech E, Zabana Y, Mañosa M, Garcia-Planella E, Cabré E, Gassull MA.

BACKGROUND: Episodic infliximab (IFX) treatment is associated with a higher risk for acute infusion reactions (AIR) and secondary loss of response (SLR), but this has not been evaluated in patients initially treated with an induction regimen with 3 IFX infusions. AIMS: To evaluate whether IFX reintroduction after > or = 4 months in patients treated with a 3-infusion induction regimen is associated with a higher incidence of AIR or SLR. METHODS: Incidence of immunogenic adverse effects was assessed in patients with inflammatory bowel disease who received > or = 4 consecutive IFX infusions (3 infusions at weeks 0, 2, and 6, plus > or = 1 maintenance infusion) (Continuous, n=47) and patients who were treated with a successful initial 3-infusion induction scheme and in whom IFX was then discontinued because of a complete response but reintroduced > or = 4 months later (Reintro, n=29). RESULTS: AIR rate was 17% in both groups, and SLR rate was 26% in the Continuous group and 15% in the Reintro group (not significant). The lack of concomitant immunomodulators and/or pretreatment with hydrocortisone were associated with AIR development (P=0.002). CONCLUSIONS: In patients who completed a 3-infusion induction regimen, IFX can be safely reintroduced even after a long time from discontinuation.

Aliment Pharmacol Ther. 2009 Oct 14.
Clinical outcome of newly diagnosed Crohn's disease: comparative, retrospective, study before and after infliximab availability.
Domènech E, Zabana Y, Garcia-Planella E, López San Román A, Nos P, Ginard D, Gordillo J, Martínez-Silva F, Beltrán B, Mañosa M, Cabré E, Gassull MA.

Summary Background: Infliximab (IFX) could change the course of Crohn's disease (CD) by reducing steroid use, surgery, or prompting earlier introduction of immunomodulators (IMM). Aim: To evaluate the impact of IFX availability on the course of early CD. Patients and methods: Two cohorts of newly diagnosed CD patients were identified: The first cohort included patients diagnosed from January 1994 to December 1997, and the second from January 2000 to December 2003. All patients were diagnosed, treated and followed in a same centre until December 1999 (first cohort) or December 2005 (second cohort). Development of disease-related complications, steroid, IMM or IFX requirements, and intestinal resections during follow-up were registered. Results: A total of 328 patients were included (146 first cohort, 182 second cohort). A similar proportion of patients in both cohorts received steroids, but steroid exposure resulted significantly more intense in the first cohort (P= 0,001). In the second cohort, 14% of patients received IFX. Thiopurines were used more (P=0,001) and earlier (P=0,012) in the second cohort. No differences in surgical requirements or the development of disease-related complications were found. Conclusions: Following a step-up therapeutic algorithm, IFX availability did not reduce surgical requirements or the development of disease-related complications.

Aliment Pharmacol Ther. 2009 Oct 10.
A new rapid home test for faecal calprotectin in ulcerative colitis.
Elkjaer M, Burisch J, Voxen Hansen V, Deibjerg Kristensen B, Slott Jensen JK, Munkholm P.

Abstract Background: Enzyme-linked immunosorbent assay (ELISA) is a time consuming method for faecal calprotectin (FC). Two new quantitative rapid tests (RT) have been developed. Aim: To compare the new rapid tests with ELISA as 'Gold Standard'. Methods: Quantitative analysis involved application of a sample onto the 'Lateral Flow Device' (LFD). The colour intensity of a test line was read using a laptop computer linked to a scanner (RT scanning). A picture taken with a mobile phone (HT photo) of the same LFD was sent to a server via Mobile Internet and the result appearing on the phone screen after 15 seconds. Results: Four hundred and four faecal samples were analysed. Mean differences of 1.7 mg/kg (range -23.4-20.1) ELISA versus RT scanning, 6.8 mg/kg (-28-14.5) ELISA versus HT photo and 2.9 mg/kg (-10.3-4.5) RT scanning versus HT photo were found with good agreement calculated by kappa statistic (86%, 87% and 95%, respectively). The Coefficients of Variation for HT photo < 10% with a sensitivity of 96.2% and a specificity of 90.1%. Conclusion: The new rapid tests are accurate, and are of utility in clinical settings. Feasibility of the home test as part of disease control and self-management are currently being investigated.

