Literature Update Immunology

Period: 1-28 February 2011

IBD

- **Long-term efficacy** and **safety** of **cyclosporine** as a **rescue therapy** in **acute, steroid-refractory severe ulcerative colitis**: **switching** to **infliximab** is more **effective** than treating with **concomitant immunomodulators**.
- Successful **long-term** use of **infliximab** in **refractory pouchitis** in an **adolescent**.
- **Duodenal Crohn's disease** successfully treated with **adalimumab**.
- **Infliximab** and/or **azathioprine** in the treatment of **Crohn's disease-like complications** after **IPAA**.
- Long-term **durability** of **infliximab** treatment in **Crohn's disease** and **efficacy** of **dose "escalation"** in patients losing response.
- Use of **biological molecules** in the treatment of **inflammatory bowel disease**.
- **Immunosuppressant** combined with **infliximab** in **Crohn's Disease**: For 6 months, for 2 years, or forever?
- **Anti-TNF** treatment of **ulcerative colitis** associated with **idiopathic thrombocytopenic purpura**.
- **Infliximab** for severe **peripheral ulcerative keratopathy** revealing **Crohn's disease**.
- **Mucosal healing** with **methotrexate** in **Crohn's disease**: a prospective **comparative study** with **azathioprine** and **infliximab**.
- **Long-term** outcome of **treatment** with **infliximab** in **pediatric-onset Crohn's disease**: A population-based study.
- **Crohn's disease** of the **ileal pouch 16 years after proctocolectomy** for **ulcerative colitis**.
- Why **innovation** in **inflammatory bowel disease drug development** will impact your practice.

Safety

- **Antinuclear antibodies** associate with **loss of response** to **antitumour necrosis factor-α therapy** in **psoriasis** but do not necessarily predict treatment failure.
- **H1N1 vaccines** in a large observational cohort of patients with **inflammatory bowel disease** treated with **immunomodulators** and **biological therapy**.
- **Preoperative infliximab** is not associated with an increased **risk** of **short-term postoperative complications** after restorative **proctocolectomy** and **ileal pouch-anal anastomosis**.
- **Demyelinating disease** in patients treated with **TNF antagonists** in **rheumatology**: Data from **BIOBADASER**, a pharmacovigilance database, and a systematic review.
- **Immunogenicity of anti-TNF antibodies**. Has the veil been lifted?
- **Cancer** in **Crohn's Disease** patients treated with **infliximab**: A **long-term multicenter matched pair study**.
- **Aortic thrombosis** in **young women** with **Crohn's disease** receiving **adalimumab**: Report of two cases.
- Successful use of **infliximab** for **perianal Crohn's disease** in **pregnancy**.
- **Interstitial lung disease** induced or exacerbated by **TNF-targeted therapies**: analysis of **122 cases.**
- **Herpes zoster** at the site of **infliximab infusion**: case report.
- Increased **risk** of **acute myocardial infarction** in patients with **psoriasis**: A **5-year population-based study** in **Taiwan**.
- **Tumour necrosis** factor **antagonists** and the **risk** of **cardiovascular disease** in patients with **rheumatoid arthritis**: a systematic literature review.
- Risk of **adverse events** including **serious infections** in **rheumatoid arthritis** patients treated with **tocilizumab**: a systematic **literature review** and **meta-analysis** of **randomized controlled trials**.
- **Rheumatic fever** in a patient receiving **infliximab therapy** for **Crohn disease**.
- **Adverse effects** of **biologics**: a **network meta-analysis** and **Cochrane overview**.
- **Safety** and **efficacy** of **etanercept** beyond **10 years of therapy** in **North American** patients with **early** and **long-standing rheumatoid arthritis**.
- **Listeria monocytogenes infection** in patients with **inflammatory bowel diseases** receiving **anti-tumor necrosis factor therapy**.
- Prednisolone treatment affects the performance of the QuantiFERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection.

IBD

J Clin Gastroenterol. 2011 Jan 26. [Epub ahead of print]
Long-term Efficacy and Safety of Cyclosporine as a Rescue Therapy in Acute, Steroid-refractory Severe Ulcerative Colitis: Switching to Infliximab is More Effective Than Treating With Concomitant Immunomodulators.
Molnár T, Farkas K, Nyári T, Szepes Z, Nagy F, Wittmann T.

No abstract available.

Gastroenterol Res Pract. 2010;2010:860394. Epub 2011 Jan 12.
Successful long-term use of infliximab in refractory pouchitis in an adolescent.
Yeates J, Rashid M.

Pouchitis is a common complication that develops after an ileal pouch-anal anastomosis after colectomy for ulcerative colitis. In some cases, pouchitis becomes chronic and refractory to conventional therapies including antibiotics, corticosteroids, immunomodulators, probiotics, and anti-inflammatory drugs. We report a case of an adolescent with chronic pouchitis who not only improved with infliximab therapy but remains in long-term remission with maintenance therapy without any adverse effects. Infliximab is a safe and effective therapy for refractory pouchitis and may obviate the need for pouch removal and a permanent ileostomy.

Endoscopy. 2011;43 Suppl 2:E22. Epub 2011 Jan 26.
Duodenal Crohn's disease successfully treated with adalimumab.
Tursi A.

