Literature Update Immunology

Period: 01-30 JUNE 2011

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IBD

Curr Opin Gastroenterol. 2011 Jul;27(4):346-57.
Inflammatory bowel disease therapy: current state-of-the-art.
Blonski W, Buchner AM, Lichtenstein GR.

PURPOSE OF REVIEW: The aim of this article is to review current evidence-based approaches to treatment of ulcerative colitis and Crohn's disease.
RECENT FINDINGS: The primary goal of treatment is to induce and to maintain remission in a safe and efficacious fashion. The 5-aminosalicylic acid (5-ASA) agents and oral steroids remain the first-line approach for the treatment of ulcerative colitis and Crohn's disease. The 'step-up' approach includes the use of immunomodulators [azathioprine (AZA), or 6-mercaptopurine (6-MP)] and newer biologic agents (infliximab, adalimumab, and natalizumab). The 'step-down' approach can also be considered individually on the basis of the severity of Crohn's disease.
SUMMARY: Current treatment regimens still involve medications with well known efficacy and safety profiles and progress to more potent treatments such as immunomodulators and biologic agents. Adverse events of potent treatment with biologics and immunomodulators have been recognized. In some cases, aggressive approaches with the use of more potent agents as first-line therapy has been proposed, but they are still not considered a routine approach.

Gastroenterology. 2011 May;140(6):1827-1837.e2.
Conventional medical management of inflammatory bowel disease.
Burger D, Travis S.

Conventional therapies for ulcerative colitis and Crohn's disease (CD) include aminosalicylates, corticosteroids, thiopurines, methotrexate, and anti-tumor necrosis factor agents. A time-structured approach is required for appropriate management. Traditional step-up therapy has been partly replaced during the last decade by potent drugs and top-down therapies, with an accelerated step-up approach being the most appropriate in the majority of patients. When patients are diagnosed with CD or ulcerative colitis, physicians should consider the probable pattern of disease progression so that effective therapy is not delayed. This can be achieved by setting arbitrary time limits for administration of biological therapies, changing therapy from mesalamine in patients with active ulcerative colitis, or using rescue therapy for acute severe colitis. In this review, we provide algorithms with a time-structured approach for guidance of therapy. Common mistakes in conventional therapy include overprescription of mesalamine for CD; inappropriate use of steroids (for perianal CD, when there is sepsis, or for maintenance); delayed introduction or underdosing with azathioprine, 6-mercaptopurine, or methotrexate; and failure to consider timely surgery. The paradox of anti-tumor necrosis factor therapy is that although it too is used inappropriately (when patients have sepsis or fibrostenotic strictures) or too frequently (for diseases that would respond to less-potent therapy), it is also often introduced too late in disease progression. Conventional drugs are the mainstay of current therapy for inflammatory bowel diseases, but drug type, timing, and context must be optimized to manage individual patients effectively.

Curr Opin Gastroenterol. 2011 Jul;27(4):358-62.
Colon salvage therapy for acute severe colitis: cyclosporine or infliximab?
Burger DC, Travis S.

PURPOSE OF REVIEW: Steroid-refractory acute severe colitis (ASC) poses a significant clinical challenge to both physicians and surgeons alike. This review highlights advances in management of these patients and the role of cyclosporine compared to infliximab.
RECENT FINDINGS: ASC affects 25% of patients with ulcerative colitis and is associated with measurable morbidity and mortality. Simple clinical and laboratory measures predict steroid refractoriness (such as stool frequency 3-8/day and C-reactive protein > 45 mg/l on day 3) and salvage therapy is appropriate at this stage. Preliminary data from randomized controlled trials suggest that early (7 and 98 day) response to cyclosporine and infliximab are comparable. Serum trough infliximab concentrations may correlate with outcome. Sequential therapy cannot usually be recommended due to limited response (70% colectomy at 3 years) and high rate of serious adverse events.

SUMMARY: Optimal salvage therapy will depend on detailed results of randomized controlled trials. Meanwhile, patients with ASC should receive either cyclosporine or infliximab before surgery as long as there is specialist expertise that allows early decision-making.

J Res Med Sci. 2011 Jan;16(1):6-15.
Promising effect of infliximab on the extent of involvement in ulcerative colitis.
Adibi P, Mollakhalili P, Fallah Z, Daryani NE, Ajdarkosh H, Khedmat H, Derakhshan F, Karbassi A, Ashkzari M, Tavakkoli H.

BACKGROUND: Ulcerative colitis (UC) is a disabling disease with increasing incidence in Iran. In spite of combined medical therapy, some patients eventually undergo total colectomy. Infliximab has proved itself as a rescue therapy and even as an early aggressive therapy for severe extensive UC. Meantime, there are concerns about its complications. The aim of this study was to evaluate the efficacy of infliximab in Iranian refractory UC patients.
METHODS: This multi centric case-series study included 29 UC patients receiving two to three of the drugs prednisolone, AZT/6MP and 5ASA but yet having flare-ups. At first, the extent of colon involvement was determined by colonoscopy; then the drug was administered at baseline, 2nd week and 6th week and colonoscopy repeated afterwards. Clinical and laboratory data were also recorded.
RESULTS: In first endoscopy 18 patients (62%) out of 29 suffered from pancolitis and none had normal results. In second examination (done on 19 patients), one was normal and only 8 of 18 (27.6%) had pancolitis. Considering missing cases, at least in 33.3% of patients the drug has reduced the extreme extent of colon involvement. Also a wilcoxon signed ranks test revealed significant reduction of the disease extension after this treatment ($p = 0.008$). There were only one leucopenic and one hypotensive reactions in short term. The drug showed effectiveness in the term of disease modifying, too.
CONCLUSIONS: These data show the usefulness of the drug in refractory UC. Longer follow ups and controlled trials are needed.

Clin Gastroenterol Hepatol. 2011 Jun;9(6):483-489.e3. Epub 2010 Dec 31.
Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis.
Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, Marmo R, Massari A, Molteni P, Maconi G, Porro GB.

