Literature Update Immunology

Period: 1-31 MAY 2011

IBD

- **Long-term** durability of **infliximab** treatment in **Crohn's disease** and **efficacy** of dose **"escalation"** in patients **losing response**.
- **IBD** in **2010**: **optimizing treatment** and **minimizing adverse events**.
- Do not assume **symptoms** indicate **failure** of **anti-tumor necrosis factor therapy** in **Crohn's disease.**
- Levels of **C-reactive protein** are associated with r**esponse to infliximab therapy** in patients with **Crohn's disease**.
- Outcome following **thiopurine** use in **children** with **ulcerative colitis**: a prospective **multicenter registry study.**
- Development of the **Crohn's disease digestive damage score**, the **Lémann score**.
- Optimizing **thiopurine** therapy in **inflammatory bowel disease**.
- **Adalimumab** for **ulcerative colitis**: A little is better than none?
- **IL-23-responsive innate lymphoid cells** are increased in **inflammatory bowel disease**.

Safety

- **Ustekinumab** and **herpes zoster**.
- **Pregnancy** during **adalimumab** use for **psoriasis.**
- **Nonmelanoma skin cancer** in **inflammatory bowel disease**: A review.
- Incidence **of tuberculosis** infection **in psoriatic patients** on **anti-TNF therapy**: report of a case series with **144 patients**
- Does **anti-tumor necrosis factor-{alpha} therapy** affect **risk of serious infection** and **cancer** in patients with **rheumatoid arthritis**?: A review of **longterm data**.
- Anti-TNF therapy: Safety aspects of taking the risk.
- The risk of **infection** and **malignancy** with **tumor necrosis factor antagonists** in adults with **psoriatic disease**: A systematic **review** and **meta-analysis** of **randomized controlled trials**.

IBD

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.

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.

Clin Gastroenterol Hepatol. 2011 May;9(5):395-9. Epub 2011 Jan 28.
Do not assume symptoms indicate failure of anti-tumor necrosis factor therapy in Crohn's disease.
Bruining DH, Sandborn WJ.

It is a challenge to monitor patients with Crohn's disease who remain symptomatic despite anti-tumor necrosis factor therapy. Clinicians must use a systematic approach for each patient and obtain objective evidence about disease activity and response to therapy. Alternate etiologies for symptoms should be sought and treated, if found. Active Crohn's disease despite therapy requires reassessment and adjustments to management plans.

Clin Gastroenterol Hepatol. 2011 May;9(5):421-427.e1. Epub 2011 Feb 17.
Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease.
Jürgens M, Mahachie John JM, Cleynen I, Schnitzler F, Fidder H, van Moerkercke W, Ballet V, Noman M, Hoffman I, van Assche G, Rutgeerts PJ, van Steen K, Vermeire S.

BACKGROUND & AIMS: Infliximab is an antibody against tumor necrosis factor-α that is used to treat patients with moderate to severe Crohn's disease (CD). C-reactive protein (CRP) is a marker used to identify and follow individuals with CD. We analyzed changes in levels of CRP in a large cohort of patients with CD undergoing treatment with infliximab.
METHODS: Serial levels of CRP were analyzed in 718 CD patients. Blood was collected before each infusion; a total of 8845 CRP levels were available for analysis. The correlations between CRP levels and need for dose adjustment, outcomes, and mucosal healing (based on endoscopic analysis of 253 patients) were evaluated. Therapy adjustment was considered successful if therapy continued without need for change. Subgroup analysis was performed by using data from 268 patients who received 8 weeks of maintenance therapy.
RESULTS: More patients with high baseline levels of CRP responded to infliximab than patients with normal levels (90.8% vs 82.6%; P = .014). Early normalization of CRP levels correlated with sustained long-term response (P < .001). CRP levels remained significantly higher among patients who lost their response to infliximab, compared with those with a sustained response (P = .001). At time of loss of response, CRP levels were significantly increased (median, 11.2 mg/L) and did not return to baseline levels (median, 18.2 mg/L; P = .039). CRP correlated with mucosal healing (P = .033).
CONCLUSIONS: CRP is a good marker of disease activity in patients treated with infliximab. Increased levels of CRP indicate mucosal inflammation and a likelihood of clinical relapse.