No abstract available.

Dis Colon Rectum. 2011 Jan;54(1):15-20.
Infliximab and/or azathioprine in the treatment of Crohn's disease-like complications after IPAA.
Haveran LA, Sehgal R, Poritz LS, McKenna KJ, Stewart DB, Koltun WA.

PURPOSE: Ileal pouch-anal anastomosis continues to be confounded by Crohn's disease-like complications after surgery. Such patients experience significant morbidity and often require either pouch excision or diversion. This study evaluated the effectiveness in our hands of infliximab and/or azathioprine/6-mercaptopurine in treating this patient population.
METHODS: We conducted a retrospective chart review of all patients who underwent IPAA who experienced Crohn's disease-like complications (pouch fistulas, stricturing small-bowel disease, or pouchitis unresponsive to antibiotics) after ileostomy closure. Patients were segregated according to treatment (azathioprine/6-mercaptopurine only, infliximab only, or both azathioprine/6-mercaptopurine and infliximab) and evaluated for clinical response defined by significant symptomatic improvement and avoidance of stoma.
RESULTS: Of 382 IPAAs, 32 (8.4%) patients developed Crohn's disease-like complications a mean of 17 months after stoma closure. Of these, 22 were treated with azathioprine/6-mercaptopurine and/or infliximab with one lost to follow-up. Overall mean follow-up was 97 ± 11.8 months. Failure rate (requiring stomas) was highest in the fistula group treated with infliximab and azathioprine/6-mercaptopurine (6/13, 46%). Patients with stricturing disease (6) or severe pouchitis (2) were all effectively treated with azathioprine/6-mercaptopurine (5/6) or infliximab (1 patient allergic to azathioprine/6-mercaptopurine) and none of these patients required stomas. In the group not receiving stomas, bowel frequency improved from 8.3 ± 1 to 5.7 ± 0.5 per day ($P < .05$).
CONCLUSION: Fistulizing disease after IPAA has the highest failure/stoma rate (46%) despite treatment with infliximab and/or azathioprine/6-mercaptopurine. IPAA patients with stricturing disease and/or antibiotic resistant pouchitis were successfully treated without stomas and all had resolution of symptoms, which suggests that fistulous disease after IPAA should be treated with infliximab, but stricturing disease and antibiotic resistant pouchitis may be effectively treated with azathioprine/6-mercaptopurine only. Such a protocol will potentially minimize the risks associated with infliximab in this difficult group of patients.

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.

J Intern Med. 2011 Jan 17. doi: 10.1111/j.1365-2796.2011.02344.x. [Epub ahead of print]
Use of biological molecules in the treatment of inflammatory bowel disease.
Nielsen OH, Seidelin JB, Munck LK, Rogler G.

The introduction of biological agents [i.e. anti-tumour necrosis factor-α and anti-integrin treatments] for the treatment of inflammatory bowel disease (IBD) [i.e., Crohn's disease (CD) and ulcerative colitis], has led to a substantial change in the treatment algorithms and guidelines, especially in CD. However, many questions still remain about the true efficacy and the best treatment regimens. Thus a need for further treatment options still exists as up to 40% of IBD patients treated with the presently available biologicals do not have positive clinical responses. Better patient selection might maximize the clinical benefit for those in most need of an effective therapy to avoid disabling disease while also minimizing the complications associated with therapy. Further, the "trough-level strategy" may help clinicians to optimize therapy and to avoid loss of response and/or immunogenicity. The idea behind this dosage regimen is that correct dosing must ensure that the patient's lowest level of drug concentration (i.e., the trough level) occurring just before the next drug administration is high enough for the full effect to be seen. Controversy continues regarding the appropriate use of biologicals, therefore in this review we focus on considerations that might lead to a more rational strategy for anti-tumor necrosis factor-α agents in IBD, emphasizing the situations in which the risks may outweigh the benefits. Finally, the need for an appropriate strategy for stopping biological treatment is discussed.

Inflamm Bowel Dis. 2011 Mar;17(3):858-9. doi: 10.1002/ibd.21407.
Immunosuppressant combined with infliximab in Crohn's Disease: For 6 months, for 2 years, or forever?
Louis E.

No abstract available.

Inflamm Bowel Dis. 2011 Mar;17(3):864-5. doi: 10.1002/ibd.21327.
Anti-TNF treatment of ulcerative colitis associated with idiopathic thrombocytopenic purpura.

Mares WG, Gerver J, Masclee AA, Pierik M.

No abstract available.

Inflamm Bowel Dis. 2011 Mar;17(3):866-7. doi: 10.1002/ibd.21358.
Infliximab for severe peripheral ulcerative keratopathy revealing Crohn's disease.
Angioi K, Kaminsky P, Peyrin-Biroulet L.

No abstract available.

Aliment Pharmacol Ther. 2011 Mar;33(6):714-21. doi: 10.1111/j.1365-2036.2010.04569.x. Epub 2011 Jan 16.
Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab.
Laharie D, Reffet A, Belleannée G, Chabrun E, Subtil C, Razaire S, Capdepont M, de Lédinghen V.
, Pessac, France.

