Literature Update Immunology

Period: 01-31JAN2010

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- **Adalimumab safety and mortality rates** from global clinical trials of six immune-mediated inflammatory diseases.
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- **Malignancy concerns** with **psoriasis treatments** using **phototherapy**, **methotrexate**, **cyclosporin**, and **biologics**: facts and controversies.
- **Sarcoidosis Appearing During Anti-Tumor Necrosis Factor α Therapy**: A New “Class Effect” Paradoxical Phenomenon. Two Case Reports and Literature Review.
- The **economic burden of disease**: **comparison** between **rheumatoid arthritis and ankylosing spondylitis.**
- When rheumatology meets hepatology: are **anti-TNFs safe** in **hepatitis B virus carriers**?

IBD

Nat Genet. 2009 Dec;41(12):1335-40. Epub 2009 Nov 15.
Common variants at five new loci associated with early-onset inflammatory bowel disease.
Imielinski M, Baldassano RN, Griffiths A, Russell RK, Annese V, Dubinsky M, Kugathasan S, Bradfield JP, Walters TD, Sleiman P, Kim CE, Muise A, Wang K, Glessner JT, Saeed S, Zhang H, Frackelton EC, Hou C, Flory JH, Otieno G, Chiavacci RM, Grundmeier R, Castro M, Latiano A, Dallapiccola B, Stempak J, Abrams DJ, Taylor K, McGovern D; Western Regional Alliance for Pediatric IBD, Silber G, Wrobel I, Quiros A; International IBD Genetics Consortium, Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmuda MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ; NIDDK IBD Genetics Consortium, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E; Belgian-French IBD Consortium; Wellcome Trust Case Control Consortium, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghori J, Bumpstead S, Gwillam R, Tremelling M, Delukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ, Heyman MB, Ferry GD, Kirschner B, Lee J, Essers J, Grand R, Stephens M, Levine A, Piccoli D, Van Limbergen J, Cucchiara S, Monos DS, Guthery SS, Denson L, Wilson DC, Grant SF, Daly M, Silverberg MS, Satsangi J, Hakonarson H.

The inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis are common causes of morbidity in children and young adults in the western world. Here we report the results of a genome-wide association study in early-onset IBD involving 3,426 affected individuals and 11,963 genetically matched controls recruited through international collaborations in Europe and North America, thereby extending the results from a previous study of 1,011 individuals with early-onset IBD. We have identified five new regions associated with early-onset IBD susceptibility, including 16p11 near the cytokine gene IL27 (rs8049439, P = 2.41 x 10(-9)), 22q12 (rs2412973, P = 1.55 x 10(-9)), 10q22 (rs1250550, P = 5.63 x 10(-9)), 2q37 (rs4676410, P = 3.64 x 10(-8)) and 19q13.11 (rs10500264, P = 4.26 x 10(-10)). Our scan also detected associations at 23 of 32 loci previously implicated in adult-onset Crohn's disease and at 8 of 17 loci implicated in adult-onset ulcerative colitis, highlighting the close pathogenetic relationship between early- and adult-onset IBD.

Am J Gastroenterol. 2010 Jan;105(1):148-54. Epub 2009 Sep 15.
Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease.
Melmed GY, Agarwal N, Frenck RW, Ippoliti AF, Ibanez P, Papadakis KA, Simpson P, Barolet-Garcia C, Ward J, Targan SR, Vasiliauskas EA.