J Am Acad Dermatol. 2010,62,162
Infliximab treatment of severe genital ulcers associated with Behçet disease.
Chikatoshi Kasugai, Daisuke Watanabe, Kimihiko Mizutani, Yuko Masuda, Masahiro Zako, Tomoyuki Mukai, Yasuhiko Tamada, Yoshinari Matsumoto

No abstract available.

J Pediatr Gastroenterol Nutr. 2010 Jan;50(1):27-31.
Rising incidence of inflammatory bowel disease among children: a 12-year study.
Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD.

OBJECTIVE: Data suggest an increase in the incidence of pediatric inflammatory bowel disease (IBD). We examined the trend of the incidence of IBD in children. PATIENTS AND METHODS: A retrospective investigation was conducted on a cohort of children diagnosed with IBD between 1991 and 2002 who were registered in the IBD center at Texas Children's Hospital. The diagnosis of IBD was based on clinical, radiological, endoscopic, and histological examinations. RESULTS: There were 272 children eligible for the analysis; 56% diagnosed with Crohn disease (CD), 22% with ulcerative colitis (UC), and 22% with indeterminate colitis. The male-to-female ratio was 1.2:1 in CD, 0.6:1 in UC, and 0.8:1 in indeterminate colitis. From 1991 to 2002, the incidence rate has doubled from 1.1/100,000/year (95% confidence interval [CI] 0.85-1.36) to 2.4/1001,000/year (95% CI 2.10-2.77). This trend was valid for CD but not for UC. Whites had higher incidence rate of IBD than African Americans or Hispanics: 4.15/100,000/year (95% CI 3.48-4.82) versus 1.83/100,000/year (95% CI 1.14-2.51), and 0.61/100,000/year (95% CI 0.33-0.89), respectively. African Americans were predominantly diagnosed with CD. CONCLUSIONS: The results demonstrate the rising incidence of IBD among children with evidence of more CD than UC. Recognition of these results will have important implications for diagnosis and management of IBD in children.

World J Gastroenterol. 2010 Jan 7;16(1):15-20.
Limitations in assessment of mucosal healing in inflammatory bowel disease.
Freeman HJ.

An emerging parameter to define the effectiveness of new therapeutic agents in clinical trials, and by extension, for use in day-to-day clinical practice has been labeled mucosal healing. It has been hypothesized that complete healing of the intestinal mucosa in inflammatory bowel diseases should result in reduced disease complications, reduced hospitalization and reduced surgical treatment. By implication, the natural history of inflammatory bowel disease might then be altered. Measurement of mucosal healing, however, is largely observational, requiring repeated invasive endoscopic examinations, sometimes with mucosal biopsies. Other indirect imaging methods may play a role in this assessment along with other surrogate markers, including intestinal permeability. These measurements may have

significant limitations that prohibit precise correlation with symptom-based disease activity indices in clinical trials. This likely reflects the dynamic nature of this evolving and individualized inflammatory process that tends to be focused, but not limited, to the mucosa of the intestinal tract.

Scand J Gastroenterol. 2009;44(12):1435-42.
A systematic review and meta-analysis of anti-adhesion molecule therapy in patients with active Crohn's disease.
Li Y, Tian Y, Yu C, Zhu W, Li J.