BACKGROUND & AIMS: It is uncertain whether mucosal healing after the first course of corticosteroids therapy predicts outcome in patients with ulcerative colitis (UC). We evaluated whether early clinical and endoscopic responses to this therapy are associated with late outcomes in UC.
METHODS: Patients with newly diagnosed UC who were prescribed corticosteroid therapy (n = 157) were followed up for 5 years. They were evaluated using clinical (Powel-Tuck [PT]) and endoscopic (Baron) indexes after 3 and 6 months, then every 6 months. Outcomes at month 3 (early response) were used to identify patients with complete (group A: PT, 0-1; Baron, 0), partial (group B: PT, 0-1; Baron, 1-3), or no response (group C: persistence of clinical and endoscopic activity). The association between early and late outcomes was assessed.
RESULTS: After 5 years, there were significant differences between complete and partial responders in the rates of hospitalization (25% in group A vs 48.7% in group B; P = .0152; odds ratio [OR], 2.85; 95% confidence interval [CI], 1.21-6.72), immunosuppression therapy (5% in group A vs 25.6% in group B; P = .0030; OR, 6.55; 95% CI, 1.67-25.67), colectomy (3.3% in group A vs 18.0% in group B; P = .0265; OR, 6.34; 95% CI, 1.24-32.37), and their combination (26.7% in group A vs 48.7% in group B; P = .0249; OR, 2.61; 95% CI, 1.12-6.11). After multivariate analysis, lack of mucosal healing was the only factor associated with negative outcomes at 5 years (immunosuppressors: hazard risk [HR], 10.581; 95% CI, 2.193-51.039; P = .0033; hospitalization: HR, 3.634; 95% CI, 1.556-8.485; P = .0029; colectomy: HR, 8.397; 95% CI, 1.278-55.186; P = .0268).
CONCLUSIONS: No mucosal healing after corticosteroid therapy is associated with a more aggressive disease course.

J Clin Gastroenterol. 2011 Feb;45(2):113-8.
Long-term durability of infliximab treatment in Crohn's disease and efficacy of dose "escalation" in patients losing response.

Chaparro M, Panes J, García V, Mañosa M, Esteve M, Merino O, Andreu M, Gutierrez A, Gomollón F, Cabriada JL, Montoro MA, Mendoza JL, Nos P, Gisbert JP.

BACKGROUND: The efficacy of infliximab therapy in patients with Crohn's disease (CD) is unknown beyond 12 months. For patients who lose their initial response, consideration can be given to dose "escalation" to regain therapeutic benefit.
AIM: Our primary goal was to evaluate the long-term durability of maintenance infliximab treatment. The secondary goals were to identify potential predictors of loss of infliximab efficacy, to evaluate the response to infliximab escalation, and the safety of the treatment with infliximab with and without escalation of dose.
METHODS: CD patients treated with infliximab with response to an induction regimen were evaluated. Maintenance of long-term response was estimated using Kaplan-Meier analysis. The effect of specific variables was calculated using logistic regression analysis. Efficacy of dose escalation in patients who lose response to infliximab was analyzed.
RESULTS: Three hundred and nine CD patients were included. The mean follow-up time with infliximab treatment was 41 months, and the majority (95%) were on concomitant immunosuppressive therapy. The annual risk of loss of response to infliximab was 12% per patient-year of treatment. After loss of response, 41% of patients were managed with infliximab therapy escalation. After the first intensified dose, 56% of patients achieved remission and 40% partial response. Concurrent immunomodulators enhanced and smoking decreased the proportion of patients who maintained response ($P<0.05$).
CONCLUSIONS: A relevant proportion of CD patients on long-term infliximab treatment loss response. After loss of response, a high proportion of these patients initially respond to infliximab dose escalation. Concurrent immunomodulators may increase and smoking may decrease maintenance of response.

Gut. 2011 Jun;60(6):780-7. Epub 2011 Jan 5.
Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial.
Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R.

Objective The aim of this study was to assess the efficacy and safety of adalimumab (ADA), a recombinant human monoclonal antibody against tumour necrosis factor α (TNF), for the induction of clinical remission in anti-TNF naïve patients with moderately to severely active ulcerative colitis. Methods This 8-week, multicentre, randomised, double-blind, placebo-controlled study (NCT00385736), conducted at 94 centres in North America and Europe, enrolled ambulatory adult patients with Mayo score of ≥6 points and endoscopic subscore of ≥2 points despite treatment with corticosteroids and/or immunosuppressants. Under the original study protocol, 186 patients were randomised (1:1) to subcutaneous treatment with ADA160/80 (160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6) or placebo. Subsequently, at the request of European regulatory authorities, the protocol was amended to include a second induction group (ADA80/40: 80 mg at week 0, 40 mg at weeks 2, 4 and 6). The primary efficacy endpoint was clinical remission (Mayo score ≤2 with no individual subscore >1) at week 8, assessed in 390 patients randomised (1:1:1) to ADA160/80, ADA80/40, or placebo. Safety was assessed in all enrolled patients. Patients, study site personnel, investigators, and the sponsor were blinded to treatment assignment. Results At week 8, 18.5% of patients in the ADA160/80 group ($p=0.031$ vs placebo) and 10.0% in the ADA80/40 group ($p=0.833$ vs placebo) were in remission, compared with 9.2% in the placebo group. Serious adverse events occurred in 7.6%, 3.8% and 4.0% of patients in the placebo, ADA80/40, and ADA160/80 groups, respectively. There were two malignancies in the placebo group, none in the ADA groups. There were no cases of tuberculosis and no deaths. Conclusions ADA160/80 was safe and effective for induction of clinical remission in patients with moderately to severely active ulcerative colitis failing treatment with corticosteroids and/or immunosuppressants. Clinical trial NCT00385736.

Gut. 2011 Jun;60(6):788-98. Epub 2011 Jan 21.
Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease.
Ciccocioppo R, Bernardo ME, Sgarella A, Maccario R, Avanzini MA, Ubezio C, Minelli A, Alvisi C, Vanoli A, Calliada F, Dionigi P, Perotti C, Locatelli F, Corazza GR.