OBJECTIVES: The treatment of inflammatory bowel disease (IBD) often includes immunosuppressive medications, which may increase the risk of vaccine-preventable illnesses. We aimed to assess the impact of immunosuppression on immune responses to pneumococcal vaccination in patients with IBD. METHODS: The study design consists of a prospective controlled clinical trial. This study was carried out at a tertiary-care IBD clinic. The subjects for the study belonged to one of the following three groups: adult patients with IBD on combination TNF-blockers and immunomodulators (Group A), those without immunosuppressive therapy (Group B), and age-matched healthy controls (Group C). The treatment consisted of immunization with 23-valent pneumococcal polysaccharide vaccines (PSVs). The main outcome was immune response for five serotypes defined as a twofold or greater increase from pre-vaccination titers and > or =1 microg post-vaccination titer. RESULTS: Sixty-four subjects participated in the study: 20 in Group A, 25 in Group B, and 19 in Group C. Pre-vaccination titers were similar among the three groups. Vaccine responses were lower in Group A than in Group B (P< or =0.01 for four out of five antigens) and Group C (P<0.01 for all five antigens). Overall vaccine response was seen in 45, 80, and 85% of Groups A, B, and C (P=0.01), respectively. CONCLUSIONS: Immune response to PSV-23 is impaired in Crohn's disease (CD) patients on combination immunosuppressive therapy but is normal among non-immunosuppressed patients. Given the unpredictable likelihood for immunosuppressive therapy, newly diagnosed patients with IBD should undergo vaccination before the initiation of immunosuppressive therapy.

Am J Gastroenterol. 2010 Jan;105(1):162-9. Epub 2009 Sep 15.
Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI.
Schoepfer AM, Beglinger C, Straumann A, Trummler M, Vavricka SR, Bruegger LE, Seibold F.

OBJECTIVES: Studies evaluating the correlation between the widely used Simple Endoscopic Score for Crohn's disease (SES-CD) and noninvasive markers are scarce. The aim of this study was to evaluate the correlation between the SES-CD and fecal calprotectin, C-reactive protein (CRP), blood leukocytes, and the Crohn's disease activity index (CDAI). METHODS: Crohn's disease patients undergoing complete ileocolonoscopy were prospectively enrolled and scored independently according to the SES-CD and the CDAI. SES-CD was defined as follows: inactive 0-3; mild 4-10; moderate 11-19; and high > or =20. RESULTS: Values in CD patients (n=140 ileocolonoscopies) compared with controls (n=43) are as follows: calprotectin, 334+/-322 vs. 18+/-5 microg/g; CRP, 26+/-29 vs. 3+/-2 mg/l; and blood leukocytes, 9.1+/-3.4 vs. 5.4+/-1.9 g/l (all P<0.001). The SES-CD correlated closest with calprotectin (Spearman's rank correlation coefficient r=0.75), followed by CRP (r=0.53), blood leukocytes (r=0.42), and the CDAI (r=0.38). Calprotectin was the only marker that could discriminate inactive endoscopic disease from mild activity (104+/-138 vs. 231+/-244 microg/g, P<0.001), mild from moderate activity (231+/-244 vs. 395+/-256 microg/g, P=0.008), and moderate from high activity (395+/-256 vs. 718+/-320 microg/g, P<0.001). The overall accuracy for the detection of endoscopically active disease was 87% for calprotectin (cutoff 70 microg/g), 66% for elevated CRP, 54% for blood leukocytosis, and 40% for the CDAI > or =150. CONCLUSIONS: Fecal calprotectin correlated closest with SES-CD, followed by CRP, blood leukocytes, and the CDAI. Furthermore, fecal calprotectin was the only marker that reliably discriminated inactive from mild, moderate, and highly active disease, which underlines its usefulness for activity monitoring.

BMC Gastroenterol. 2010 Jan 10;10(1):1.
How do patients with inflammatory bowel disease want their biological therapy administered?
Allen PB, Lindsay H, Tham TC.