Am J Gastroenterol. 2011 May;106(5):981-7. Epub 2011 Jan 11.
Outcome following thiopurine use in children with ulcerative colitis: a prospective multicenter registry study.
Hyams JS, Lerer T, Mack D, Bousvaros A, Griffiths A, Rosh J, Otley A, Evans J, Stephens M, Kay M, Keljo D, Pfefferkorn M, Saeed S, Crandall W, Michail S, Kappelman MD, Grossman A, Samson C, Sudel B, Oliva-Hemker M, Leleiko N, Markowitz J.

OBJECTIVES: Despite little supporting data, thiopurine use is common in pediatric ulcerative colitis (UC). Our aim was to determine outcome following thiopurine use in a multicenter inception cohort of children diagnosed with UC.
METHODS: Data were obtained from a prospective observational study of newly diagnosed children <16 years of age. Data are recorded at diagnosis, 30 days, and quarterly. Patients are managed by physician dictates not protocol. Disease activity is classified by physician global assessment. The primary outcome was corticosteroid (CS)-free inactive UC at 1 year following thiopurine initiation without the need for rescue therapy (infliximab, calcineurin inhibitors, or colectomy).
RESULTS: Of 1,490 patients in our registry, 394 have UC (mean age at diagnosis 11.3±3.7 years); 197 (50%) received thiopurine (49% ≤3 months from diagnosis). Also, 84% were receiving CSs and 60% 5-aminosalicylates at thiopurine start. Of the 197 patients, there was insufficient follow-up (41), previous or concomitant use of infliximab (16), or calcineurin inhibitor (7), leaving 133 patients evaluable at 1 year. Of these, 65 (49%) had CS-free inactive UC without rescue therapy. CS-free inactive disease at 1 year after initiating thiopurine was not affected by starting thiopurine ≤3 months vs. >3 months from diagnosis, gender, age, or concomitant treatment with 5-aminosalicylates. Kaplan-Meier analysis showed that the likelihood of remaining free of rescue therapy in the thiopurine-treated patients was 73% at 1 year.
CONCLUSIONS: Approximately 50% of children with UC starting thiopurine without previous or concomitant biologic or calcineurin inhibitor therapy have CS-free inactive disease 1 year later without the need for rescue therapy.

Inflamm Bowel Dis. 2011 Jun;17(6):1415-22. doi: 10.1002/ibd.21506. Epub 2010 Nov 28.
Development of the Crohn's disease digestive damage score, the Lémann score.
Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, Chowers Y, D'Haens G, Feagan BG, Hibi T, Hommes DW, Irvine EJ, Kamm MA, Loftus EV Jr, Louis E, Michetti P, Munkholm P, Oresland T, Panés J, Peyrin-Biroulet L, Reinisch W, Sands BE, Schoelmerich J, Schreiber S, Tilg H, Travis S, van Assche G, Vecchi M, Mary JY, Colombel JF, Lémann M.

Crohn's disease (CD) is a chronic progressive destructive disease. Currently available instruments measure disease activity at a specific point in time. An instrument to measure cumulative structural damage to the bowel, which may predict long-term disability, is needed. The aim of this article is to outline the methods to develop an instrument that can measure cumulative bowel damage. The project is being conducted by the International Program to develop New Indexes in Crohn's disease (IPNIC) group. This instrument, called the Crohn's Disease Digestive Damage Score (the Lémann score), should take into

account damage location, severity, extent, progression, and reversibility, as measured by diagnostic imaging modalities and the history of surgical resection. It should not be "diagnostic modality driven": for each lesion and location, a modality appropriate for the anatomic site (for example: computed tomography or magnetic resonance imaging enterography, and colonoscopy) will be used. A total of 24 centers from 15 countries will be involved in a cross-sectional study, which will include up to 240 patients with stratification according to disease location and duration. At least 120 additional patients will be included in the study to validate the score. The Lémann score is expected to be able to portray a patient's disease course on a double-axis graph, with time as the x-axis, bowel damage severity as the y-axis, and the slope of the line connecting data points as a measure of disease progression. This instrument could be used to assess the effect of various medical therapies on the progression of bowel damage. (Inflamm Bowel Dis 2011).

Inflamm Bowel Dis. 2011 Jun;17(6):1428-35. doi: 10.1002/ibd.21494. Epub 2010 Oct 14.
Optimizing thiopurine therapy in inflammatory bowel disease.
Chevaux JB, Peyrin-Biroulet L, Sparrow MP.