Objective External fistulas represent a disabling manifestation of Crohn's disease with a difficult curability and a high relapse rate despite a large therapeutic armamentarium. Stem cell therapy is a novel and promising approach for treatment of chronic inflammatory conditions. We therefore investigated the feasibility, safety and efficacy of serial intrafistular injections of autologous bone marrow-derived mesenchymal stromal cells (MSCs) in the treatment of fistulising Crohn's disease. Patients and methods We enrolled 12 consecutive outpatients (eight males, median age 32 years) refractory to or unsuitable for current available therapies. MSCs were isolated from bone marrow and expanded ex vivo to be used for both therapeutic and experimental purposes. Ten patients (two refused) received intrafistular MSC injections (median 4) scheduled every 4 weeks, and were monitored by surgical, MRI and endoscopic evaluation for 12 months afterwards. The feasibility of obtaining at least 50×10(6) MSCs from each patient, the appearance of adverse events, and the efficacy in terms of fistula healing and reduction of both Crohn's disease and perianal disease activity indexes were evaluated. In addition, the percentage of both mucosal and circulating regulatory T cells expressing FoxP3, and the ability of MSCs to influence mucosal T cell apoptosis were investigated. Results MSC expansion was successful in all cases; sustained complete closure (seven cases) or incomplete closure (three cases) of fistula tracks with a parallel reduction of Crohn's disease and perianal disease activity indexes ($p<0.01$ for both), and rectal mucosal healing were induced by treatment without any adverse effects. The percentage of mucosal and circulating regulatory T cells significantly increased during the treatment and remained stable until the end of follow up ($p<0.0001$ and $p<0.01$, respectively). Furthermore, MSCs have been proven to affect mucosal T cell apoptotic rate. Conclusions Locally injected MSCs represent a feasible, safe and beneficial therapy in refractory fistulising Crohn's disease.

J Exp Med. 2011 Jun 6;208(6):1127-33. Epub 2011 May 16.
IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease.
Geremia A, Arancibia-Cárcamo CV, Fleming MP, Rust N, Singh B, Mortensen NJ, Travis SP, Powrie F.

Results of experimental and genetic studies have highlighted the role of the IL-23/IL-17 axis in the pathogenesis of inflammatory bowel disease (IBD). IL-23-driven inflammation has been primarily linked to Th17 cells; however, we have recently identified a novel population of innate lymphoid cells (ILCs) in mice that produces IL-17, IL-22, and IFN-γ in response to IL-23 and mediates innate colitis. The relevance of ILC populations in human health and disease is currently poorly understood. In this study, we have analyzed the role of IL-23-responsive ILCs in the human intestine in control and IBD patients. Our results show increased expression of the Th17-associated cytokine genes IL17A and IL17F among intestinal CD3(-) cells in IBD. IL17A and IL17F expression is restricted to CD56(-) ILCs, whereas IL-23 induces IL22 and IL26 in the CD56(+) ILC compartment. Furthermore, we observed a significant and selective increase in CD127(+)CD56(-) ILCs in the inflamed intestine in Crohn's disease (CD) patients but not in ulcerative colitis patients. These results indicate that IL-23-responsive ILCs are present in the human intestine and that intestinal inflammation in CD is associated with the selective accumulation of a phenotypically distinct ILC population characterized by inflammatory cytokine expression. ILCs may contribute to intestinal inflammation through cytokine production, lymphocyte recruitment, and organization of the inflammatory tissue and may represent a novel tissue-specific target for subtypes of IBD.

Nat Rev Gastroenterol Hepatol. 2011 Feb;8(2):74-6.
IBD in 2010: optimizing treatment and minimizing adverse events.
De Vroey B, Colombel JF.

The management of IBD remains a challenge, with the main issue being to combine therapeutic efficiency with minimal side effects and optimal quality of life. Efforts towards achieving this objective continued in 2010—we discuss some of the most relevant publications and their potential impact on daily practice in the future.

Gut. 2011 Jun;60(6):741-2. Epub 2011 Jan 21.
Does it all ADA up? Adalimumab for ulcerative colitis.
Travis S.

No abstract available.

Gut. 2011 Jun;60(6):742-4. Epub 2011 Mar 22.
Mesenchymal stem cell therapy of Crohn's disease: are the far-away hills getting closer?
Panés J, Benitez-Ribas D, Salas A.

No abstract available.

Scand J Gastroenterol. 2011 Feb;46(2):248-9. Epub 2010 Oct 6.
Long-term outcome of infliximab therapy is highly comparable in a Danish and in a Hungarian tertiary center.
Molnár T, Farkas K, Szepes Z, Nagy F, Wittmann T.

No abstract available

Inflamm Bowel Dis. 2011 Jul;17(7):1626-8. doi: 10.1002/ibd.21498. Epub 2010 Nov 4.
Infliximab decreases colectomy rates in moderate to severe ulcerative colitis: Big news or big deal?
Cheifetz AS, Rosenberg L.

No abstract available

Clin Gastroenterol Hepatol. 2011 Jun;9(6):456-7. Epub 2011 Mar 21.
We Once Were Blind and Now We See: Is it Time to Treat Ulcerative Colitis to Achieve Mucosal Healing?
Rubin DT.

No abstract available

J Crohns Colitis. 2011 Jun;5(3):177-88. Epub 2011 Mar 25.
Medical and surgical therapy of inflammatory bowel disease in the elderly - Prospects and complications.
Stallmach A, Hagel S, Gharbi A, Settmacher U, Hartmann M, Schmidt C, Bruns T.

Population ageing is a global phenomenon. People aged 65years and older comprise approximately 16% of the population of Europe. The medical management of elderly patients with inflammatory bowel disease (IBD) is challenging with respect to diagnosis, pharmaceutical and surgical treatment, and complications. IBD has a late onset in 10%-15% of patients, with the first flare occurring at 60 to 70years of age; others suffer from the disease for several decades. Even though the natural course of the disease in geriatric populations and the diagnostic options may not differ much from those in younger patients, distinct problems exist in the choice of medical therapy. Recommended clinical practise has been rapidly evolving towards an intensified initial treatment in IBD. However, in patients older than 65years, a gentler approach should be used, and a combination of immunosuppressive agents should be avoided because of increased risk of infectious and neoplastic complications. Furthermore, elderly patients with severe IBD show prolonged, complicated post-operative clinical courses with worse hospital outcomes, so early surgical intervention for elderly patients is recommended. This article provides an overview of elderly IBD patient care, including medical and surgical therapeutic considerations and emphasises the necessity of close collaborations between gastroenterologists and surgeons.