ABSTRACT: BACKGROUND: Infliximab is usually administered by two monthly intravenous (iv) infusions, therefore requiring visits to hospital. Adalimumab is administered by self subcutaneous (sc) injections every other week. Both of these anti-TNF drugs appear to be equally efficacious in the treatment of Crohn's Disease and therefore the decision regarding which drug to choose will depend to some extent on patient choice, which may be based on the mode of administration. The aims of this study were to compare preferences in Inflammatory Bowel Disease (IBD) patients for two currently available anti-TNF agents and the reasons for their choices. METHODS: An anonymous questionnaire was distributed to IBD patients who had attended the Gastroenterology service (Ulster Hospital, Dundonald, Belfast, N. Ireland. UK) between January 2007 and December 2007. The patients were asked in a hypothetical situation if the following administering methods of anti-TNF drugs (intravenous or subcutaneous) were available, which drug route of administration would they choose. RESULTS: One hundred and twenty-five patients fulfilled the inclusion criteria and were issued questionnaires, of these 78 questionnaires were returned (62 percent response). The mean age of respondent was 44 years. Of the total number of respondents, 33 patients (42 percent) preferred infliximab and 19 patients (24 percent) preferred adalimumab (p=0.07). Twenty-six patients (33 percent) did not indicate a preference for either biological therapy and were not included in the final analysis. The commonest reason cited for those who chose infliximab (iv) was: "I do not like the idea of self-injecting," (67 percent). For those patients who preferred adalimumab (sc) the commonest reason cited was: "I prefer the convenience of injecting at home," (79 percent). Of those patients who had previously been treated with an anti-TNF therapy (n=10, all infliximab) six patients stated that they would prefer infliximab if given the choice in the future (p=0.75). CONCLUSIONS: There was a trend towards patient preference for infliximab (iv) treatment as opposed to adalimumab (sc) in patients with IBD. This difference may be due to the frequency of administration, mode of administration or differing 'times in the market-place', as infliximab had been approved for a longer period of time in Crohn's disease. Further studies are required in IBD patients to investigate whether patient choice will affect compliance, patient satisfaction and efficacy of treatment with anti-TNF therapies.

J Investig Med. 2010 Jan 7.
Neutrophil Gelatinase-Associated Lipocalin Levels in Patients With Crohn Disease Undergoing Treatment With Infliximab.
Bolignano D, Della Torre A, Lacquaniti A, Costantino G, Fries W, Buemi M.

Increased levels of neutrophil gelatinase-associated lipocalin (NGAL), a small 25-kd stress protein released by several injured cells, have been reported in different pathological conditions such as kidney and chronic inflammatory bowel diseases. As NGAL is also emerging as a biomarker for monitoring the response to different types of treatment, the aims of this pilot study were to analyze urinary NGAL levels in a small cohort of patients affected by Crohn disease and to evaluate the eventual impact of the intravenous administration of infliximab on these levels.Crohn disease patients presented increased NGAL values compared with controls (210.5 ng/mL [88.3-1100.0 ng/mL] vs 7.6 [4.4] ng/mL; P = 0.001); the infusion of a single high dose of infliximab induced an impressive reduction in these levels to 80.1 ng/mL (38.6-400.2 ng/mL; P = 0.006) with a mean reduction ratio of 62.1%. These findings suggest a pivotal role of NGAL in the systemic adaptations to Crohn disease, also confirming the potential usefulness of NGAL measurement in the evaluation of early responses to therapy or in predicting different clinical outcomes.

Dig Dis Sci. 2010 Jan;55(1):131-6.
C-reactive protein and disease activity in children with Crohn's disease.
Tilakaratne S, Lemberg DA, Leach ST, Day AS.

BACKGROUND AND AIMS: Various markers are used to monitor disease activity in paediatric Crohn's disease (CD). We sought to determine whether C-reactive protein measurement was useful in the assessment of disease activity in children with CD, with comparison to the other markers of disease activity. METHODS: Details of disease activity, C-reactive protein and inflammatory markers were obtained retrospectively from the records of 100 outpatient visits by 63 children with CD. RESULTS: The children were 12.6 (+/-3.4) years of age. C-reactive protein values correlated positively with disease activity ($P < 0.0001$). Children with inactive disease (according to pediatric CD activity index scores) had significantly lower C-reactive protein values compared to children with mild disease ($P < 0.001$). In addition, C-reactive protein values correlated well with ESR ($P < 0.0001$). Conclusions C-reactive protein measurements provided useful information in assessing children with CD and correlated well with a validated measure of disease activity.

Digestion 2010;81:78-85
Clinical Experience with Adalimumab in a Multicenter Swiss Cohort of Patients with Crohn’s Disease
Nichita, C. ; Stelle, M. ; Vavricka, S. ; El-Wafa Ali, A. ; Ballabeni, P. ; de Saussure, P. ; Straumann, A. ; Rogler, G. ; Michetti, P.

