Literature Update Immunology

Period: 1-28 February 2010

IBD

- **Infliximab safety profile** and **long-term applicability in inflammatory bowel disease**: 9-year experience in clinical practice.
- **Endoscopy** and **MR enteroclysis**: Equivalent tools in predicting clinical recurrence in patients with **Crohn's disease after ileocolic resection**.
- **Hospitalizations** are **increasing** among **minority patients with Crohn's disease** and **ulcerative colitis**.
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- **Severe sporotrichoid fishtank granuloma** following **infliximab therapy** for **Crohn's disease**.
- **Does methotrexate induce mucosal healing in Crohn's disease?**
- **Veto on vedolizumab (MLN0002) for Crohn's disease.**
- **Fulminant Ulcerative Colitis.**

Safety

- **Lymphoma** in patients treated with **anti-TNF**: results of the 3-year prospective French RATIO registry.
- Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice.
- **Longterm Safety** of Patients Receiving **Rituximab** in **Rheumatoid Arthritis Clinical Trials.**
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- **Possible Reactivation** of **Potential Hepatitis B Virus Occult Infection** by **Tumor Necrosis Factor-Blocker** in the Treatment of **Rheumatic Diseases.**
- **Neuromeningeal Tuberculosis** in a Patient with **Rheumatoid Arthritis Previously Exposed** to **Ineffective Etanercept Therapy** and **Revealed by Infliximab.**

IBD

Aliment Pharmacol Ther..
Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice.
Zabana Y, Domènech E, Mañosa M, Garcia-Planella E, Bernal I, Cabré E, Gassull MA.

Summary Background: Most available data on IFX therapy come from large, short-term, pivotal RCTs, and concerns about long-term safety profile still remain. Aim: To evaluate the long-term safety profile of infliximab (IFX) in inflammatory bowel disease (IBD) in a clinical practice setting. Methods: Since 1999, all IBD patients treated with IFX were registered and clinical outcomes prospectively recorded up to March 2008, loss of follow-up, or patient's death. IFX regimens and preventive measures were in accordance with the prevalent guidelines or the manufacturer recommendations. Results: One hundred fifty-two patients were included (121 Crohn's disease, 24 ulcerative colitis, 7 indeterminate colitis), with a median of 5 IFX infusions (IQR 3-8), and 87% of patients received at least 3 infusions. Seventy-nine per cent of them received concomitant immunomodulators, and 70% were pre-medicated with hydrocortisone from the first infusion. After a median follow-up of 142 weeks, 13% presented infusion reactions, 13% viral or bacterial infections, and 2 patients developed neoplasia. The mortality rate was 2.6% (4 patients). Conclusions: IFX therapy is safe when the recommended preventive measures are implemented, with a rate of serious adverse events lower than 10%. No new safety signals were found.

Inflamm Bowel Dis. 2010 Feb;16(2):198-203.
Endoscopy and MR enteroclysis: equivalent tools in predicting clinical recurrence in patients with Crohn's disease after ileocolic resection.
Koilakou S, Sailer J, Peloschek P, Ferlitsch A, Vogelsang H, Miehsler W, Fletcher J, Turetschek K, Schima W, Reinisch W.

BACKGROUND: Ileocolonoscopy poses the gold standard in the evaluation of postoperative recurrence of Crohn's disease (CD) at the site of ileocolonic anastomosis. Magnetic resonance enteroclysis (MRE) on the other hand is a promising technique for small bowel imaging. The aim was to compare MRE and ileocolonoscopy for predicting clinical recurrence in CD patients who have undergone ileocolonic resection. METHODS: We included 29 patients in the study. The median time since index operation was 35 months and between ileocolonoscopy and MRE was 3 days. Patients were followed up for a maximum of 2 years unless clinical recurrence occurred earlier. Endoscopic findings were evaluated on a 5-grade scale (i0-i4), whereas MRE findings on the neoterminal ileum and anastomosis were assessed according to a previously validated 4-grade scale MR score (MR0-MR3). RESULTS: By classifying patients into subgroups of endoscopic severity of postoperative recurrence using as a threshold an endoscopic score of i3, we found that 10% of patients in the i0 to i2 group had a clinical recurrence during the 2-year follow-up period as compared to 52.6% of subjects with i3 to i4 (P = 0.043). The corresponding clinical exacerbation rates in the subgroups based on MRE severity assessment were 12.5% for MR0 to MR1 and 50% for MR2 to MR3 (P = 0.09). CONCLUSIONS: Our data suggest that colonoscopy and MR enteroclysis are of similar value to predict the risk of clinical recurrence in postoperative patients with Crohn's disease.