J Crohns Colitis. 2011 Jun;5(3):234-8. Epub 2011 Feb 22.
The effects of azathioprine on birth outcomes in women with inflammatory bowel disease (IBD).
Shim L, Eslick GD, Simring AA, Murray H, Weltman MD.

AIM: To investigate the effects of azathioprine/6-mercaptopurine (AZA/6-MP) on birth outcomes in women with inflammatory bowel disease (IBD).
METHODS: Details of pregnant women with IBD were obtained through an ObstetriX Database in 3 major teaching hospitals in Sydney from 1996 to 2006. Medical records were reviewed. Birth outcomes of

interest were single live births, low birth weight (LBW) at term (<2500g), preterm births (<37weeks gestation), neonatal adverse outcomes, and congenital anomaly. Placental blood flow during third trimester of pregnancy was measured using arterial Doppler ultrasonography, where available.
RESULTS: All women had IBD diagnosed before pregnancy. 19 births were exposed to AZA/6-MP. 74 births that were never exposed to AZA/6-MP were selected as controls. Preterm birth was seen in 26.3% of the exposed group as compared to 13.5% of controls (p<0.001). However, in univariate analysis, preterm birth was not associated with AZA/6-MP (OR=2.28; CI: 0.67-7.73). There was 1 neonatal adverse outcome in the exposed group as compared to 4 in controls (5.3% vs 5.4%, p=0.97). One congenital anomaly was seen in each group (p=0.27). No LBW at term was seen in either group. Placental blood flow in 4 women exposed to AZA/6-MP was normal.
CONCLUSION: The use of AZA/6-MP during pregnancy in IBD women was not associated with an increased risk of preterm birth, LBW at term, neonatal adverse outcomes and congenital anomalies.

J Crohns Colitis. 2011 Jun;5(3):196-202. Epub 2011 Feb 10.
Evolution and predictive factors of relapse in ulcerative colitis patients treated with mesalazine after a first course of corticosteroids.
Bello C, Belaiche J, Louis E, Reenaers C.

INTRODUCTION: Mesalazine remains the first line treatment for the induction and the maintenance of remission in mild to moderate ulcerative colitis (UC). Its efficacy as a maintenance treatment after a first flare treated with corticosteroids has not been specifically studied. The aims of our work were to study a cohort of UC patients treated with mesalazine after a course of oral systemic corticosteroids and to identify predictive factors of relapse and of colectomy.
MATERIAL AND METHOD: We studied retrospectively a cohort of 143 UC patients, who never received immunosuppressive drugs, and treated for the first time with oral corticosteroids for a flare. Among patients responding to corticosteroids, we studied the group treated by mesalazine after the flare.
RESULTS: Fifty% (n=52) achieved a complete clinical remission with steroid weaning. In this group, 67% (n=35) received oral mesalazine. Seventy-five % of patients treated by mesalazine relapsed (median 29 months, range: 1-156). Fourteen % required a colectomy (median 11 months, range: 1-24). Kaplan Meier curve showed a relapse rate and a colectomy rate over one year of 26% and 11% respectively. In multivariate analysis, male gender and short duration of disease were predictive factors of the time-to-relapse. No factor was predictive of time-to-colectomy.
CONCLUSION: Maintenance efficacy of mesalazine over one year after a first course of corticosteroids for a disease flare is reasonably high. The longer-term relapse rate becomes higher in male patients with a short disease duration. An immunosuppressive treatment could be discussed in case of further relapse despite improved medication-adherence. Medication-adherence should first be assessed and promoted. An immunosuppressive treatment could be discussed in case of further relapse despite improved medication-adherence.

Gastroenterology. 2011 May;140(6):1756-67.
Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases.
Strober W, Fuss IJ.

The cytokine responses characterizing the inflammatory bowel diseases are the key pathophysiologic elements that govern the initiation, evolution, and, ultimately, the resolution of these forms of inflammation. Studies during the last 2 decades now provide a detailed (but not yet complete) picture of the nature of these responses. The first tier of cytokine responses are governed by the T-cell differentiation patterns dominating the disease. In Crohn's disease, the major cytokines arise from T-helper cell (Th) 1 and Th17 CD4(+) T-cell differentiation and consist of interferon-γ and interleukin (IL)-17/IL-22 generated by these types of differentiation. The relative importance of these cytokines to Crohn's inflammation is still unclear, although evidence is mounting that interferon-γ is primus inter pare (first among equals). In contrast, in ulcerative colitis, a Th2-like differentiation process is paramount, which results in expansion of natural killer T cells producing IL-13 (and perhaps IL-5). These disease-specific cytokine patterns give rise to a second tier of cytokines that span the Th1/Th17-Th2 divide and act as upstream facilitators and downstream mediators of inflammation. These cytokines include the well-known tumor necrosis factor-α, IL-1β, IL-6 triumphirate, as well as a more recently studied cytokine known as TL1A (tumor necrosis factor-like ligand). In this review, we will explore this cytokine landscape with the view of providing an understanding of how recent and future anticytokine therapies actually function.

Gastroenterology. 2011 May;140(6):1768-75.
Regulation of homeostasis and inflammation in the intestine.
MacDonald TT, Monteleone I, Fantini MC, Monteleone G.

The gastrointestinal tract is the largest immune interface with the environment. Exposure to large numbers of dietary and microbial antigens requires complex and highly regulated immune responses by different mucosal cell types, which result in the induction and maintenance of intestinal homeostasis. Defects in this equilibrium can disrupt the homeostatic mechanisms and lead to chronic intestinal inflammation. We review the cell populations and mechanisms involved in the control of intestinal homeostasis and inflammation, focusing on inflammatory bowel diseases. We describe some aspects of gut immunity that could alter the delicate balance between inflammatory and tolerogenic responses and result in chronic gastrointestinal tract inflammation in patients.

Gastroenterology. 2011 May;140(6):1776-84.
Blocking lymphocyte localization to the gastrointestinal mucosa as a therapeutic strategy for inflammatory bowel diseases.
Villablanca EJ, Cassani B, von Andrian UH, Mora JR.