Aliment Pharmacol Ther 2011; 33: 714-721 SUMMARY: Background Mucosal healing has become a new therapeutic goal in Crohn's disease and can be achieved with azathioprine (AZA) or biologics. Methotrexate (MTX) is an effective drug for both the induction and maintenance of remission in Crohn's disease. However, mucosal healing with MTX has been poorly investigated. Aim To assess the mucosal healing rate in patients with Crohn's disease with clinical response to MTX as compared with AZA or infliximab (IFX). Methods From October 2007 to May 2009, consecutive patients with Crohn's disease were prospectively enrolled into a single-centre study when they met the following criteria: previous identification of mucosal ulcerations with ileo-colonoscopy, clinical remission within at least 3 months with MTX, AZA or IFX monotherapy, usual indication for colonoscopy in Crohn's disease (dysplasia/cancer screening, suspected stenosis) excluding assessment for mucosal healing. Mucosal healing was defined as absence of mucosal ulceration in all segments. Results Fifty-one patients with Crohn's disease (38 female; median age: 42 years) were included: 18 receiving MTX, 18 AZA and 15 IFX. Mucosal healing was achieved in 2/18 (11%) with MTX, in 9/18 (50%) with AZA (P = 0.011 vs. MTX) and in 9/15 (60%) with IFX (P = 0.008 vs. MTX). Conclusion In patients with Crohn's disease in sustained clinical remission, mucosal healing is less frequently achieved with MTX as compared with AZA or IFX.

Inflamm Bowel Dis. 2011 Feb 1. doi: 10.1002/ibd.21615. [Epub ahead of print]
Long-term outcome of treatment with infliximab in pediatric-onset Crohn's disease: A population-based study.
Cromb V, Salleron J, Savoye G, Dupas JL, Vernier-Massouille G, Lerebours E, Cortot A, Merle V, Vasseur F, Turck D, Gower-Rousseau C, Lémann M, Colombel JF, Duhamel A.

BACKGROUND: We examined short- and long-term benefits and safety of infliximab (IFX) in a population-based cohort of Crohn's disease (CD) patients <17 years old at diagnosis.
METHODS: The following parameters were assessed: short- and long-term efficacy of IFX, impact of drug efficacy, and mode of administration on rate of resection surgery, growth and nutritional catch-up, and adverse events (AEs).
RESULTS: In all, 120 patients (69 female) required IFX with a median duration of 32 months (Q1 = 8-Q3 = 60). Median age at diagnosis was 14.5 years (12-16) and median interval between diagnosis and IFX initiation was 41 months (22-78). Median follow-up since CD diagnosis was 111 months (75-161). Fifty patients (42%) received episodic and 70 (58%) maintenance therapy. Sixty-five (54%) patients were in the "IFX efficacy" group: 38 (32%) still receiving IFX at the last visit and 27 (22%) stopping IFX while in remission. The "IFX failure" group included 55 (46%) patients: 17 (14%) who stopped IFX due to AEs and 38 (32%) nonresponders. The risk of surgery was reduced (P = 0.009) in the "IFX efficacy" group and lower (P = 0.03) in patients with scheduled versus episodic therapy. Patients in the "IFX efficacy" group had significant catch-up growth (P = 0.04), while those in the "IFX failure" group did not. Twenty-four patients presented AEs leading to cessation of IFX in 17 of them.
CONCLUSIONS: In this population-based cohort of pediatric-onset CD, IFX treatment was effective in more than half of patients during a median follow-up of 32 months. Long-term IFX responders had a lower

rate of surgery and improved catch-up in growth, especially when receiving scheduled IFX therapy. (Inflamm Bowel Dis 2011;).

Clin Gastroenterol Hepatol. 2011 Mar;9(3):198-201. Epub 2010 Nov 5.
Crohn's disease of the ileal pouch 16 years after proctocolectomy for ulcerative colitis.
Tremaine WJ.

No abstract available.

Clin Gastroenterol Hepatol. 2011 Mar;9(3):211-3.
Why innovation in inflammatory bowel disease drug development will impact your practice.
Sandborn WJ.

No abstract available.

Safety

Br J Dermatol. 2011 Feb;164(2):459-60. doi: 10.1111/j.1365-2133.2010.10101.x.
Antinuclear antibodies associate with loss of response to antitumour necrosis factor-α therapy in psoriasis but do not necessarily predict treatment failure.
Golberg O, Osborne JE, Hutchinson PE.

No abstract available.

Gut. 2011 Jan 26. [Epub ahead of print]
H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy.
Rahier JF, Papay P, Salleron J, Sebastian S, Marzo M, Peyrin-Biroulet L, Garcia-Sanchez V, Fries W, van Asseldonk DP, Farkas K, de Boer NK, Sipponen T, Ellul P, Louis E, Peake ST, Kopylov U, Maul J, Makhoul B, Fiorino G, Yazdanpanah Y, Chaparro M; for the European Crohn's and Colitis Organisation (ECCO).