No abstract available.

Digestion 2010;81:113-119
Patients’ Preferences regarding Shared Decision-Making in the Treatment of Inflammatory Bowel Disease: Results from a Patient-Empowerment Study
Baars, J.E. ; Markus, T. ; Kuipers, E.J. ; van der Woude, C.J.

No abstract available.

Dig Dis. 2009;27(4):536-41.
Medical management of Crohn's disease: treatment algorithms 2009.
Hanauer SB.

There has been a continual evolution of therapy for Crohn's disease (CD) over the past decade since the introduction of biological therapies targeting tumor necrosis factor-alpha. Conventional agents continue to be safe and effective for patients with mild to moderately active CD and, in population series, less than half of the patients with CD require corticosteroid therapy. In contrast, patients presenting at young ages, those with extensive disease, deep ulcerations, transmural complications or extraintestinal complications that require corticosteroid therapy have a poor prognosis. Introduction of immunosuppressives late in the course or for patients with steroid-dependent or steroid-refractory disease have not changed the 'natural history' of CD or the need for eventual surgical resections. There is increasing evidence that early

intervention with immunosuppressives or biologic agents at the same time as corticosteroids, or biologic agents targeting tumor necrosis factor or adhesion molecules, can have rapid and prolonged benefits, including steroid sparing, reductions in hospitalizations and, perhaps, reductions in the need for surgery. Treatment should be optimized according to the patient status and response with whichever level of therapy is introduced and maintained.

J. Exp. Med. 2010;207 4-5
Fiona Powrie: Gut diplomacy
Amy Maxmen

No abstract available.

J Crohn Colit 2010 15JAN.
The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis.
Gert Van Assche, Axel Dignass, Julian Panes, Laurent Beaugerie, John Karagiannis, Mathieu Allez, Thomas Ochsenkühn, Tim Orchard, Gerhard Rogler, Edouard Louis, Limas Kupcinskas, Gerassimos Mantzaris, Simon Travis, Eduard Stange

No abstract available.

J Crohn Colit 2010 15JAN.
The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management.
A. Dignass, G. Van Assche, J.O. Lindsay, M. Lémann, J. Söderholm, J.F. Colombel, S. Danese, A. D'Hoore, M. Gassull, F. Gomollón, D.W. Hommes, P. Michetti, C. O'Morain, T. Öresland, A. Windsor, E.F. Stange, S.P.L.

No abstract available.

J Crohn Colit 2010 6JAN.
On the updated ECCO consensus guidelines for medical management of Crohn's disease (letter to editor).
Dirk Esser, Freddy Cornillie, Robert H. Diamond, Robert J. Spiegel

No abstract available.

J Crohn Colit 2010 16JAN.
Infliximab administered with shortened infusion times in a specialized IBD infusion unit: A prospective cohort study.
Gert Van Assche, Séverine Vermeire, Maja Noman, Christine Amant, Ellen Weyts, Anita Vleminckx, Marie-Josée Vermeyen, Paul Rutgeerts

No abstract available.

Arch Surg. 2010 Jan;145(1):42-7.
Recurrence and impact of postoperative prophylaxis in laparoscopically treated primary ileocolic crohn disease.
Malireddy K, Larson DW, Sandborn WJ, Loftus EV, Faubion WA, Pardi DS, Qin R, Gullerud RE, Cima RR, Wolff B, Dozois EJ.