Lymphocyte migration (homing) to specific tissues has an important role during protective and pathological immune responses, including inflammatory bowel diseases. Lymphocytes use integrin α4β7 and the chemokine receptor CCR9 to localize to the gastrointestinal mucosa; their respective ligands, mucosal addressin cell adhesion molecule-1 and CCL25, are displayed on endothelial cells in intestinal postcapillary venules. Although gastrointestinal-homing receptors are required for lymphocyte migration to the intestine in the noninflamed steady state, their role during inflammation is a matter of debate. Reagents designed to block interactions between these receptors and their ligands have had variable degrees of success in animal models of inflammatory bowel diseases and patients. We discuss the mechanisms involved in lymphocyte localization to the intestinal mucosa and how they can be applied to therapy for inflammatory bowel diseases.

Gastroenterology. 2011 May;140(6):1785-94.
Epidemiology and natural history of inflammatory bowel diseases.
Cosnes J, Gower-Rousseau C, Seksik P, Cortot A.

In the West, the incidence and prevalence of inflammatory bowel diseases has increased in the past 50 years, up to 8-14/100,000 and 120-200/100,000 persons, respectively, for ulcerative colitis (UC) and 6-15/100,000 and 50-200/100,000 persons, respectively, for Crohn's disease (CD). Studies of migrant populations and populations of developing countries demonstrated a recent, slow increase in the incidence of UC, whereas that of CD remained low, but CD incidence eventually increased to the level of UC. CD and UC are incurable; they begin in young adulthood and continue throughout life. The anatomic evolution of CD has been determined from studies of postoperative recurrence; CD begins with aphthous ulcers that develop into strictures or fistulas. Lesions usually arise in a single digestive segment; this site tends to be stable over time. Strictures and fistulas are more frequent in patients with ileal disease, whereas Crohn's colitis remains uncomplicated for many years. Among patients with CD, intestinal surgery is required for as many as 80% and a permanent stoma required in more than 10%. In patients with UC, the lesions usually remain superficial and extend proximally; colectomy is required for 10%-30% of patients. Prognosis is difficult to determine. The mortality of patients with UC is not greater than that of the population, but patients with CD have greater mortality than the population. It has been proposed that only aggressive therapeutic approaches, based on treatment of early recurrent lesions in asymptomatic individuals, have a significant impact on progression of these chronic diseases.

Gastroenterology. 2011 May;140(6):1817-1826.e2.
The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease.
Lewis JD.

Fecal and serologic biomarkers can be used in the diagnosis and management of inflammatory bowel disease (IBD). Fecal markers such as calprotectin and lactoferrin have been studied for their ability to identify patients with IBD, assess disease activity, and predict relapse. Antibodies against

Saccharomyces cerevisiae and perinuclear antineutrophil cytoplasmic proteins have been used in diagnosis of IBD, to distinguish Crohn's disease (CD) from ulcerative colitis, and to predict the risk of complications of CD. Tests for C-reactive protein and erythrocyte sedimentation rate have been used to assess inflammatory processes and predict the course of IBD progression. Levels of drug metabolites and antibodies against therapeutic agents might be measured to determine why patients do not respond to therapy and to select alternative treatments. This review addresses the potential for biomarker assays to improve treatment strategies and challenges to their use and development.

Gastroenterology. 2011 May;140(6):1838-46.
Future therapeutic approaches for inflammatory bowel diseases.
Plevy SE, Targan SR.

In this review, we speculate about future therapeutic approaches for inflammatory bowel diseases (IBDs), focusing on the need for better preclinical and clinical models and approaches beyond small molecules and systemically administered biologics. We offer ideas to change clinical trial programs and to use immunologic and genetic biomarkers to personalize medicine. We attempt to reconcile past therapeutic successes and failures to improve future approaches. Some of our ideas might be provocative, but we hope that the examples we provide will stimulate discussion about what will advance the field of IBD therapy.

Curr Gastroenterol Rep. 2011 Feb;13(1):95-100.
Prevention and treatment of postoperative Crohn's disease recurrence: an update for a new decade.
Schwartz M, Regueiro M.

Poorly controlled Crohn's disease (CD) often requires surgery for such complications as strictures, fistulas, and abscesses. The goal of postoperative treatment is to suppress or prevent inflammation and maintain mucosal healing. Probiotics, antibiotics, 5-aminosalicylates, immunomodulators, and antibodies to tumor necrosis factor are all used to prevent postoperative recurrence. In this article, recent studies are reviewed. Azathioprine/6-mercaptopurine are moderately effective at preventing and treating postoperative CD, whereas infliximab/adalimumab are highly effective and probiotics and 5-aminosalicylates minimally effective. We base the choice of postoperative medical therapy on the patient's risk profile for postoperative recurrence. Whatever postoperative therapy is used, the mucosa should be assessed within 12 months to determine if the approach is effective. If active inflammation is found, then treatment should be intensified. By treating CD aggressively after a first surgery, future surgeries can be delayed or averted.

Expert Rev Gastroenterol Hepatol. 2011 Jun;5(3):311-4.
Update on Crohn's disease and ulcerative colitis.
Billioud V, Allen PB, Peyrin-Biroulet L.

The 6th European Crohn's and Colitis Organisation Congress took place in Dublin, Ireland, on the occasion of the 10th European Crohn's and Colitis Organisation anniversary. This key annual event attracted a record number of participants and presented updated information in the field of inflammatory bowel disease in children and adults. The extensive program combined the original basic scientific program that dealt with pathogenesis and new therapeutic targets, while the clinical program focused on the possibility of optimizing current therapies, the importance of mucosal healing and features of inflammatory bowel disease-related cancer.

J Crohns Colitis. 2011 Sep;5(4):324-31. Epub 2011 Mar 10.
Adalimumab as second line anti-tumour necrosis factor alpha therapy for Crohn's disease: A single centre experience.
Sprakes MB, Hamlin PJ, Warren L, Greer D, Ford AC.