OBJECTIVE: Due to the crucial role played by adhesion molecules in the pathogenesis of Crohn's disease (CD), targeting of these molecules has recently been proposed as a new direction for the development of anti-inflammatory strategies for CD. The aim of this study was to provide up-to-date evidence on the effectiveness and safety of anti-adhesion molecule therapy in treating active CD. MATERIAL AND METHODS: We studied articles retrieved by PubMed, EMBASE, the Cochrane Library and the Science Citation Index for randomized controlled trials (RCTs) relevant to CD and anti-adhesion molecule therapy. RESULTS: Seven RCTs comparing anti-adhesion molecule therapy with placebo were included in a meta-analysis to evaluate the efficacy and safety of anti-adhesion molecule strategies in active CD. On the basis of pooled results of the seven RCTs (n = 2228), we found a significant difference in clinical remission rates between groups [relative risk (RR) 1.31, 95% confidence interval (CI) 1.12-1.52, fixed-effect model]. Five RCTs (n = 2178) compared the response rates of anti-adhesion molecule therapy and placebo; in overall analysis, anti-adhesion molecule therapy was effective for active CD (RR 1.28, 95% CI 1.16-1.42, random-effect model). In five studies enrolling 1867 individuals, anti-adhesion molecule therapy did not increase adverse events (RR 1.03, 95% CI 0.98-1.08, fixed-effect model). CONCLUSIONS: Anti-adhesion molecule therapy, which could prevent leukocyte recruitment, was effective and safe for treating active CD. Because of the small number of studies included in this meta-analysis, the results should be interpreted with caution.

Scand J Gastroenterol. 2010;45(1):46-50.
Reproductive wish represents an important factor influencing therapeutic strategy in inflammatory bowel diseases.
Zelinkova Z, Mensink PB, Dees J, Kuipers EJ, van der Woude CJ.

OBJECTIVE: Inflammatory bowel disease (IBD) affects patients in reproductive age but little is known about the peri-conceptional use of medication for IBD. The aim of this study was to assess the type of medication used by IBD patients with the desire to reproduce and changes in medication in the peri-conceptional period. MATERIAL AND METHODS: IBD patients with active conception plans and pregnant patients were prospectively recruited from the outpatient clinic of a single academic medical center. IBD-related medication and changes in this medication for reasons of a desire to conceive or pregnancy were analyzed. RESULTS: In total, 61 patients (51 females; 40 with Crohn's disease, 21 with ulcerative colitis) were included. Thirteen patients (21%) used no medication, 44 (72%) used monotherapy and four (7%) used combination treatment. Of patients on monotherapy, 11 (19%) used 5-aminosalicylates, five (9%) used steroids, 11 (19%) used thiopurines, five (9%) used methotrexate and 11 (19%) used anti-tumor necrosis factor agents. Thirty-seven patients (61%) consulted a physician prior to conception. About one-third of these patients required a change in their medication due to their conception plans. CONCLUSIONS: In a referral center, the majority of IBD patients with conception plans require medication for which limited information on the safety of peri-conceptional use is available. In addition, the desire to reproduce leads to medication changes in about one-third of these patients.

Safety

Arthritis Rheum. 2009 Nov 30;60(12):3572-3581.
MLN3897 plus methotrexate in patients with rheumatoid arthritis: Safety, efficacy, pharmacokinetics, and pharmacodynamics of an oral CCR1 antagonist in a phase IIa, double-blind, placebo-controlled, randomized, proof-of-concept study.
Vergunst CE, Gerlag DM, von Moltke L, Karol M, Wyant T, Chi X, Matzkin E, Leach T, Tak PP.

OBJECTIVE: To assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of the CC chemokine receptor CCR1 antagonist MLN3897 in patients with rheumatoid arthritis (RA) receiving methotrexate (MTX). METHODS: In this phase IIa, proof-of-concept study, patients meeting the American College of Rheumatology (ACR) criteria for RA who had been taking MTX for >/=6 months with evidence of active disease were randomly assigned to receive either 10 mg oral MLN3897 or matching placebo once daily for 12 weeks (days 1-83) while continuing to receive MTX once a week. Clinical assessments, safety monitoring, and sampling for pharmacokinetic and pharmacodynamic analyses were performed throughout the study. The primary efficacy end point was the difference in the percentage of patients meeting the ACR 20% improvement criteria (achieving an ACR20 response) on day 84 in the MLN3897-treated group compared with that in the placebo-treated group. RESULTS: MLN3897 was well tolerated, with no evidence of systemic immunosuppression. In the intent-to-treat population, there was no significant difference in day 84 ACR20 response rates between MLN3897-treated patients and placebo-treated patients (35% versus 33%, respectively; P = 0.72). Results were similar for the per-protocol population. Pharmacokinetic analyses demonstrated no interactions between MLN3897 and MTX. MLN3897 was associated with a high degree of CCR1 occupancy (>/=90% on days 28, 56, and 84 in 82% of patients, by macrophage inflammatory protein 1alpha internalization assay). CONCLUSION: MLN3897 at a concentration of 10 mg once daily had no discernible activity in patients with RA who were also receiving MTX. The results suggest that CCR1 antagonism is unlikely to be a viable strategy for the treatment of RA when used in isolation at the receptor occupancy levels reached in this study.