OBJECTIVES: To define risk factors for recurrence and to determine whether postoperative prophylaxis would influence time to recurrence after primary laparoscopic ileocolectomy for Crohn disease. DESIGN: Retrospective record review. SETTING: Tertiary academic medical center. PATIENTS: All patients who underwent primary laparoscopic ileocolectomy for terminal ileal Crohn disease between April 28, 1994,

and August 3, 2006, at the Mayo Clinic, Rochester, Minnesota. MAIN OUTCOME MEASURES: All patients were reviewed for follow-up, recurrence, risk factors for recurrence, and use of postoperative immunosuppressive prophylaxis. RESULTS: One hundred nine patients were identified, of whom 89 were followed up postoperatively at Mayo Clinic with a median follow-up of 3.5 years (range, 1.8 months to 11.9 years). Recurrence was discovered in 54 patients (61%) at a median of 13.1 months (range, 1.3 months to 8.7 years). Forty-four patients (49%) received postoperative immunosuppressive prophylaxis (37 [42%] received azathioprine, 8 [9%] received 6-mercaptopurine, and 3 [3%] received infliximab). In a multivariate model of various risk factors for recurrence, presence of granulomas was the only significant predictor of recurrence (P = .01). The 2-year cumulative recurrence rates in the prophylaxis and nonprophylaxis groups were 37.5% and 52.6%, respectively (log-rank test, P = .87). CONCLUSIONS: Recurrence occurred in more than half of the patients with Crohn disease after primary laparoscopic ileocolectomy. In this highly selected patient population, use of immunosuppressive prophylaxis was not associated with a delay in recurrence. Presence of granulomas was the only significant predictor of recurrence. These findings should be further explored in larger and less selected patient populations.

Colorectal Dis. 2010 12JAN.
Short-term outcome of infliximab and other medications on patients with inflammatory bowel disease undergoing ileostomy reversal.
Regadas FS, Pinto RA, Murad-Regadas SM, Canedo JA, Leal M, Nogueras JJ, Wexner SD.

No abstract available.

Int Rev Immunol. 2010;29(1):4-37.
Mechanisms and efficacy of immunobiologic therapies for inflammatory bowel diseases.
Ghosh N, Chaki R, Mandal V, Lin GD, Mandal SC.

Current advances in understanding of the pathogenesis of inflammatory bowel disease have encouraged the development of many new therapies targeted at specific and non-specific mediators of the inflammatory bowel disease inflammatory pathway. Crohn's disease and ulcerative colitis, two common inflammatory bowel diseases likely result from interaction of multiple genetic and environmental risk and protective factors, deregulation of mucosal immunity in gut and breakdown of delicate balance of proinflammatory and anti-inflammatory cytokines. Immunobiologic agents targeted against TNF, leukocyte adhesion, Th1 polarization, T cell activation, nuclear factor-kappaB (NF-kappaB), and others are being assessed and will open exciting perspectives on development of therapies for inflammatory bowel disease.

Safety

J Rheumatol. 2010 Jan;37(1):9-17. Epub 2009 Dec 15.
Can tumor necrosis factor inhibitors be safely used in pregnancy?
Ali YM, Kuriya B, Orozco C, Cush JJ, Keystone EC.

OBJECTIVE: We review available safety data for use of currently approved tumor necrosis factor (TNF) inhibitors during pregnancy and lactation and suggest guidelines for use of these agents among women of reproductive age. Method. Although regulatory agencies encourage the inclusion of pregnant women and those of child-bearing age in randomized controlled trials, pregnant and lactating women have universally been excluded from studies because of unknown or potential risks to the fetus. Thus, strong evidence-based treatment recommendations during pregnancy are usually lacking and safety information is derived from voluntary reports of adverse events during postmarketing surveillance or via uncontrolled, observational studies, reviewed here. RESULTS: Uncommon adverse pregnancy outcomes observed with TNF inhibitor therapy appear to approximate those seen in women not receiving such therapy and may include premature birth, miscarriage, low birthweight, hypertension, and preeclampsia. There are rare reports of fetal malformations or congenital anomalies in patients exposed to TNF inhibitors during conception or pregnancy. However, the incidence of these events appears to be far below the 3% rate of congenital anomalies in the general population. CONCLUSION: If the activity or disease severity precludes the cessation of a TNF inhibitor and/or DMARD, uncontrolled observations suggest that conception and early pregnancy are not adversely affected by use of TNF inhibitors. Nearly 70% of

pregnant patients can discontinue their TNF inhibitor early in the pregnancy (or with determination of pregnancy) without augmenting maternal or fetal risks.