Despite recent advances, the therapeutic armamentarium for inflammatory bowel disease (IBD) is still limited. In addition, a step-up approach is recommended for most IBD patients. Thus, optimizing each medical therapy before switching to another drug class is the rule in clinical practice. Conventional therapies for IBD have not received the same amount of attention as biologic therapies over the last decade. However, due to their efficacy, safety, and low cost the thiopurine drugs azathioprine and 6-mercaptopurine remain the backbone of therapy for IBD. Pharmacogenomic advances and increased knowledge of their metabolism are allowing dosage optimization. Herein, after describing the pharmacogenetics and pharmacokinetics of thiopurines, we will discuss how to optimize thiopurine therapy. We will then underscore the need to take into account safety issues when optimizing thiopurine treatment. (Inflamm Bowel Dis 2011).

Inflamm Bowel Dis. 2011 May 3. doi: 10.1002/ibd.21773. [Epub ahead of print]
Adalimumab for ulcerative colitis: A little is better than none?
Danese S.

No abstract available.

J Exp Med. 2011 May 16. [Epub ahead of print]
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.

Safety

Dermatology. 2011;222(2):119-22. Epub 2011 Jan 22.
Ustekinumab and herpes zoster.
Failla V, Nikkels AF.

Background: TNF-α antagonists may increase the risk of herpes zoster (HZ), as well as the duration and severity. Recently, the monoclonal antibody ustekinumab, blocking the p40 subunit of IL-12 and IL-23, has been introduced for treating moderate to severe plaque psoriasis. There are no PubMed reports of HZ occurring in people receiving ustekinumab treatment. Common HZ was reported in clinical trials. Observation: Two patients with severe psoriasis treated with ustekinumab developed severe contiguous multidermatomal HZ 1 and 9 months after treatment initiation. Discussion: The occurrence of HZ after the instauration of ustekinumab suggests a causal relationship. Indeed, the inhibition of the p40 subunit of IL-12 shifts the immune response towards a Th1 profile with diminished IFN-γ and TNF-α expression, decreasing the antiviral immune response. Conclusion: Ustekinumab is probably a risk factor for developing HZ. Anti-HZ vaccination prior to ustekinumab treatment should be considered.

J Eur Acad Dermatol Venereol. 2010 Jun 21. [Epub ahead of print]
Pregnancy during adalimumab use for psoriasis.
Dessinioti C, Stefanaki I, Stratigos A, Kostaki M, Katsambas A, Antoniou C.

No abstract available.

Inflamm Bowel Dis. 2011 Jun;17(6):1423-7. doi: 10.1002/ibd.21484. Epub 2010 Nov 4.
Nonmelanoma skin cancer in inflammatory bowel disease: A review.
Long MD, Kappelman MD, Pipkin CA.

At least 1 million new cases of nonmelanoma skin cancer (NMSC) are diagnosed in the United States each year and the incidence is increasing. A higher incidence of NMSC in organ transplant recipients on immunosuppression has been documented for some time, and recent studies indicate that patients with inflammatory bowel disease (IBD), particularly those treated with immunosuppressive medications, might also be at higher risk for this condition. In this review we summarize recent data evaluating the associations between immunomodulators, antitumor necrosis factor-α biologic agents and NMSC in patients with IBD and other autoimmune conditions such as rheumatoid arthritis. We also offer recommendations for prevention of NMSC in these populations.

Journal of the Academy of Dermatology and Venereology 2011; 259(6): 730-3. doi: 10.1111/j.1468-3083.2010.03836.x. Epub 2010 Sep 14.
Incidence of tuberculosis infection in psoriatic patients on anti-TNF therapy: report of a case series with 144 patients
AI Sánchez-Moya and E Dauden

Background Worldwide clinical trials and post-marketing surveillance data have demonstrated an increased incidence of tuberculosis (TB) disease associated with antitumour necrosis factor (anti-TNF) agents. The majority of these cases are presumed to result from a reactivation of latent disease, while the rate of new infections is unknown. A study was performed to evaluate the incidence of latent tuberculosis infection (LTBI) in psoriatic patients screened for biological therapy in a high-incidence area, such as Madrid, Spain. Patients and methods One hundred and forty-four patients with moderate-to-severe psoriasis treated with anti-TNF agents were recruited. All of them were screened for active TB or LTBI before therapy. The screening included a detailed medical study, physical examination, chest X-ray, tuberculin skin test (TST) with purified protein derivative and re-TST. Results A total of 42 (29%) patients were diagnosed with LTBI based on a positive TST or re-TST, and/or signs of past TB in the chest X-ray. All of them received chemoprophylaxis with isoniazide. One patient developed a primary active lymphnode TB. Conclusion This is the first study to underscore the incidence of LTBI in patients with psoriasis treated with anti-TNF therapy in the Spanish population. We support that the use of TST is still reliable and an effective diagnostic method for the detection of LTBI in anti-TNF therapy.