BACKGROUND AND AIMS: Non-response, loss of response, or intolerance to anti-tumour necrosis factor alpha (anti-TNFα) therapy is well recognised in Crohn's disease (CD) patients. Data concerning outcomes following the use of a second anti-TNFα therapy, particularly in patients who do not respond to a first anti-

TNFα agent, are still emerging. The aim of this study was to assess response and tolerability to adalimumab following infliximab failure in a single centre cohort of CD patients.
METHODS: Data were collected prospectively on 44 patients who received adalimumab therapy following infliximab failure. Initial response to adalimumab therapy at 6weeks following induction was defined using a two point decrease in the Harvey-Bradshaw Index, with remission at this point defined using a Harvey Bradshaw index≤4. Sustained clinical benefit at the last point of follow up was determined using a physician's global assessment. Corticosteroid-free sustained clinical benefit was also assessed at this point.
RESULTS: Thirty-four (77%) patients had initial response to adalimumab therapy, with 28 (64%) having sustained clinical benefit. Corticosteroid-free sustained clinical benefit was achieved in nine (53%) of 17 patients requiring steroids at commencement of adalimumab. Four (44%) of the 9 patients who were primary non-responders to infliximab responded to adalimumab. The majority of CD patients who failed adalimumab therapy required surgery.
CONCLUSIONS: Second-line anti-TNFα therapy with adalimumab is effective at both inducing remission and maintaining response in CD patients who have failed infliximab, regardless of the reason for infliximab failure.

J Crohns Colitis. 2011 Sep;5(4):338-41. Epub 2011 Mar 10.
Perianal disease in patients with ulcerative colitis: A case-control study.
Zabana Y, Van Domselaar M, Garcia-Planella E, Mañosa M, San Román AL, Gordillo J, Cabré E, Domènech E.

BACKGROUND: Patients with ulcerative colitis (UC) and concomitant perianal disease (PAD) are occasionally seen, but the impact of PAD on UC outcome has been scarcely assessed.
AIMS: To evaluate the prevalence, clinical features and outcomes of PAD among UC patients.
METHODS: Patients with an initial diagnosis of UC who ever developed PAD were identified from three IBD hospital databases. Each case was matched by age, disease extent at diagnosis, and year of diagnosis, with two UC patients who never developed PAD.
RESULTS: Thirty-seven UC patients (5% of the whole series) developed PAD (complex in about a half of them), being more frequent among men (62%), with distal (50%) or extense (34%) disease. Proximal spread of UC occurred in 19% of cases. No differences in demographic features, rate of proximal spread or colectomy during follow-up were found as compared to controls, but greater requirements of steroids (P=0.019) were detected in UC-PAD patients. A change in disease diagnosis occurred in 6 patients mainly because of transmural involvement in colectomy specimen, small intestinal involvement, and/or endoscopic appearance.
CONCLUSIONS: PAD may occur in up to 5% of UC patients. When complex it leads to a change in disease diagnosis in one third of cases. UC-related therapeutic requirements are not increased in these patients, except for steroids.

J Crohns Colitis. 2011 Sep;5(4):342-9. Epub 2011 Apr 2.
Construction and validation of a web-based epidemiological database for inflammatory bowel diseases in Europe An EpiCom study.
Burisch J, Cukovic-Cavka S, Kaimakliotis I, Shonová O, Andersen V, Dahlerup JF, Elkjaer M, Langholz E, Pedersen N, Salupere R, Kolho KL, Manninen P, Lakatos PL, Shuhaibar M, Odes S, Martinato M, Mihu I, Magro F, Belousova E, Fernandez A, Almer S, Halfvarson J, Hart A, Munkholm P.

BACKGROUND: The EpiCom-study investigates a possible East-West-gradient in Europe in the incidence of IBD and the association with environmental factors. A secured web-based database is used to facilitate and centralize data registration.
AIM: To construct and validate a web-based inception cohort database available in both English and Russian language.
METHOD: The EpiCom database has been constructed in collaboration with all 34 participating centers. The database was translated into Russian using forward translation, patient questionnaires were translated by simplified forward-backward translation. Data insertion implies fulfillment of international diagnostic criteria, disease activity, medical therapy, quality of life, work productivity and activity impairment, outcome of pregnancy, surgery, cancer and death. Data is secured by the WinLog3 System, developed in cooperation with the Danish Data Protection Agency. Validation of the database has been performed in two consecutive rounds, each followed by corrections in accordance with comments.

RESULTS: The EpiCom database fulfills the requirements of the participating countries' local data security agencies by being stored at a single location. The database was found overall to be "good" or "very good" by 81% of the participants after the second validation round and the general applicability of the database was evaluated as "good" or "very good" by 77%. In the inclusion period January 1st - December 31st 2010 1336 IBD patients have been included in the database.
CONCLUSION: A user-friendly, tailor-made and secure web-based inception cohort database has been successfully constructed, facilitating remote data input. The incidence of IBD in 23 European countries can be found at www.epicom-ecco.eu.

Inflamm Bowel Dis. 2011 Jul;17(7):1530-1539. doi: 10.1002/ibd.21521. Epub 2010 Dec 22.
Efficacy and safety of certolizumab pegol in an unselected crohn's disease population: 26-week data of the FACTS II survey.
Vavricka SR, Schoepfer AM, Bansky G, Binek J, Felley C, Geyer M, Manz M, Rogler G, de Saussure P, Sauter B, Scharl M, Seibold F, Straumann A, Michetti P; for the Swiss IBDnet.

BACKGROUND: Certolizumab pegol (Cimzia, CZP) was approved for the treatment of Crohn's disease (CD) patients in 2007 in Switzerland as the first country worldwide. This prospective phase IV study aimed to evaluate the efficacy and safety of CZP over 26 weeks in a multicenter cohort of practice-based patients.
METHODS: Evaluation questionnaires at baseline, week 6, and week 26 were completed by gastroenterologists in hospitals and private practices. Adverse events were evaluated according to World Health Organization (WHO) guidelines.
RESULTS: Sixty patients (38F/22M) were included; 53% had complicated disease (stricturing or penetrating), 45% had undergone prior CD-related surgery. All patients had prior exposure to systemic steroids, 96% to immunomodulators, 73% to infliximab, and 43% to adalimumab. A significant decrease of the Harvey-Bradshaw Index (HBI) was observed under CZP therapy (12.2 ± 4.9 at week 0 versus 6.3 ± 4.7 at week 6 and 6.7 ± 5.3 at week 26, both $P < 0.001$). Response and remission rates were 70% and 40% (week 6) and 67% and 36%, respectively (week 26). The complete perianal fistula closure rate was 36% at week 6 and 55% at week 26. The frequency of adverse drug reactions attributed to CZP was 5%. CZP was continued in 88% of patients beyond week 6 and in 67% beyond week 26.
CONCLUSIONS: In a population of CD patients with predominantly complicated disease behavior, CZP proved to be effective in induction and maintenance of response and remission. This series provides the first evidence of CZP's effectiveness in perianal fistulizing CD in clinical practice. (Inflamm Bowel Dis 2011;).