Am J Gastroenterol. 2010 Jan;105(1):219; author reply 219-20.
Use of infliximab in pregnancy.
Mahadevan U, Kane S.

No abstract available.

J Rheumatol. 2010 Jan;37(1):209.
Recommended screening strategy for preventing tuberculosis flare in patients with inflammatory rheumatic diseases receiving tumor necrosis factor-alpha inhibitors in India - followup report.
Malaviya AN, Kapoor S, Garg S, Rawat R.

No abstract available.

J Eur Acad Dermatol Venereol. 2009 Dec 10.
Psoriasis is independently associated with psychiatric morbidity and adverse cardiovascular risk factors, but not with cardiovascular events in a population-based sample.
Schmitt J, Ford DE.

Abstract Background Psoriasis may significantly reduce quality of life. Previous studies reported an association of psoriasis and cardiovascular risk factors and cardiovascular events. The extent to which psoriasis is associated with psychiatric morbidity and the role of psychiatric comorbidity as a potential confounder of the association between psoriasis and cardiovascular morbidity require further investigation. Objectives To study the association between psoriasis, psychiatric morbidity and cardiovascular morbidity. Methods Case-control study utilizing an interdisciplinary administrative outpatient database from Germany. Patients with confirmed diagnosis of prevalent psoriasis within the study period (2003-2004) (n = 3147, mean age 57 years) were individually matched for age and gender with 3147 controls without psoriasis. The relationship of psoriasis with psychiatric morbidities (depression, stress-related disorders, behaviour disorders and schizophrenic disorders), cardiovascular risk factors (diabetes, hypertension, obesity and dyslipidaemia) and cardiovascular events [myocardial infarction (MI), stroke] was investigated using logistic and linear regression models. Results Crude analyses suggested an association of psoriasis with depression, stress-related disorders, behaviour disorders and cardiovascular risk factors, but not with MI [odds ratio (OR) 1.14; 95% confidence interval (95% CI) 0.81-1.62] or stroke (OR 0.97; 95% CI 0.61-1.54). Multivariate models controlling for age, gender and consulting behaviour indicated that psoriasis is independently associated with depression (OR 1.49; 95% CI 1.20-1.86), stress-related disorders (OR 1.41; 95% CI 1.22-1.62), behaviour disorders (OR 1.58; 95% CI 1.05-2.39), diabetes (OR 1.21 95% CI 1.04-1.40), hypertension (OR 1.34; 95% CI 1.18-1.51), dyslipidaemia (OR 1.29; 95% CI 1.07-1.55), and obesity (OR 1.63; 95% CI 1.39-1.90). For each psychiatric condition, the likelihood of being affected significantly increased with each physician visit due to psoriasis, suggesting that the risk of psychiatric comorbidity increases with the severity of psoriasis. Conclusion Psoriasis appears to be independently associated with major psychiatric disorders and with cardiovascular risk factors, but not with cardiovascular events.

Eur Heart J. 2009 Dec 27.
Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database.
Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM.

No abstract available.

Ann Rheum Dis. 2009 Dec;68(12):1863-9. Epub 2009 Jan 15.
Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases.
Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, Pangan AL.

OBJECTIVES: Clinical trials of tumour necrosis factor antagonists have raised questions about the potential risk of certain serious adverse events (SAE). To assess the safety of adalimumab in rheumatoid arthritis (RA) over time and across five other immune-mediated inflammatory diseases and to compare adalimumab malignancy and mortality rates with data on the general population. METHODS: This analysis included 19,041 patients exposed to adalimumab in 36 global clinical trials in RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), psoriasis and juvenile idiopathic arthritis (JIA) to 15 April 2007. Events per 100 patient-years were calculated using SAE reported after the first dose to 70 days after the last dose. Standardised incidence rates were calculated for malignancies using national and state-specific databases. Standardised mortality rates (SMR) were calculated for each disease using data from the World Health Organization. RESULTS: Cumulative rates of SAE of interest in RA have remained stable over time. Rates of SAE of interest for PsA, AS, CD, psoriasis and JIA were similar to or lower than rates for RA. Overall malignancy rates for adalimumab-treated patients were as expected for the general population. SMR across all six diseases indicated that no more deaths occurred with adalimumab than expected in the general population. CONCLUSIONS: Based on 10 years of clinical trial experience across six diseases, this safety report and the established efficacy of adalimumab in these diseases provide the foundation for a better understanding of its benefit-risk profile.