Background Safety data are lacking on influenza vaccination in general and on A (H1N1)v vaccination in particular in patients with inflammatory bowel disease (IBD) receiving immmunomodulators and/or biological therapy. Aims and methods The authors conducted a multicentre observational cohort study to evaluate symptoms associated with influenza H1N1 adjuvanted (Pandemrix, Focetria, FluvalP) and non-adjuvanted (Celvapan) vaccines and to assess the risk of flare of IBD after vaccination. Patients with stable IBD treated with immunomodulators and/or biological therapy were recruited from November 2009 until March 2010 in 12 European countries. Harvey-Bradshaw Index and Partial Mayo Score were used to assess disease activity before and 4 weeks after vaccination in Crohn's disease (CD) and ulcerative colitis (UC). Vaccination-related events up to 7 days after vaccination were recorded. Results Of 575 patients enrolled (407 CD, 159 UC and nine indeterminate colitis; 53.9% female; mean age 40.3 years, SD 13.9), local and systemic symptoms were reported by 34.6% and 15.5% of patients, respectively. The most common local and systemic reactions were pain in 32.8% and fatigue in 6.1% of subjects. Local symptoms were more common with adjuvanted (39.3%) than non-adjuvanted (3.9%) vaccines ($p<0.0001$), whereas rates of systemic symptoms were similar with both types (15.0% vs 18.4%, $p=0.44$). Among the adjuvanted group, Pandemrix more often induced local reactions than FluvalP and Focetria (51.2% vs 27.6% and 15.4%, $p<0.0001$). Solicited adverse events were not associated with any patient characteristics, specific immunomodulatory treatment, or biological therapy. Four weeks after vaccination, absence of flare was observed in 377 patients with CD (96.7%) and 151 with UC (95.6%). Conclusion Influenza A (H1N1)v vaccines are well tolerated in patients with IBD. Non-adjuvanted vaccines are associated with fewer local reactions. The risk of IBD flare is probably not increased after H1N1 vaccination.

J Gastrointest Surg. 2011 Jan 19. [Epub ahead of print]
Preoperative infliximab is not associated with an increased risk of short-term postoperative complications after restorative proctocolectomy and ileal pouch-anal anastomosis.
Gainsbury ML, Chu DI, Howard LA, Coukos JA, Farraye FA, Stucchi AF, Becker JM.

INTRODUCTION: Considerable controversy exists over whether the preoperative use of infliximab (IFX) for refractory ulcerative colitis (UC) increases the risk for surgical complications after restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA). The aim of this study was to assess the association between preoperative IFX use and short-term surgical complications in a single-surgeon cohort at a tertiary care academic center.
METHODS: UC patients who underwent IPAA from September 2005 through May 2009 were retrospectively identified. Twenty-nine patients treated with IFX within 12 weeks of surgery and 52 non-IFX control subjects were identified. Short-term postoperative outcomes were compared between groups occurring within 30 days of loop ileostomy closure.
RESULTS: Patients were similar with respect to demographics, co-morbidities, rate of emergency surgery, hand-sewn anastomosis, and preoperative use of cyclosporine, azathioprine, and high-dose steroids. IFX patients were more likely to have received a laparoscopic hand-assisted IPAA, low-, medium-, and any-dose steroids, 6-mercaptopurine (6-MP), methotrexate, and to have failed medical therapy. There was no short-term mortality. Overall postoperative and infectious complications were similar between IFX and non-IFX groups. Multivariate regression models revealed no independent predictors for postoperative complications when including IFX [odds ratio (OR) 0.78, p□=□0.67], laparoscopic hand-assisted IPAA, 6-MP, methotrexate, steroids, failure of medical therapy, and body mass index.
CONCLUSIONS: Preoperative IFX use was not associated with an increased risk of short-term postoperative complications after IPAA.

Semin Arthritis Rheum. 2011 Feb;40(4):330-7. Epub 2010 Sep 22.
Demyelinating disease in patients treated with TNF antagonists in rheumatology: Data from BIOBADASER, a pharmacovigilance database, and a systematic review.
Fernández-Espartero MC, Pérez-Zafrilla B, Naranjo A, Esteban C, Ortiz AM, Gómez-Reino JJ, Carmona L; BIOBADASER Study Group.

OBJECTIVES: To estimate the rate of demyelinating diseases in patients with rheumatic diseases treated with tumor necrosis factor (TNF) antagonists and to describe the cases reported to 3 different pharmacovigilance sources.
METHODS: All confirmed cases of demyelinating disease, optic neuritis, and multiple sclerosis (MS) in patients with rheumatic diseases treated with TNF-antagonists were reviewed from 3 different sources: (1) the Spanish Registry of biological therapies in rheumatic diseases (BIOBADASER); (2) the Spanish Pharmacovigilance Database of Adverse Drug Reactions (FEDRA); and (3) a systematic review (PubMed, EMBASE, and the Cochrane Library). In BIOBADASER, the incidence rate per 1000 patients was estimated with a 95% confidence interval (95%CI).
RESULTS: In 21,425 patient-years in BIOBADASER, there were 9 patients with confirmed demyelinating disease, 4 with optic neuritis, and 1 with MS. In addition, 22 patients presented polyneuropathies, paresthesias, dysesthesias, facial palsy, or vocal cord paralysis without confirmed demyelination. The incidence rate of demyelinating disease in patients with rheumatic diseases exposed to TNF antagonists in BIOBADASER was 0.65 per 1000 patient-years (95%CI: 0.39-1.1). The incidence of MS in BIOBADASER was 0.05 (95%CI: 0.01-0.33), while the incidence in the general Spanish population was 0.02 to 0.04 cases per 1000. Compared with BIOBADASER, cases in FEDRA (n = 19) and in the literature (n = 48) tend to be younger, have shorter exposure to TNF-antagonists, and recover after discontinuation of the drug.
CONCLUSIONS: It is not clear whether TNF antagonists increase the incidence of demyelinating diseases in patients with rheumatic diseases. Differences between cases depending on the pharmacovigilance source could be explained by selective reporting bias outside registries.