Inflamm Bowel Dis. 2010 Feb;16(2):204-7.
Hospitalizations are increasing among minority patients with Crohn's disease and ulcerative colitis.
Sewell JL, Yee HF Jr, Inadomi JM.

BACKGROUND: Rates of inflammatory bowel disease (IBD) appear to be increasing among nonwhite populations outside the United States, but national data describing the incidence and prevalence of IBD are not available for minority patients. The aim of this study was to examine time trends of hospital discharge among minority patients with IBD. METHODS: Nationally representative data describing hospital discharges were obtained from the National Hospital Discharge Survey for the years 1994 to 2006. Race-specific annual proportions of hospitalizations including a discharge diagnosis of ulcerative colitis and Crohn's disease were calculated. Trends in proportions were assessed for statistical significance using the extended Mantel-Haenszel chi-square test for trend. RESULTS: The proportion of

hospitalizations including a discharge diagnosis of IBD increased significantly from 1994 to 2006 among the total population and among Asian, black, and white patients separately. Increases were statistically significant when analysis was performed for Crohn's disease and ulcerative colitis combined and separately. Marked increases were seen among Asians. CONCLUSIONS: The proportion of hospitalizations including a discharge diagnosis of IBD increased significantly among minority and nonminority patients from 1994 through 2006. The causes underlying these changes are not certain and should be further investigated.

Inflamm Bowel Dis. 2010 Feb;16(2):233-42.
Fontolizumab in moderate to severe Crohn's disease: a phase 2, randomized, double-blind, placebo-controlled, multiple-dose study.
Reinisch W, de Villiers W, Bene L, Simon L, Rácz I, Katz S, Altorjay I, Feagan B, Riff D, Bernstein CN, Hommes D, Rutgeerts P, Cortot A, Gaspari M, Cheng M, Pearce T, Sands BE.

BACKGROUND: The safety and efficacy of fontolizumab, a humanized anti-interferon gamma antibody, was investigated in patients with Crohn's disease (CD). Elevated gut mucosal levels of interferon gamma, a key cytokine involved in the inflammatory process of CD, are associated with disease symptoms. METHODS: A total of 201 patients with Crohn's Disease Activity Index (CDAI) scores between 250 and 450 were randomized to receive an initial intravenous dose of 1.0 or 4.0 mg/kg fontolizumab or placebo, followed by up to 3 subcutaneous doses of 0.1 or 1.0 mg/kg fontolizumab or placebo every 4 weeks. Clinical response at day 29, the primary efficacy endpoint, was defined as a decrease in the CDAI of at least 100 points from baseline levels. RESULTS: Of 201 patients, 135 (67%) completed the study. Day 29 response rates were similar in all treatment groups (31%-38%). At subsequent timepoints a significantly greater proportion of patients in the 1.0 mg/kg intravenous / 1.0 mg/kg subcutaneous fontolizumab group had clinical response and significantly greater improvement in the CDAI score compared with patients who received placebo. All fontolizumab groups had significant improvement in C-reactive protein levels. The overall frequency of adverse events was similar in all groups (58%-75%); most events were related to exacerbation of CD. There was a low frequency (5.2%) of neutralizing antibodies to fontolizumab. CONCLUSIONS: Although a strong clinical response to fontolizumab was not observed, significant decreases in C-reactive protein levels suggest a biological effect. Fontolizumab was well tolerated, and further studies to assess its efficacy are warranted.

Inflamm Bowel Dis. 2010 Feb;16(2):243-9.
Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: a Belgian case series.
Ferrante M, D'Haens G, Dewit O, Baert F, Holvoet J, Geboes K, De Hertogh G, Van Assche G, Vermeire S, Rutgeerts P; Belgian IBD Research Group.