Am J Gastroenterol. 2009 Dec;104(12):3042-9. Epub 2009 Sep 1.

Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in Pediatric Crohn's Disease.

Rosh JR, Lerer T, Markowitz J, Goli SR, Mamula P, Noe JD, Pfefferkorn MD, Kelleher KT, Griffiths AM, Kugathasan S, Keljo D, Oliva-Hemker M, Crandall W, Carvalho RS, Mack DR, Hyams JS.

OBJECTIVES:Adalimumab, an anti-tumor necrosis factor immunoglobulin-1 antibody, is increasingly being reported as a potential treatment option for children with moderate-to-severe Crohn's disease (CD). The aim of this study was to characterize common indications, safety, tolerability, and clinical response to adalimumab in pediatric CD in a large, multicenter, patient cohort.METHODS:Data were obtained using a retrospective, uncontrolled chart review at 12 sites of the Pediatric Inflammatory Bowel Disease Collaborative Research Group. Clinical, laboratory, and demographic data were obtained for CD patients who received at least one dose of adalimumab. Indication for adalimumab, concomitant medications, and clinical outcome at 3, 6, and 12 months for each patient were recorded using physician global assessment (PGA) and Pediatric CD Activity Index scores. Serious adverse events were identified.RESULTS:A total of 115 patients (54% female) received at least one dose of adalimumab. The mean age at the diagnosis of CD was 11.1+/-3.1 years, with the first adalimumab dose administered at 4.7+/-2.8 years after diagnosis. The most common dosing frequency was every other week with induction doses of 160/80 mg in 19%, 80/40 mg in 44%, and 40/40 mg in 15% of patients. Maintenance dosing was 40 mg every other week in 88% of patients. Mean follow-up after initial adalimumab dose was 10+/-8.6 months. Infliximab treatment preceded adalimumab in 95% of patients, with a mean of 12 infliximab infusions (range: 1-44). Infliximab discontinuation was due to loss of response (47%), infusion reaction or infliximab intolerance (45%), or preference for a subcutaneous medication (9%). Concomitant medications at the commencement of adalimumab were corticosteroids (38%), azathioprine/6-mercaptopurine (41%), and methotrexate (23%). Clinical response measured by PGA at 3, 6, and 12 months was 65, 71, and 70%, respectively, with steroid-free remission at 3, 6, and 12 months of 22, 33, and 42%, respectively. There were no malignancies, serious infections, or deaths in the study subjects.CONCLUSIONS:Adalimumab was a well-tolerated and effective rescue therapy for moderate-to-severe pediatric CD patients previously treated with infliximab. Adalimumab demonstrated a steroid-sparing effect, and >70% of patients achieved rapid response that was sustained through 12 months.

Arthritis Res Ther. 2009 Nov 26;11(6):R179.

Safety of TNF blocking agents in rheumatic patients with serology suggesting past-hepatitis B state: results from a cohort of 21 patients.

Charpin C, Guis S, Colson P, Borentain P, Mattei JP, Alcaraz P, Balandraud N, Thomachot B, Roudier J, Gerolami R.

ABSTRACT: INTRODUCTION: Reactivation of hepatitis B virus (HBV) infection in patients with past infection has been described in 5-10% of individuals undergoing immunosuppressive therapies. No data