J Rheumatol. 2011 May 15. [Epub ahead of print]
Does anti-tumor necrosis factor-{alpha} therapy affect risk of serious infection and cancer in patients with rheumatoid arthritis?: A review of longterm data.
Keystone EC.

Given the important role tumor necrosis factor-α (TNF-α) antagonists play in managing rheumatoid arthritis and the concern for safety during longterm therapy, we reviewed the latest evidence regarding longterm risk of infection and malignancy with TNF-α antagonists. Our objective was to provide clinicians with information that can be used to counsel and monitor patients who may be candidates for biologic therapy for rheumatoid arthritis (RA). Risk is examined in the context of background infection and malignancy rates in RA. Randomized controlled trial (RCT) data and observational studies summarizing the risk of infection and/or malignancy in RA and specific risks associated with the use of anti-TNF-α biologic agents (adalimumab, infliximab, and etanercept) were identified through a PubMed search. Overall, patients with RA appear to have an approximately 2-fold increased risk of serious infection compared to the general population and non-RA controls, irrespective of TNF-α antagonist use. Although data on infection rates with TNF-α antagonist use are contradictory, caution is merited. Recent analyses suggest that the risk of infection is highest within the first year. Regarding malignancy risk, RCT and observational data are also conflicting; however, caution is warranted regarding lymphoproliferative cancers in children and adolescents.

Autoimmun Rev. 2011 May 5. [Epub ahead of print]
Anti-TNF therapy: Safety aspects of taking the risk.
Rosenblum H, Amital H.

Rheumatoid arthritis (RA) therapy has been revolutionized in recent years following the introduction of three main anti-tumor necrosis factor-alpha inhibitors (anti-TNF) agents, infliximab, adalimumab and etanercept. Evidence in the literature indicates that patients treated with anti-TNF agents are at increased risk for bacterial infections, but it is not clear if this is a result of the treatment or of disease severity. The treatment has been recognized as a clear risk factor for reactivation of latent TB infections. So far, observational studies have not indicated any increased overall risk of cancer in RA patients treated with anti-TNF. The overall risk of lymphoma in these patients does not appear to differ greatly from that recorded among untreated patients, but rather is associated with the degree of disease activity rather than the type of therapy. There is a consensus in the literature that the likelihood of drug survival with infliximab is inferior to both adalimumab and etanercept, mostly due to increased risk of infection or allergic reactions. Due to the lack of head to head studies, there is no agreement as to which agent has the highest rates of treatment response and disease remission.

J Am Acad Dermatol. 2011 Jun;64(6):1035-50. Epub 2011 Feb 18.
The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: A systematic review and meta-analysis of randomized controlled trials.
Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM.

BACKGROUND: There is a need to better understand the safety of tumor necrosis factor (TNF) inhibitors in patients with psoriatic disease in whom TNF inhibitors are frequently used as monotherapy.
OBJECTIVE: We sought to examine the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease.
METHODS: We conducted a systematic search for trials of TNF antagonists for adults with plaque psoriasis and psoriatic arthritis. We included randomized, placebo-controlled trials of etanercept, infliximab, adalimumab, golimumab, and certolizumab for the treatment of plaque psoriasis and psoriatic arthritis. Twenty of 820 identified studies with a total of 6810 patients were included. Results were calculated using fixed effects models and reported as pooled odds ratios.
RESULTS: Odds ratios for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% confidence interval [CI] 1.05-1.33) and 0.70 (95% CI 0.40-1.21), respectively. When adjusting for patient-years, the incidence rate ratio for overall infection was 1.01 (95% CI 0.92-1.11). The odds ratio for malignancy was 1.48 (95% CI 0.71-3.09) and 1.26 (95% CI 0.39-4.15) when nonmelanoma skin cancer was excluded.
LIMITATIONS: Short duration of follow-up and rarity of malignancies and serious infections are limitations.

CONCLUSIONS: There is a small increased risk of overall infection with the short-term use of TNF antagonists for psoriasis that may be attributable to differences in follow-up time between treatment and placebo groups. There was no evidence of an increased risk of serious infection and a statistically significant increased risk in cancer was not observed with short-term use of TNF inhibitors.