BACKGROUND: Up to 25% of inflammatory bowel disease (IBD) patients undergoing surgery with an ileal pouch-anal anastomosis (IPAA) will develop chronic pouchitis not responding to antibiotics. In case reports, thiopurine analogs and infliximab (IFX) have been proposed as effective therapy in this setting. We analyzed the long-term efficacy of IFX in Belgian patients with refractory pouch complications. METHODS: We identified 28 IPAA patients who received IFX for refractory luminal inflammation (pouchitis and/or pre-pouch ileitis, n = 25) and/or pouch fistula (n = 7). Patients with elements of Crohn's disease after review of the colectomy specimen were excluded. Clinical response was defined as complete in case of cessation of diarrhea, blood loss, and abdominal pain, and as partial in case of marked clinical improvement. Fistula response was defined as complete in case of cessation and as partial in case of reduction of fistula drainage. RESULTS: Eighty-two percent of patients were concomitantly treated with immunomodulatory agents. At week 10 following start of IFX, 88% of patients with refractory luminal inflammation showed clinical response (14 partial, 8 complete), while 6 patients (86%) showed fistula response (3 partial, 3 complete). The mPDAI dropped significantly from 9.0 (interquartile range [IQR] 8.0-10.0) to 4.5 (3.0-7.0) points ($P < 0.001$). After a median follow-up of 20 (7-36) months, 56% showed sustained clinical response while 3 out of 7 fistula patients showed sustained fistula response. Five patients needed permanent ileostomy. CONCLUSIONS: In this series, IFX was effective long-term in IPAA patients with refractory luminal inflammation and pouch fistula. These results warrant a prospective multicenter randomized controlled trial.

Inflamm Bowel Dis. 2010 Feb;16(2):338-46.

Importance of mucosal healing in ulcerative colitis.
Lichtenstein GR, Rutgeerts P.

Treatment of patients with ulcerative colitis (UC) has traditionally focused on improving symptoms, with the main objective of inducing and maintaining symptomatic remission. However, new evidence suggests that concentrating exclusively on clinical outcome measures may not be adequate to achieve long-term treatment success. Indeed, physicians should also be assessing the reduction of endoscopic activity, with the intention of achieving complete mucosal healing (defined as the absence of all mucosal ulceration, both microscopic and macroscopic, providing a sigmoidoscopy score of 0, as assessed on the Ulcerative Colitis Disease Activity Index). As a consequence of the customary reliance on symptomatic outcome measures, relatively few clinical trials have used mucosal healing or a composite including mucosal healing as a primary endpoint. This situation may soon change as new guidelines recommend the incorporation of mucosal healing into the primary endpoint of all new clinical trials in patients with UC. These recommendations are derived, in part, from data that have illustrated a correlation between mucosal healing and several important factors including long-term remission rates, disease-related complications (e.g., risk of colorectal cancer), healthcare utilization (e.g., need for colectomy), and patient quality of life. We already have drugs available to us that can effectively induce and maintain complete mucosal healing over long periods of time. This review evaluates the effect of medical therapy on mucosal healing in patients with UC and explores the importance of this outcome measure, both from the patient's perspective and clinical trial experience.

Inflamm Bowel Dis. 2010 Feb;16(2):347-53.
Overall and cause-specific mortality in Crohn's disease: a meta-analysis of population-based studies.
Duricova D, Pedersen N, Elkjaer M, Gamborg M, Munkholm P, Jess T.