are available to date on the outcome of patients treated by TNFalpha inhibitors for chronic arthritis with a serological pattern of past HBV infection. The aim of our study was to monitor HBV markers in HBsAg-negative/anti-HBc antibodies positive patients treated by a TNFalpha inhibitor for inflammatory arthritides. METHODS: 21 HBsAg-negative/anti-HBc Ab-positive patients were included. HBV serological patterns were compared with those determined before starting TNFalpha inhibitors. Serum HBV DNA testing by polymerase chain reaction (PCR) was additionally performed. Spearman correlation analysis was used and P<0.05 was chosen as the significant threshold. RESULTS: Before starting therapy, mean anti-HBsAb titre was 725 IU/L, no patient had anti-HBsAb titre <10 IU/L, 18 patients had anti-HBsAb>100 IU/L. At a mean time of 27.2 months following therapy introduction, mean anti-HBsAb titre was 675 IU/L, anti-HBsAb titre remained >100 IU/L in 17 patients. There was a strong correlation between the first and second anti-HBsAb titres (r=0.98, P=0.013). Moreover, no patient had anti-HBsAb titre below 10 IU/L nor HBV reactivation (HBsAg seroreversion or positive HBV DNA detection). However, the anti-HBsAb titre decreased by more than 30% in 6 patients. The mean anti-HBsAb titre at baseline was significantly lower (P=0.006) and the mean duration of anti-TNFalpha therapy, although non significant (P=0.09), was longer in these six patients as compared to patients without decrease in anti-HBsAb titre. CONCLUSIONS: Anti-TNFalpha are likely to be safe in patients with past hepatitis B serological pattern. However, the significant decrease of anti-HBsAb titre observed in a proportion of patients deserves HBV virological follow-up in these patients, especially in those with a low anti-HBsAb titre at baseline.

Med Clin North Am. 2010 Jan;94(1):53-73.
Pregnancy and inflammatory bowel disease.
Mahadevan U.

This review covers important questions that arise for physicians caring for women with inflammatory bowel disease. Fertility, pregnancy outcomes and the safety of medications in pregnancy and lactation are discussed.

Gastroenterol Clin North Am. 2009 Dec;38(4):669-89.
Safety profile of IBD: lymphoma risks.
Bewtra M, Lewis JD.
Republished in:
Med Clin North Am. 2010 Jan;94(1):93-113.

This article describes the cancer risks of commonly used inflammatory bowel disease (IBD) medications, with an emphasis on hematologic malignancy risks. The increasing use of immunosuppressant therapies in the treatment of IBD has raised this question to an even greater importance. Studies evaluating these medications are complicated due to varying disease severity and concomitant use of other immunosuppressant medication. The potential risks of all therapies must be weighed against the benefits these therapies can offer these patients.

Gastroenterol Clin North Am. 2009 Dec;38(4):691-709.
Safety profile of IBD therapeutics: infectious risks.
Afif W, Loftus EV Jr.
Republished in:
Med Clin North Am. 2010 Jan;94(1):115-33.

Over the last decade, the medical treatment of inflammatory bowel disease (IBD) has been revolutionized, with increasing use of both immunomodulatory and biologic medications. Corticosteroids have increasingly been associated with an elevated risk of serious and opportunistic infections, both independently and in combination with immunomodulator and biologic agents. There are limited data on the infectious risk of immunomodulators. It is unclear if anti-tumor necrosis factor agents increase overall infectious risk in patients with IBD, but the available literature has demonstrated an increased risk of opportunistic infections, particularly in terms of tuberculosis and histoplasmosis. Combination therapy likely increases the risk of opportunistic infections in patients with IBD but this has not yet been conclusively proved.

J Rheumatol. 2009 Nov 16.

Agreement Between Quantiferon-TB Gold Test and Tuberculin Skin Test in the Identification of Latent Tuberculosis Infection in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis.
Inanc N, Aydin SZ, Karakurt S, Atagunduz P, Yavuz S, Direskeneli H.