Gut. 2011 Mar;60(3):285-6. Epub 2010 Dec 29.
Immunogenicity of anti-TNF antibodies. Has the veil been lifted?
Van Assche G.

No abstract available.

Inflamm Bowel Dis. 2011 Mar;17(3):758-66. doi: 10.1002/ibd.21416.
Cancer in Crohn's Disease patients treated with infliximab: A long-term multicenter matched pair study.
Biancone L, Petruzziello C, Orlando A, Kohn A, Ardizzone S, Daperno M, Angelucci E, Castiglione F, D'Incà R, Zorzi F, Papi C, Meucci G, Riegler G, Sica G, Rizzello F, Mocciaro F, Onali S, Calabrese E, Cottone M, Pallone F.

BACKGROUND: The long-term risk of neoplasia in Crohn's disease (CD) patients treated with infliximab is undefined. The aim was to assess, in a multicenter, matched-pair study, whether infliximab use in CD is associated with an increased frequency of neoplasia in the long term.
METHODS: A multicenter, long-term, matched-pair study was conducted in 12 referral inflammatory bowel disease (IBD) centers. An initial cohort of 808 CD patients, including 404 infliximab-treated (CD-IFX) and 404 matched CD controls never treated with infliximab (CD-C) studied from 1999 to 2004, was followed up for an additional 4 years (2004-2008). Cases and controls were matched for: sex, age (±5 years), CD site, follow-up (±5 years), immunosuppressant use, and CD duration (±5 years). From 1999 to 2008 the frequency and characteristics of neoplasia were compared between CD-IFX and CD-C.
RESULTS: In 2008, 591 patients (304 CD-IFX, 287 CD-C) were in follow-up. Matched couples included 442 patients: 221 CD-IFX and 221 CD-C (median follow-up, months: 72, range 48-114 versus 75, range 44-114). From 1999 to 2008 the frequency of neoplasia among the 591 patients did not differ between CD-IFX (12/304; 3.94%) and CD-C (12/287; 4.19%; P = 0.95). A comparable frequency of neoplasia was also observed between the 221 matched couples (CD-IFX: 8/221; 3.61% versus CD-C: 9/221; 4.07%; P = 1). No specific histotype of cancer appeared associated with infliximab use.
CONCLUSIONS: The frequency of neoplasia was comparable in an adult population of CD patients treated or not with infliximab, matched for clinical variables and followed up for a median of 6 years. (Inflamm Bowel Dis 2011).

Inflamm Bowel Dis. 2011 Mar;17(3):862-3. doi: 10.1002/ibd.21397.
Aortic thrombosis in young women with Crohn's disease receiving adalimumab: Report of two cases.
Leblanc S, Linares CL, Cacheux W, Mouthon L, Chaussade S.

No abstract available.

Inflamm Bowel Dis. 2011 Mar;17(3):868-9. doi: 10.1002/ibd.21368.
Successful use of infliximab for perianal Crohn's disease in pregnancy.
Chaparro M, Gisbert JP.

No abstract available.

Semin Arthritis Rheum. 2011 Jan 28. [Epub ahead of print]
Interstitial Lung Disease Induced or Exacerbated by TNF-Targeted Therapies: Analysis of 122 Cases.
Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, Brito-Zeron P, Bosch X, Ramos-Casals M.

OBJECTIVES: To analyze the clinical characteristics, outcomes, and patterns of association with the different biologic agents used in all reported cases of adult patients developing interstitial lung disease (ILD) after biologic therapy.
METHODS: In 2006, the Study Group on Autoimmune Diseases of the Spanish Society of Internal Medicine created the BIOGEAS project. One objective was to collect data on autoimmune diseases secondary to the use of biologic agents by quarterly Medline search surveillance of reported cases. For this study, the baseline included articles published between January 1990 and March 2010, including the MeSH term "lung diseases, interstitial" as the key research term. In addition, we report an unpublished case of ILD secondary to biologic therapy.
RESULTS: There are 122 reported cases of new-onset or exacerbation of ILD secondary to administration of biologic therapies. Biologic agents associated with ILD were overwhelmingly anti-tumor