BACKGROUND: An overview of mortality risk among unselected patients with Crohn's disease (CD) is lacking. We therefore performed a systematic review and meta-analysis of population-based studies on overall and cause-specific mortality in CD. METHODS: MEDLINE (January 1965 to February 2008), abstracts from international conferences and reference lists of selected articles were searched systematically. All articles fulfilling the predefined inclusion criteria were scrutinized for data on population size, time of follow-up, gender, age, and observed to expected deaths. STATA meta-analysis software was used to calculate overall and cause-specific pooled standardized mortality ratios (SMR, observed/expected). RESULTS: Nine studies were included with overall SMRs ranging from 0.72-3.2, resulting in a significantly increased pooled SMR of 1.39 (95% confidence interval [CI]: 1.30-1.49). Regarding cause-specific mortality, a significantly increased risk of death from cancer (SMR 1.50, 95% CI: 1.18-1.92), in particular of pulmonary cancer (SMR 2.72, 95% CI: 1.35-5.45), as well as chronic obstructive pulmonary disease (SMR 2.55, 95% CI: 1.19-5.47), gastrointestinal diseases (SMR 6.76, 95% CI: 4.37-10.45), and genitourinary diseases (SMR 3.28, 95% CI: 1.69-6.35) was observed. CONCLUSIONS: Among unselected patients with CD, overall mortality was slightly but significantly higher than in the general population-primarily explained by deaths from gastrointestinal, respiratory, and genitourinary diseases. Notably, mortality from colorectal cancer was not increased.

Inflamm Bowel Dis. 2010 Feb;16(2):356-7.
Appendicitis, not appendectomy, is protective against ulcerative colitis, both in the general population and first-degree relatives of patients with IBD.
Beaugerie L, Sokol H.

No abstract available.

Inflamm Bowel Dis. 2010 Mar;16(3):362-3.
Current smoking, not duration of remission, delays Crohn's disease relapse following azathioprine withdrawal.
Sokol H, Seksik P, Nion-Larmurier I, Vienne A, Beaugerie L, Cosnes J.

No abstract available.

Inflamm Bowel Dis. 2010 Mar;16(3):371-2.
Acute lymphoid leukemia in a Crohn's disease patient during treatment with adalimumab after a prolonged treatment with azathioprine and steroids.
Cesarini M, Vernia P, Angelucci E.

No abstract available.

Inflamm Bowel Dis. 2010 Mar;16(3):375-6.
Severe sporotrichoid fishtank granuloma following infliximab therapy for Crohn's disease.
Ben Said B, Kanitakis J, Graber I, Berard F, Nicolas JF, Saurin JC, Augey F.

No abstract available.

Inflamm Bowel Dis. 2010 Mar;16(3):377-8.
Does methotrexate induce mucosal healing in Crohn's disease?
Mañosa M, Naves JE, Leal C, Cabré E, Moreno V, Lorenzo-Zuñiga V, Boix J, Domènech E.

No abstract available.

Inflamm Bowel Dis. 2010 Mar;16(3):537-8.
Veto on vedolizumab (MLN0002) for Crohn's disease.
Baumgart DC.

No abstract available.

N Engl J Med. 2010 Feb 18;362(7):635.
Fulminant ulcerative colitis.
Swaminath A, Feingold D.

No abstract available.

Safety

Ann Rheum Dis. 2010 Feb;69(2):400-8. Epub 2009 Oct 14.
Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry.
Mariette X, Tubach F, Bagheri H, Bardet M, Berthelot JM, Gaudin P, Heresbach D, Martin A, Schaeverbeke T, Salmon D, Lemann M, Hermine O, Raphael M, Ravaud P.

OBJECTIVE: To describe cases of lymphoma associated with anti-TNF therapy, identify risk factors, estimate the incidence and compare the risks for different anti-TNF agents. METHODS: A national prospective registry was designed (Research Axed on Tolerance of bIOtherapies; RATIO) to collect all cases of lymphoma in French patients receiving anti-TNF therapy from 2004 to 2006, whatever the indication. A case-control analysis was conducted including two controls treated with anti-TNF per case and an incidence study of lymphoma with the French population was used as the reference. RESULTS: 38 cases of lymphoma, 31 non-Hodgkin's lymphoma (NHL) (26 B cell and five T cell), five Hodgkin's lymphoma (HL) and two Hodgkin's-like lymphoma were collected. Epstein-Barr virus was detected in both of two Hodgkin's-like lymphoma, three of five HL and one NHL. Patients receiving adalimumab or infliximab had a higher risk than those treated with etanercept: standardised incidence ratio (SIR) 4.1 (2.3-7.1) and 3.6 (2.3-5.6) versus 0.9 (0.4-1.8). The exposure to adalimumab or infliximab versus etanercept was an independent risk factor for lymphoma in the case-control study: odds ratio 4.7 (1.3-17.7) and 4.1 (1.4-12.5), respectively. The sex and age-adjusted incidence rate of lymphoma was 42.1 per 100 000 patient-years. The SIR was 2.4 (95% CI 1.7 to 3.2). CONCLUSION: The two to threefold increased risk of lymphoma in patients receiving anti-TNF therapy is similar to that expected for such patients with severe inflammatory diseases. Some lymphomas associated with immunosuppression may

occur, and the risk of lymphoma is higher with monoclonal-antibody therapy than with soluble-receptor therapy.