J Pediatr Gastroenterol Nutr. 2011 Jun;52(6):702-707.
Do Children With IBD Really Respond Better Than Adults to Thiopurines?
Goodhand J, Tshuma N, Rao A, Kotta S, Wahed M, Croft N, Sanderson I, Epstein J, Rampton D.

BACKGROUND AND OBJECTIVES: Children and adolescents with inflammatory bowel disease (IBD) have more extensive and severe disease than adults. Despite a lack of comparative studies, thiopurines are frequently cited as being more efficacious in children. To test this assertion, we compared the efficacy of thiopurines in children with IBD with that in adults matched for disease phenotype.
PATIENTS AND METHODS: Fifty paediatric and adult patients with IBD started on a thiopurine were matched for sex, disease type, and extent. Retrospective data were obtained by electronic case note review, and corticosteroid-free clinical remission and tolerance rates at 6 months as well as relapse rates during the subsequent year were recorded.
RESULTS: Adverse effects caused discontinuation of thiopurines in 1 of 50 children and 16% (8/50) of adults ($P < 0.05$). At 6 months, steroid-free remission was achieved in 30% (15/50) of children and 38% (19/50) of adults ($P = 0.53$). No differences in remission rates were seen according to disease type. At the end of the following year, 73% (11/15) of children and 68% (13/19) of adults remained in remission ($P = 1$).
CONCLUSIONS: Thiopurines are tolerated better by children. When phenotype is matched, there is no difference in the therapeutic response to thiopurines between children and adults with IBD.

J Pediatr Gastroenterol Nutr. 2011 Jun;52(6):708-13.
Agreement Between Patient- and Physician-completed Pediatric Ulcerative Colitis Activity Index Scores.

Lee JJ, Colman RJ, Mitchell PD, Atmadja ML, Bousvaros A, Lightdale JR.

OBJECTIVES: : Currently validated ulcerative colitis (UC) activity measures are physician based, but incorporate patient reports of symptoms. We aimed to assess whether patient-completed Pediatric UC Activity Index (PUCAI) scores are comparable to those of physician scores.
PATIENTS AND METHODS: : We performed a single-center prospective study to assess agreement between patient- and physician-completed PUCAI scores. Seventy patients with UC (ages 4-29) representative of all of the disease activity categories (inactive, mild, moderate, and severe) in the currently published physician-completed scoring system were recruited. Agreement was analyzed for PUCAI scores both as continuous and categorical measures. To ascertain validity, we compared both patient- and physician-completed PUCAI scores with the physician global assessment and serum inflammatory markers.
RESULTS: : Patient- and physician-completed PUCAI summary scores were identical 49% of the time, were different but within the minimal clinically important difference (MCID) of 20 points 48% of the time, and were at or beyond the MCID only 3% of the time. In general, patients reported higher mean disease severity on their questionnaires than did their physicians, with a mean difference in PUCAI scores of 3 ± 8 (95% confidence interval 2%-5%). A categorical comparison of the 2 sets of questionnaires using the disease activity groups demonstrated perfect agreement for 60 (86%) pairs (kappa coefficient 0.78; 95% confidence interval 0.65%-0.90%). Both patient- and physician-completed PUCAI scores also correlated well with the physician global assessment and serum inflammatory markers.
CONCLUSIONS: : Our data indicate strong agreement between PUCAI scores obtained directly from patients and those completed by physicians. Hence, a patient-based PUCAI could complement existing instruments in both clinical and research settings.

Safety

Pharmazie. 2011 Apr;66(4):233-43.
Golimumab and immunogenicity? 2010 and beyond.
Zidi I, Bouaziz A, Ben Amor N.

Immunogenicity is a frequent adverse event observed with biological agents' therapy. Challenges of management in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis treated with golimumab, an anti-TNF-alpha blocker, include limited generation of antibodies like anti-nuclear, anti-golimumab, and anti-double stranded DNA antibodies. We conducted here a meta-analysis study in order to evaluate and compare the newly generated antibody levels after golimumab therapy. The examination of original clinical trials revealed that their levels were neither higher nor significant. Moreover, no evident associations between the induced-antibodies and lupus-like syndromes and/or infusion site reaction were reported. The reduced patients cohort and the absence of systematic newly generated antibodies follow-up might be implicated in the difficulty to evaluate their risk in delaying diseases therapy, and/or predicting for their worse prognosis. Hence, further studies are required to ascertain the real impact of the induced antibodies after golimumab's therapy.

Eur J Gastroenterol Hepatol. 2011 Jul;23(7):603-6.
Safety of infliximab in 10 years of clinical practice.
O'donnell S, Murphy S, Anwar MM, O'sullivan M, Breslin N, O'connor HJ, Ryan BM, O'morain CA.

ABSTRACT: Assessment of the long-term safety of anti-tumour necrosis factor therapies is vital for the safe treatment of inflammatory bowel disease, a disease affecting a young cohort of patients.
AIMS: The aim of this retrospective study was to assess the safety and long-term outcome of infliximab use in clinical practice in our institution on an intention to treat basis over the 10-year period from December 1998 to 31 December 2008.
METHODS: All cases receiving infliximab for ulcerative colitis or Crohn's disease over a 10-year period were identified from hospital pharmacy records. The study was based on a single centre cohort, with an unselected patient group.
RESULTS: A total of 271 patients were identified as receiving infliximab for either Crohn's disease or ulcerative colitis over the 10-year study period. In total, 2169 infusions were given to the patient cohort.

Fifty adverse events led to discontinuation of infliximab therapy in 47 cases. Two patients stopped due to neurological complications. There were six malignancies diagnosed within the cohort during the study period. Four of these were diagnosed while the individual was receiving Infliximab and two occurred at an interval of 21-52 months post their final infliximab infusion. A total of five deaths (1.5%) were observed during the study period.
CONCLUSION: Infliximab therapy seems to be safe and efficacious in the long term. Although the development of malignancy remains a concern, we have not seen an increased risk of serious infection within our cohort.