necrosis factor agents (etanercept in 58 cases and infliximab in 56) and were administered for rheumatoid arthritis in 108 (89%) patients. ILD appeared a mean of 26 weeks after initiation of biologic agents. ILD was confirmed by pulmonary biopsy in 26 cases, although a specific histopathologic description was detailed in only 20: 7 patients were classified as usual interstitial pneumonia, 6 as nonspecific interstitial pneumonia, 5 as organizing pneumonia, 1 as diffuse alveolar damage, and 1 as lymphoid interstitial pneumonia. Treatment of ILD included withdrawal of biologic agents in all cases but 1. The outcome of ILD was detailed in 52 cases. Complete resolution was reported in 21 (40%) cases, improvement or partial resolution in 13 (25%), and no resolution in 18 (35%). Fifteen (29%) patients died during the follow-up, the majority (70%) during the first 5 weeks after initiating biologic therapy. In comparison with survivors, patients who died were aged >65 years (67% vs 33%, P = 0.036), with later onset of ILD (46 weeks vs 15 weeks, P = 0.006), received immunosuppressive drugs more frequently (33% vs 8%, P = 0.036), and more often had a previous diagnosis of ILD (67% vs 29%, P = 0.025).
CONCLUSIONS: We found that 97% of cases of ILD associated with biologic agents were associated with agents blocking tumor necrosis factor-α, a cytokine that has been implicated in the pathophysiology of pulmonary fibrosis. Strikingly, drug-induced ILD had a poor prognosis, with an overall mortality rate of around one third, rising to two thirds in patients with preexisting ILD.

Cutan Ocul Toxicol. 2011 Feb 8. [Epub ahead of print]
Herpes zoster at the site of infliximab infusion: case report.
Cruz MJ, Baudrier T, Ferreira O, Azevedo F.

Worldwide, many patients have been treated with tumor necrosis factor-? (TNF-?) antagonists for indications that include chronic inflammatory diseases such as rheumatoid and psoriatic arthritis, inflammatory bowel disease and others. Since their approval, concerns regarding safety have been raised. Increased susceptibility to bacterial infections, especially due to intracellular bacteria like Mycobacterium tuberculosis that is responsible for the most serious complications associated with this treatment. Viral infections are less frequently reported but probably relatively common, representing an important cause of morbidity to remember. Varicella zoster virus is one of the most frequently implicated viruses. We present the case of a 20-year-old man with Crohn?s disease under infliximab treatment who developed herpes zoster at the site of infliximab?s 7th and 9th infusion.

J Am Acad Dermatol. 2011 Mar;64(3):495-501. Epub 2011 Jan 8.
Increased risk of acute myocardial infarction in patients with psoriasis: A 5-year population-based study in Taiwan.
Lin HW, Wang KH, Lin HC, Lin HC.

BACKGROUND: No previous study has investigated the incidence or risk of acute myocardial infarction (AMI) developing after the diagnosis of psoriasis in Asian populations.
OBJECTIVE: We sought to evaluate the association between psoriasis and subsequent AMI during a 5-year follow-up period, using a nationwide Taiwanese population-based claims database, and taking clinical and demographic characteristics into consideration.
METHODS: Our study cohort consisted of all patients with a first recorded diagnosis of psoriasis (N = 4752) between 1999 and 2001 and of patients without a diagnosis of psoriasis (N = 23,760) who were matched by age and sex (1:5) to the patients with psoriasis. Each patient was tracked using hospitalization data from 2001 until the end of 2006. Stratified Cox proportional hazard regressions (stratified by age and sex) were performed as a means of computing the 5-year AMI-free survivals after adjusting for possible confounding factors.
RESULTS: Of the total sample, 70 patients (0.2%) had AMIs during the 5-year follow-up period: 22 (0.5% of the patients with psoriasis) from the study cohort and 48 (0.2%) from the comparison cohort. After adjusting for other factors, the hazard of AMI during the 5-year follow-up period was 2.10 times greater (95% confidence interval 1.27-3.43, P = .004) for patients with psoriasis than for comparison patients.
LIMITATIONS: We could not take into account some known risk factors for AMI, such as smoking and body mass index.
CONCLUSIONS: Psoriasis may confer an independent risk of AMI in Asian populations. We suggest that patients with psoriasis be made aware of the increased risk of AMI.

Rheumatology (Oxford). 2011 Mar;50(3):518-31. Epub 2010 Nov 11.

Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review.
Westlake SL, Colebatch AN, Baird J, Curzen N, Kiely P, Quinn M, Choy E, Ostor AJ, Edwards CJ.

Objectives. RA is associated with early ischaemic heart disease. This appears to be driven largely by the presence of chronic inflammation. Studies suggest that treatment with disease-modifying drugs such as MTX may reduce the incidence of cardiovascular events in RA. Anti-TNF therapies significantly reduce inflammation in RA. However, the extent to which these agents also reduce cardiovascular disease (CVD) is uncertain. The purpose of this study was to explore the effect of anti-TNF agents on CVD in RA using a systematic literature review. Methods. We searched for studies of adults with RA treated with TNF antagonists where cardiovascular outcomes were recorded using MEDLINE, EMBASE, Cochrane Database, Database of Abstracts and Reviews of Effects, Health Technology Appraisal, Science Citation Index and Clinical Evidence from 1989 to 2010. Conference proceedings for the British Society of Rheumatology, ACR and EULAR between 2005 and 2009 were hand searched. Two reviewers assessed abstracts for inclusion and then quality of selected papers was assessed. Results. A total of 1840 abstracts were identified and 20 articles were suitable for inclusion. Information was obtained on the effect of TNF antagonists on overall CVD events, myocardial infarction, strokes and heart failure. Conclusion. In many studies, TNF antagonists appear to reduce the likelihood of CVD in individuals with RA. Reassuringly, there does not appear to be an increased risk of cardiac failure. However, the reduction in CVD is not as consistently seen as with studies of MTX.