OBJECTIVE: To compare the Quantiferon-TB Gold test (QTF-G) with the tuberculin skin test (TST) for the detection of latent tuberculosis infection (LTBI) among patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), with reevaluation of the patients treated with tumor necrosis factor-alpha (TNF-alpha) antagonists in the followup. METHODS: The study involved 140 consecutive patients, 82 with RA and 58 with AS. Thirty patients were evaluated with QTF-G for detection of LTBI before and after 6 months of TNF-alpha antagonist treatment. QTF-G was also performed on 49 healthy controls. QTF-G results were recorded as positive, negative, or indeterminate. A positive TST was defined as >/= 5 mm for RA and AS. RESULTS: The percentages of positive QTF-G were comparable in RA and AS (37% vs 32%). The rate of positive QTF-G in healthy controls (29%) was also similar to RA and AS. In contrast to QTF-G results, a high rate of TST positivity was observed in AS compared to RA (82% vs 55%; p = 0.02). The total agreement between QTF-G and TST was observed to be 61% (kappa = 0.29) in the whole group, 70% (kappa = 0.42) in RA, and 49% (kappa = 0.14) in AS. After 6 months of treatment with TNF-alpha antagonists, a high rate of QTF-G change was observed in patients with indeterminate results (23% vs 3%; p = 0.03). CONCLUSION: The comparable prevalence of LTBI among the study groups according to QTF-G supports the view that QTF-G is less susceptible to external factors than TST. Sequential testing for QTF-G in patients with indeterminate or negative results may also be helpful in discriminating LTBI better.

Rheumatology (Oxford). 2010 Jan;49(1):82-90. Epub 2009 Nov 11.
Initiation of rheumatoid arthritis treatments and the risk of serious infections.
Grijalva CG, Kaltenbach L, Arbogast PG, Mitchel EF Jr, Griffin MR.

OBJECTIVE: In clinical trials of RA patients on traditional DMARDs, the addition of TNF-alpha antagonists increased infections compared with addition of placebo. Our objective was to compare serious infections following initiation of different RA regimens. Prior comparative studies of DMARD initiation have yielded conflicting results. METHODS: We estimated hospitalization rates for infections following initiation of TNF-alpha antagonists, other DMARDs and oral glucocorticoids in Tennessee Medicaid-enrolled RA patients (1995-2005). Exposure time was measured using pharmacy information and infections were identified using validated definitions. Initiation of RA regimens was compared using Cox regression models with MTX as the reference. Sensitivity analyses excluded glucocorticoid users, applied a first exposure carried forward approach, restricted observations to 2002-05 and first episodes of use and explored effects of unmeasured confounders. RESULTS: We identified 28 906 new episodes of medication use, including TNF-alpha antagonists (8%), MTX alone (15%) and glucocorticoids alone (57%). Compared with MTX initiation, TNF-alpha antagonist initiation did not significantly increase the risk of hospitalizations for pneumonia [adjusted hazard ratio (aHR) 1.61; 95% CI 0.85, 3.03] or any infection (aHR 1.31; 95% CI 0.78, 2.19). Initiation of LEF, SSZ or HCQ did not increase serious infections, compared with MTX. Both initiation and concurrent glucocorticoid use were associated with a dose-dependent increase in serious infections. Sensitivity analyses showed consistent results. CONCLUSIONS: Compared with initiation of MTX alone, initiation of TNF-alpha antagonists was not associated with a large increase in the risk of serious infections. Glucocorticoid use was associated with a dose-dependent increase in the risk of these infections.

Rheumatology (Oxford). 2010 Jan;49(1):42. Epub 2009 Sep 4.
Intramedullary tuberculoma during infliximab therapy.
Ottaviani S, Meyer O, Dieudé

No abstract available.

Ann Rheum Dis 2010 69: i61-i64.
Heart disease and rheumatoid arthritis: understanding the risks
S E Gabriel

No abstract available.

Allergy. 2009 Nov 27.
Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions.
Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, Romagnani S, Maggi E.