Biomed Mater Eng. 2009;19(4-5):355-64.
Arterial and venous thromboembolic events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006.
Petitpain N, Gambier N, Wahl D, Chary-Valckenaere I, Loeuille D, Gillet P; French Network of Pharmacovigilance Centers.

BACKGROUND: Systemic inflammation such as rheumatoid arthritis (RA) and Crohn's disease (CD) may be responsible for vascular comorbidity. TNF-alpha blockade was expected to lower these comorbidities but several cases of arterial and venous thromboembolic events (TE) have been reported. OBJECTIVES: The aim of this work was to study retrospectively the main characteristics of spontaneously notified TNF-alpha blockers related TE over a 7-year period. METHODS: TE related to infliximab, etanercept and adalimumab spontaneously notified to the French adverse drug reporting system database between January 2000 and December 2006 were analyzed. Separate analysis of arterial TE and venous TE was performed. Risk factors for each category of TE were assessed with consensual criteria. RESULTS: 85 TE were analyzed, representing 4.5% of all the spontaneously notified adverse reactions of the 3 TNF-alpha blockers in the database. 42 were arterial events and 43 were venous events. The incidence was not significantly different between the 3 TNF-alpha blockers. Mean delay of TE onset after treatment initiation was 10.6 months. It was significantly shorter for etanercept (6.1 months, p=0.001) especially for venous TE (2.4 months). 16 among the 42 patients with arterial TE had 2 or more risk factors whereas 39 among the 43 patients with venous TE had no RF or only one. Most of patients (79/85) received concomitant systemic corticosteroids and/or methotrexate and/or COX-2 selective inhibitors. 23 patients had been investigated for autoimmunity, 13 had antinuclear and/or antiphospholipid antibodies. Main limitations of this study were underreporting and heterogeneous report contents. CONCLUSION: Despite its limitations, this study suggests that venous TE could be favoured by TNF-alpha blockers therapy since they occurred in patients with no or few risk factors for venous thrombosis. However, this needs to be more evaluated by controlled studies.

Arthritis Res Ther. 2010 Jan 8;12(1):R5.
Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT.
Strangfeld A, Hierse F, Rau R, Burmester GR, Krummel-Lorenz B, Demary W, Listing J, Zink A.

ABSTRACT: INTRODUCTION: We used the data of the German biologics register RABBIT, a nationwide prospective cohort study, to investigate the risk of new or recurrent malignancy in patients with rheumatoid arthritis (RA) receiving biologics compared to conventional disease modifying anti-rheumatic drugs (DMARDs). METHODS: The analysis was based on patients with RA enrolled in RABBIT at start of a biologic or conventional DMARD therapy between 01 May 2001 and 31 December 2006. Incidences of first or recurrent malignancies were analysed separately. A nested case-control design was used to investigate the risk of developing a first malignancy. Matching criteria were: age, gender, follow-up time, DAS28 at study entry, smoking status, and selected chronic co-morbid conditions (obstructive or other lung disease, kidney, liver or gastrointestinal disease, psoriasis). RESULTS: A prior malignancy was