Rheumatology (Oxford). 2011 Mar;50(3):552-62. Epub 2010 Nov 14.
Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials.
Campbell L, Chen C, Bhagat SS, Parker RA, Ostör AJ.

Objective. To assess the risk of adverse events (AEs) in patients with RA treated with tocilizumab, an IL-6 receptor antibody, in published randomized controlled trials (RCTs). Methods. A systematic literature search was conducted using the Cochrane library, PUBMED and EMBASE for all RCTs (of the use of tocilizumab for RA) until September 2009. Fixed effect meta-analyses were conducted to compare the incidence of AEs after treatment with tocilizumab 8 and 4□mg/kg in combination with MTX, and 8□mg/kg tocilizumab monotherapy, with controls. Pooled summary odds ratios (ORs) were calculated using the Mantel-Haenszel method. Results. Six trials were analysed (four trials included 8□mg/kg tocilizumab and MTX combination therapy, three of which also assessed the 4□mg/kg dose). Three studies assessed tocilizumab monotherapy at 8□mg/kg. Pooled ORs revealed statistical significance for an increased risk of AEs in the 8□mg/kg combination group compared with controls (OR□=□1.53; 95% CI 1.26, 1.86). The risk of infection was significantly higher in the 8□mg/kg combination group compared with controls (OR□=□1.30; 95% CI 1.07, 1.58). No increased incidence of malignancy, tuberculosis reactivation or hepatitis was seen. Conclusion. Tocilizumab in combination with MTX as a treatment for RA is associated with a small but significantly increased risk of AEs, which is comparable with that of other biologics. Vigilance for untoward effects is, therefore, imperative in any patient treated with these immuno-suppressive agents.

J Pediatr Gastroenterol Nutr. 2011 Mar;52(3):360-1.
Rheumatic Fever in a patient receiving infliximab therapy for crohn disease.
Abu-El-Haija M, Stasheff S, Atkins DL, Bishop WP.

No abstract available.

Cochrane Database Syst Rev. 2011 Feb 16;2:CD008794.
Adverse effects of biologics: a network meta-analysis and Cochrane overview.
Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R.

BACKGROUND: Biologics are used for the treatment of rheumatoid arthritis and many other conditions. While the efficacy of biologics has been established, there is uncertainty regarding the adverse effects of this treatment. Since serious risks such as tuberculosis (TB) reactivation, serious infections, and

lymphomas may be common to the biologics but occur in small numbers across the various indications, we planned to combine the results from biologics used in many conditions to obtain the much needed risk estimates.
OBJECTIVES: To compare the adverse effects of tumor necrosis factor blocker (etanercept, adalimumab, infliximab, golimumab, certolizumab), interleukin (IL)-1 antagonist (anakinra), IL-6 antagonist (tocilizumab), anti-CD28 (abatacept), and anti-B cell (rituximab) therapy in patients with any disease condition except human immunodeficiency disease (HIV/AIDS).
METHODS: Randomized controlled trials (RCTs), controlled clinical trials (CCTs) and open-label extension (OLE) studies that studied one of the nine biologics for use in any indication (with the exception of HIV/AIDS) and that reported our pre-specified adverse outcomes were considered for inclusion. We searched The Cochrane Library, MEDLINE, and EMBASE (to January 2010). Identifying search results and data extraction were performed independently and in duplicate. For the network meta-analysis, we performed mixed-effects logistic regression using an arm-based, random-effects model within an empirical Bayes framework.
MAIN RESULTS: We included 163 RCTs with 50,010 participants and 46 extension studies with 11,954 participants. The median duration of RCTs was six months and 13 months for OLEs. Data were limited for tuberculosis (TB) reactivation, lymphoma, and congestive heart failure. Adjusted for dose, biologics as a group were associated with a statistically significant higher rate of total adverse events (odds ratio (OR) 1.19, 95% CI 1.09 to 1.30; number needed to treat to harm (NNTH) = 30, 95% CI 21 to 60) and withdrawals due to adverse events (OR 1.32, 95% CI 1.06 to 1.64; NNTH = 37, 95% CI 19 to 190) and an increased risk of TB reactivation (OR 4.68, 95% CI 1.18 to 18.60; NNTH = 681, 95% CI 143 to 14706) compared to control.The rate of serious adverse events, serious infections, lymphoma, and congestive heart failure were not statistically significantly different between biologics and control treatment. Certolizumab pegol was associated with significantly higher risk of serious infections compared to control treatment (OR 3.51, 95% CI 1.59 to 7.79; NNTH = 17, 95% CI 7 to 68). Infliximab was associated with significantly higher risk of withdrawals due to adverse events compared to control (OR 2.04, 95% CI 1.43 to 2.91; NNTH = 12, 95% CI 8 to 28). Indirect comparisons revealed that abatacept and anakinra were associated with a significantly lower risk of serious adverse events compared to most other biologics. Although the overall numbers are relatively small, certolizumab pegol was associated with significantly higher odds of serious infections compared to etanercept, adalimumab, abatacept, anakinra, golimumab, infliximab, and rituximab; abatacept was significantly less likely than infliximab and tocilizumab to be associated with serious infections. Abatacept, adalimumab, etanercept and golimumab were significantly less likely than infliximab to result in withdrawals due to adverse events.
AUTHORS' CONCLUSIONS: Overall, in the short term biologics were associated with significantly higher rates of total adverse events, withdrawals due to adverse events and TB reactivation. Some biologics had a statistically higher association with certain adverse outcomes compared to control, but there was no consistency across the outcomes so caution is needed in interpreting these results.There is an urgent need for more research regarding the long-term safety of biologics and the comparative safety of different biologics. National and international registries and other types of large databases are relevant sources for providing complementary evidence regarding the short- and longer-term safety of biologics.