Background: Infliximab is a chimeric monoclonal antibody against TNF-alpha useful in the treatment of many chronic inflammatory diseases. Severe anaphylaxis has been reported during therapy, although the exact mechanism has not been fully defined. The reactions have been related to the infliximab immunogenicity and development of specific antibodies. Aims of the study: Evaluation of the development of IgE and non-IgE antibodies to infliximab and their relationship with infusion reaction. Methods: Seventy-one patients (11 reactives, 11 therapeutically nonresponders, and 49 unreactive therapeutically responders) and 20 non-infliximab-exposed control subjects (ten rheumatoid arthritis, five spondyloarthropathies, five vasculitis) were evaluated for the presence of IgE (ImmunoCAP assay), IgM, and non-isotype-specific (ELISA assays) anti-infliximab antibodies. Sera were obtained at baseline and during the course of treatment, before each infliximab infusion. Results: Eleven out of 71 patients had a hypersensitivity reaction to infliximab. Non-isotype-specific anti-infliximab antibodies were detected in eight reactive and two nonresponder patients. Three patients with severe reactions displayed anti-infliximab IgE antibodies and positive skin testing. Detectable levels of anti-infliximab IgM antibodies were shown in three additional IgE- and skin testing-negative patients. IgE and IgM antibodies to infliximab were not detectable in the two nonresponder patients. Antibodies developed before the 2nd and the 3rd infusion, and their appearance was strictly related to the timing of the reaction. Conclusions: This report indicates that in some patients with infliximab-related severe reactions, IgE or IgM antibodies against infliximab were detectable. The majority of reactions could be predicted by the appearance of anti-infliximab antibodies.

Radiographics. 2009 Oct;29(6):1811-25.
MR imaging of the small bowel.
Fidler JL, Guimaraes L, Einstein DM.

Cross-sectional imaging techniques are playing an increasing role in the evaluation of suspected small-bowel disorders, and a growing awareness of the risks of ionizing radiation exposure has prompted the exploration of alternative imaging techniques. Advantages of magnetic resonance (MR) imaging include a lack of ionizing radiation, the ability to provide dynamic information regarding bowel distention and motility, improved soft-tissue contrast, and a relatively safe intravenous contrast agent profile. Limitations of MR imaging include cost, imager access, variability in examination quality, and lower spatial and temporal resolution compared with those of computed tomography (CT). MR imaging of the small bowel is indicated for patients with Crohn disease, those for whom exposure to radiation is a concern, those with contraindications to CT, and those with low-grade small-bowel obstruction. MR imaging may be performed with enterography or enteroclysis. In enterography, large volumes of fluid are ingested. Several different contrast agents may be used. These agents are classified according to their signal intensity on T1- and T2-weighted images. In enteroclysis, enteric contrast material is administered through a nasoenteric tube. Crohn disease is the primary indication for MR imaging of the small bowel because many patients require multiple follow-up examinations. Findings suggestive of active inflammation include bowel wall thickening and hyperenhancement, ulcerations, increased mesenteric vascularity, and perienteric inflammation. Complications are well depicted and may include penetrating disease and small-bowel obstruction.

Ann Rheum Dis 2010;69:i61-i64 doi:10.1136/ard.2009.
Heart disease and rheumatoid arthritis: understanding the risks.
S E Gabriel

No abstract available.

Clin Gastroenterol Hepatol. 2009 Nov;7(11):1257. Epub 2009 Sep 22.
Reply to de Vries HE, Van Oijen MGH, de Jong DJ. Safety of infliximab in inflammatory bowel disease needs to be debated. Clin Gastroenterol Hepatol 2009;7:603-604.
Caspersen S, Mortensen C, Riis L, Jess T, Bendtsen F.

Comment on:

Clin Gastroenterol Hepatol. 2009 May;7(5):603-4.

No abstract available.

J Clin Gastroenterol. 2010 Jan;44(1):e20-2.
Adalimumab-induced autoimmune hepatitis.
Adar T, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O.

Antitumor necrosis factor antibodies are widely used in the treatment of autoimmune diseases. We describe the occurrence of autoimmune hepatitis in a patient treated with adalimumab, a fully human IgG antibody against tumor necrosis factor, for psoriatic arthritis. The patient made a full recovery after discontinuation of adalimumab and treatment with steroids. This is the first reported case of adalimumab-induced autoimmune hepatitis.

Inflamm Bowel Dis. 2009 Dec 21.
Safety of adalimumab in Crohn's disease during pregnancy: Case report and review of the literature.
Jürgens M, Brand S, Filik L, Hübener C, Hasbargen U, Beigel F, Tillack C, Göke B, Ochsenkühn T, Seiderer J.

No abstract available.

J Rheumatol..
Can Tumor Necrosis Factor Inhibitors Be Safely Used in Pregnancy?
Ali YM, Kuriya B, Orozco C, Cush JJ, Keystone EC.