Aliment Pharmacol Ther..
Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice.
Zabana Y, Domènech E, Mañosa M, Garcia-Planella E, Bernal I, Cabré E, Gassull MA.

Summary Background: Most available data on IFX therapy come from large, short-term, pivotal RCTs, and concerns about long-term safety profile still remain. Aim: To evaluate the long-term safety profile of infliximab (IFX) in inflammatory bowel disease (IBD) in a clinical practice setting. Methods: Since 1999, all IBD patients treated with IFX were registered and clinical outcomes prospectively recorded up to March 2008, loss of follow-up, or patient's death. IFX regimens and preventive measures were in accordance with the prevalent guidelines or the manufacturer recommendations. Results: One hundred fifty-two patients were included (121 Crohn's disease, 24 ulcerative colitis, 7 indeterminate colitis), with a median of 5 IFX infusions (IQR 3-8), and 87% of patients received at least 3 infusions. Seventy-nine per cent of them received concomitant immunomodulators, and 70% were pre-medicated with hydrocortisone from the first infusion. After a median follow-up of 142 weeks, 13% presented infusion reactions, 13% viral or bacterial infections, and 2 patients developed neoplasia. The mortality rate was 2.6% (4 patients). Conclusions: IFX therapy is safe when the recommended preventive measures are implemented, with a rate of serious adverse events lower than 10%. No new safety signals were found.

J Rheumatol. 2010 Jan 28.
Longterm Safety of Patients Receiving Rituximab in Rheumatoid Arthritis Clinical Trials.
van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann R, Furst DE, Macey K, Sweetser M, Kelman A, Rao R.

OBJECTIVE: To evaluate the longterm safety of rituximab in clinical trials in patients with rheumatoid arthritis (RA). METHODS: Pooled analysis of safety data, including adverse events (AE) and infections, from patients treated with rituximab in combination with methotrexate in a global clinical trial program. RESULTS: A total of 2578 patients with RA received at least 1 course of rituximab. Safety analyses were based on 5013 patient-years of rituximab exposure. The most frequent AE was infusion-related reactions (25% of patients during the first infusion of Course 1). Less than 1% of infusion-related reactions were considered serious. Rates of AE and serious AE (SAE; 17.85 events/100 patient-yrs, 95% CI 16.72, 19.06) were stable following each course. The overall serious infection rate was 4.31/100 patient-years (95% CI 3.77, 4.92). Infections and serious infections over time remained stable across 5 courses at 4-6 events/100 patient-years. Compared with other patients with RA and with the general US population, there was no increased risk of malignancy. CONCLUSION: In this longterm safety update in RA clinical trial patients, rituximab remained well tolerated over multiple courses. SAE and infections remained stable over time and by treatment course.

Inflamm Bowel Dis. 2010 Feb;16(2):182-3.
Adalimumab-induced psoriasis of the scalp with diffuse alopecia: a severe potentially irreversible cutaneous side effect of TNF-alpha blockers.
El Shabrawi-Caelen L, La Placa M, Vincenzi C, Haidn T, Muellegger R, Tosti A.

No abstract available.

J Rheumatol. 2010 Feb;37(2):346-50. Epub 2009 Dec 15.
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.

J Rheumatol. 2010 Feb;37(2):471.
Neuromeningeal tuberculosis in a patient with rheumatoid arthritis previously exposed to ineffective etanercept therapy and revealed by infliximab.
Dasilva V, Roux CH, Bernard E, Brocq O, Albert C, Chami H, Grisot C, Allam Y, Dellamonica P, Euller-Ziegler L.

No abstract available.