Arthritis Care Res (Hoboken). 2010 Oct 18. [Epub ahead of print]
Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis.
Weinblatt ME, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH, Martin RW, Baumgartner SW, Park GS, Mancini EL, Genovese MC.

OBJECTIVE.: To evaluate long-term safety and efficacy of etanercept therapy in rheumatoid arthritis (RA) patients. METHODS.: Adult patients with early RA (ERA) or long-standing RA (LRA) received etanercept in open-label extension studies following initial double-blind trials of etanercept. RESULTS.: Of 558 ERA and 714 LRA patients who received at least 1 dose of etanercept, a total of 194 ERA and 217 LRA patients were treated with 25 mg etanercept twice weekly through 10 years. Five opportunistic infections were reported: in ERA, 1 Candida septicemia; in LRA, 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified), and 1 fungal sepsis (unspecified). Twenty-nine cases of sepsis occurred (10, ERA; 19, LRA). Occurrence of all malignancies was similar to that expected in the general population, but the occurrence of lymphomas was higher than expected in the general population. Fourteen lymphomas (7, ERA; 7, LRA) and 2 cases of demyelinating disease (1, ERA; 1, LRA) were reported. Deaths occurred in 18 ERA patients and 43 LRA patients. Both patient groups showed sustained improvement in American College of Rheumatology responses, swollen joint counts, Health Assessment Questionnaire scores, and C-reactive protein levels. CONCLUSION.: Etanercept maintained

therapeutic benefits beyond 10 years of therapy in both ERA and LRA patients, suggesting that etanercept is well tolerated and effective as a long-term, continuous therapy for the treatment of RA with a favorable risk-benefit ratio.

Rev Esp Enferm Dig. 2010 Oct;102(10):614-6.
Listeria monocytogenes infection in patients with inflammatory bowel diseases receiving anti-tumor necrosis factor therapy.
Ramos JM, García-Sepulcre MF, Masiá M, Brotons A, Grau MC, Gutiérrez F.

No abstract available.

Inflamm Bowel Dis. 2011 Feb 11. doi: 10.1002/ibd.21605. [Epub ahead of print]
Prednisolone treatment affects the performance of the QuantiFERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection.
Bélard E, Semb S, Ruhwald M, Werlinrud AM, Soborg B, Jensen FK, Thomsen H, Brylov A, Hetland ML, Nordgaard-Lassen I, Ravn P.

BACKGROUND: During screening for latent tuberculosis infection (LTBI), before anti-tumor-necrosis-factor-α treatment, most patients are already receiving immunosuppressive therapy. The objective was to evaluate the performance of the QuantiFERON Gold In-Tube (QFT-IT) and the Tuberculin Skin Test (TST).
METHODS: A prospective multicenter study included 248 patients with ulcerative colitis (39), Crohn's disease (54), rheumatoid arthritis (111), and spondylo-arthropathy (44).
RESULTS: QFT-IT was positive in 7/248 (3%), negative in 229 (92%), and indeterminate in 12 (5%). TST was positive in 54/238 (23%) patients. Chest x-ray was suspect for tuberculosis in 5/236 (2%), and 35/167 (21%) had ≥1 risk-factors for infection with Mycobacterium tuberculosis. The main finding was a pronounced negative effect on QFT-IT and TST performance associated with prednisolone treatment. During prednisolone treatment interferon gamma (IFN-γ) response to mitogen stimulation was impaired (median IFN-γ response 4.9 IU/mL; interquartile range [IQR] 0.8 to ≥10.0) compared to patients 1) not receiving corticosteroids (median ≥10.0; IQR 5.0 to ≥10.0; P = 0.0015) or 2) receiving long-acting corticosteroids (median >10.0; IQR 9.7 to >10.0; P = 0.0058). Prednisolone treatment was strongly associated with negative TST, adjusted odds ratio (AOR) 0.22 (0.1-0.8; P = 0.018), and with an increased risk of indeterminate QFT-IT results AOR 16.1 (4.1-63.2; P < 0.001), whereas no negative effect was found for long-acting corticosteroids. Doses of ≥10 mg prednisolone were associated with a 27% risk of indeterminate results. Single use of azathioprine, methotrexate, or 5-aminosalicylate (5-ASA) did not affect the test results.
CONCLUSIONS: Oral prednisolone severely suppressed QFT-IT and TST performance, whereas the long-acting corticosteroids methotrexate, azathioprine, and 5-ASA did not have a similar detrimental effect. Patients should be screened for LTBI with QFT-IT or TST prior to initiation of prednisolone therapy and negative QFT-IT or TST results interpreted with caution in patients treated with any corticosteroid until further data are available. (Inflamm Bowel Dis 2011).