OBJECTIVE: We review available safety data for use of currently approved tumor necrosis factor (TNF) inhibitors during pregnancy and lactation and suggest guidelines for use of these agents among women of reproductive age. METHODS: Although regulatory agencies encourage the inclusion of pregnant women and those of child-bearing age in randomized controlled trials, pregnant and lactating women have universally been excluded from studies because of unknown or potential risks to the fetus. Thus, strong evidence-based treatment recommendations during pregnancy are usually lacking and safety information is derived from voluntary reports of adverse events during postmarketing surveillance or via uncontrolled, observational studies, reviewed here. RESULTS: Uncommon adverse pregnancy outcomes observed with TNF inhibitor therapy appear to approximate those seen in women not receiving such therapy and may include premature birth, miscarriage, low birthweight, hypertension, and preeclampsia. There are rare reports of fetal malformations or congenital anomalies in patients exposed to TNF inhibitors during conception or pregnancy. However, the incidence of these events appears to be far below the 3% rate of congenital anomalies in the general population. CONCLUSION: If the activity or disease severity precludes the cessation of a TNF inhibitor and/or DMARD, uncontrolled observations suggest that conception and early pregnancy are not adversely affected by use of TNF inhibitors. Nearly 70% of pregnant patients can discontinue their TNF inhibitor early in the pregnancy (or with determination of pregnancy) without augmenting maternal or fetal risks.

J Rheumatol..
Possible Reactivation of Potential Hepatitis B Virus Occult Infection by Tumor Necrosis Factor-{alpha} Blocker in the Treatment of Rheumatic Diseases.
Kim YJ, Bae SC, Sung YK, Kim TH, Jun JB, Yoo DH, Kim TY, Sohn JH, Lee HS.

OBJECTIVE: To assess the safety of anti-tumor necrosis factor (TNF-alpha) therapy in patients with rheumatic diseases in terms of the reactivation of potential hepatitis B virus (HBV) occult infection. METHODS: Patients who had taken anti-TNF-alpha for the treatment of rheumatic diseases from January 2002 to May 2008 were included in the study. In this patient group, we retrospectively investigated a series of serum aminotransferase levels, HBV serologic status, the type of anti-TNF-alpha therapy,

duration of the anti-TNF-alpha treatment, and concurrent use of hepatotoxic drugs. RESULTS: A total of 266 cases were documented using 3 serologic markers for HBV infection: HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), and HBV core IgG Ab (HBcAb). Of these, 8 cases had chronic hepatitis B (HBsAg+), 170 cases were HBcAb-negative, and 88 cases were identified as having potential HBV occult infections represented by HBsAg-negative and HBcAb-positive, irrespective of the status of the HBsAb. The frequency of clinically significant (> 2 times normal value) and persistent increase (> 2 consecutive tests) of aminotransferase levels was significantly higher in the group with a potential HBV occult infection compared to the HBcAb-negative group. In the multiple logistic regression analysis controlling for various potential confounding factors such as prophylactic anti-tuberculosis medication, methotrexate, nonsteroidal antiinflammatory drugs, and the type of anti-TNF-alpha therapy, only potential HBV occult infection was a significant risk factor for abnormal liver function test (LFT). CONCLUSION: All rheumatic patients who plan to take anti-TNF-alpha treatment should undergo a test for HBV serology, including HBcAb, and have a close followup with an LFT test during therapy. Further prospective studies for hepatitis B viral load using HBV-polymerase chain reaction in patients who are HbcAb positive are needed to identify whether the abnormal LFT comes from the reactivation of occult HBV infection.

Ocul Immunol Inflamm. 2009 Nov-Dec;17(6):403-14.
Clinical review: Anti-TNFalpha therapies in uveitis: perspective on 5 years of clinical experience.
Sharma SM, Nestel AR, Lee RW, Dick AD.

No abstract available.

N Engl J Med. 2009 Dec 17;361(25):2487-8; author reply 2489-90.
Asymptomatic reactivation of JC virus in patients treated with natalizumab.
Gorelik L, Goelz S, Sandrock AW.

Comment on:
N Engl J Med. 2009 Sep 10;361(11):1067-74.
No abstract available.