Arthritis Res Ther. 2011 May 25;13 Suppl 1:S4.
Structural damage in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: traditional views, novel insights gained from TNF blockade, and concepts for the future.
Schett G, Coates LC, Ash ZR, Finzel S, Conaghan PG.

Structural changes of bone and cartilage are a hallmark of inflammatory joint diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Despite certain similarities - in particular, inflammation as the driving force for structural changes - the three major inflammatory joint diseases show considerably different pathologies. Whereas RA primarily results in bone and cartilage resorption, PsA combines destructive elements with anabolic bone responses, and AS is the prototype of a hyper-responsive joint disease associated with substantial bone and cartilage apposition. In the present review we summarize the clinical picture and pathophysiologic processes of bone and cartilage damage in RA, PsA, and AS, we describe the key insights obtained from the introduction of TNF blockade, and we discuss the future challenges and frontiers of structural damage in arthritis.

Joint Bone Spine 2011 78 Supplement 1 Pages 15-185
TNF alpha antagonist therapy and safety monitoring
Thao Pham, Hervé Bachelez, Jean-Marie Berthelot, Jacques Blacher, Yoram Bouhnik, Pascal Claudepierre, Arnaud Constantin, Bruno Fautrel, Philippe Gaudin, Vincent Goëb, Laure Gossec, Philippe Goupille, Séverine Guillaume-Czitrom, Eric Hachulla, Isabelle Huet, Denis Jullien, Odile Launay, Marc Lemann, Jean-Francis Maillefert, Jean-Pierre Marolleau, et al.

No abstract available.

Drug Saf. 2011 Jul 1;34(7):577-85. doi: 10.2165/11590200-000000000-00000.
Sources of information on lymphoma associated with anti-tumour necrosis factor agents: comparison of published case reports and cases reported to the French pharmacovigilance system.
Théophile H, Schaeverbeke T, Miremont-Salamé G, Abouelfath A, Kahn V, Haramburu F, Bégaud B.

Background: Anti-tumour necrosis factor (TNF) agents, through their intense immunoregulatory effect, have been suspected to increase the risk of malignant lymphoma. However, the classical epidemiological approaches conducted over about the last 10 years have not totally succeeded in addressing the question of a causal or artifactual association. Therefore, the analysis of a substantial set of case reports, although usually considered as poorly generalizable to the general population, could be particularly informative. Two main sources of case reports in postmarketing settings are available; publications in medical journals and reports to pharmacovigilance systems. Objective: The aim of the study was to compare the characteristics of case reports from both these sources in order to understand whether they provided the same information for the investigation of the causal link between lymphoma and anti-TNF agents. Methods: All case reports of malignant lymphoma in patients treated with an anti-TNF agent published in MEDLINE and all reports to the French pharmacovigilance system up to 1 February 2010 were identified. Cases of malignant lymphoma identified in postmarketing surveillance from both sources were compared regarding the following variables: age, sex, anti-TNF agent involved, indication for use, type of lymphoma, prior or concomitant immunosuppressive drugs and time to onset of lymphoma. Results: A total of 81 published case reports and 61 cases reported to the French pharmacovigilance system were compared. In published reports, patients were younger (p=0.03) and more frequently receiving a first anti-TNF treatment (p=0.03), particularly infliximab (p=0.03). Conversely, in the pharmacovigilance system reports, a succession of different anti-TNFs (p=0.03) and adalimumab

(p<0.0001) were more frequently reported. Lymphomas in patients treated with anti-TNF agents for Crohn's disease were more prevalent in published cases than in pharmacovigilance reports (p<0.0001), and in particular involved hepatosplenic T-cell lymphoma. Conversely, rheumatoid arthritis was the main indication for anti-TNF agents in pharmacovigilance reports (p=0.01). Time to onset was markedly shorter in published cases (median 12 months) than in pharmacovigilance reports (median 30 months; p=0.0001). Conclusions: Characteristics of published cases and those reported to the French pharmacovigilance system differed markedly for all characteristics tested, except sex and the use of prior or concomitant immunosuppressive drugs. Published case reports favoured convincing arguments for drug causation whereas cases reported to the pharmacovigilance system were more disparate but could describe more accurately the reality of lymphoma occurrence in this particular population. These results argue for the use of the pharmacovigilance reports when case reports are used to investigate the causal link between lymphoma and anti-TNF agents at the population level. Data from cases notified to the French pharmacovigilance system did not indicate an increased risk of lymphoma during the early phase of anti-TNF treatment. To confirm this hypothesis, a study combining pharmacovigilance reports from several countries, or, if feasible, a cohort study both with a large sample size and a long duration of follow-up would be required.

Reprod Toxicol. 2011 May 20. [Epub ahead of print]
Safety of infliximab use during pregnancy.
Djokanovic N, Klieger-Grossmann C, Pupco A, Koren G.

Infliximab is a chimeric IgG1 monoclonal antibody to tumor necrosis factor alpha (TNF)-α used in the treatment of inflammatory bowel disease and rheumatoid arthritis. Infliximab does not actively cross the placenta during the first trimester, but undergoes efficient placental transfer during the late second and third trimesters and is detectable in the infant's serum for several months after birth. This raises concerns about immunological risks of infection and response to vaccines. Available evidence from registry studies and case reports involving more than 300 pregnancy outcomes suggest that infliximab carries low fetal risk and is compatible with use during conception and the first two trimesters of pregnancy. The long-term effects of infliximab exposure on the developing immune system are yet unknown. Based on limited data from several case reports, infants born with detectable levels of infliximab do not seem to have an increased risk of infections in their first year of life and have normal responses to nonlive vaccines. However, a fatal case of disseminated mycobacterial infection has been reported in an infant who received BCG vaccine at 3 months of age, to a mother who had been treated with infliximab throughout her pregnancy. Vaccination with live viruses should be postponed in infants exposed to infliximab in utero, until serum levels are undetectable which may require more than 6 months. Discontinuing infliximab early in the third trimester should be considered in order to minimize late fetal exposure.