reported in 122 out of 5,120 patients. 58 of these patients had received anti-TNFalpha agents, 9 anakinra, and 55 conventional DMARDs at study entry. In 14 patients (ever exposed to anti-TNFalpha: eight, to anakinra: one) 15 recurrent cancers were observed. The average time period since the onset of the 1st malignancy was 9 years. Crude recurrence rates per 1,000 patient-years (pyrs) were 45.5 for patients exposed to anti-TNFalpha agents, 32.3 for anakinra patients and 31.4 for patients exposed to DMARDs only (Incidence rate ratio anti-TNFalpha vs. DMARD = 1.4, p=0.6.). In patients without prior cancer, 74 patients (70% female, mean age: 61.3) developed a first malignancy during the observation. This corresponds to an incidence rate (IR) of 6.0 /1,000 pyrs. 44 of these patients were ever exposed to anti-TNFalpha treatment (IR= 5.1/1,000 pyrs). In a nested case-control study comparing cancer patients to cancer-free controls, 44 of the cancer patients and 44 of the cancer-free controls were ever exposed to anti-TNFalpha agents (P=1.0). CONCLUSION: No significant differences in the overall incidence of malignancies in patients exposed or unexposed to anti-TNFalpha or anakinra treatment were found. The same applied to the risk of recurrent malignancies. However, in particular this last finding needs further validation in larger data sets.

Rheumatol Int. 2010 Jan 5.
Multiple organ tuberculosis of lung, pleura, and peritoneum in ankylosing spondylitis during adalimumab therapy.
Yoo WH.

A case of multiple organ tuberculosis (TBc) involving lung, pleura, and peritoneum in a 39-year-old man with long-standing ankylosing spondylitis (AS) treated with adalimumab was presented. The relationship between antitumor necrosis factor-alpha (anti-TNF-alpha) therapy and TBc was also reviewed. This case illustrates that TBc can develop in multiple organs during adalimumab therapy, and thus, the awareness of serious complications of multiple organs and atypical extrapulmonary pattern of TBc during anti-TNF-alpha therapy needs to be increased.

Clin Rheumatol. 2010 Jan 12.
Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs.
Atteno M, Peluso R, Costa L, Padula S, Iervolino S, Caso F, Sanduzzi A, Lubrano E, Del Puente A, Scarpa R.

The aim of this study is to compare effectiveness and safety of Infliximab (INF), Etanercept (ETN), and Adalimumab (ADA) in patients with psoriatic arthritis (PsA) with inadequate response to a previous disease-modifying antirheumatic drug (DMARD). One hundred consecutive PsA patients with inadequate response to a previous DMARD entered this study. Clinical and laboratory assessment at baseline (T0) and 12 (T12) months were performed and included physical examination, vital signs, global Psoriasis Area and Severity Index (PASI; extension of psoriasis), tender joints count (TJC), swollen joint count, health assessment questionnaire (HAQ; questionnaire for measuring disability), and monitoring of adverse events (AEs). After enrolment, all patients were randomly given INF 5 mg/Kg every 6-8 weeks, ETN 50 mg weekly, or ADA 40 mg every other week. Baseline therapy with DMARD remained unchanged. Effectiveness was defined as percentage of ACR20 responders and as clinical remission and/or minimal disease activity at 12 months treatment. INF, ETN, and ADA all effectively controlled signs and symptoms of PsA. All variables tested showed at T12 for each treatment a significant variation from the baseline value. In particular, patients on INF and ADA showed the greatest improvement in terms of PASI, while patients on ETN showed the greatest improvement on TJC and HAQ. ACR response rates were 72% of patients on ETN, 70% of those on ADA, and 75% of those patients on INF. Occurrence of AEs was reported in 15% of the cases. Only two AEs in patients on INF were considered drug related, pneumonitis and thrombocytopenia, respectively. All tumor necrosis factor-alpha blockers significantly controlled signs and symptoms of PsA. An increased knowledge of the different profiles of these agents may help in optimizing their use.

Rheumatology (Oxford). 2010 Jan 7.
Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register.
Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL; on behalf of the BSRBR.

Objectives. To evaluate the risk-benefit profile of anti-TNF therapies in PsA and to study the predictors of treatment response and disease remission [disease activity score (DAS)-28 < 2.6]. Methods. The study included PsA patients (n = 596) registered with the British Society for Rheumatology Biologics Register (BSRBR). Response was assessed using the European League against Rheumatism (EULAR) improvement criteria. Univariate and multivariate logistic regression models were developed to examine factors associated with EULAR response and disease remission using a range of covariates. Poisson regression was used to calculate incidence rate ratios (IRRs) for serious adverse events (SAEs) vs seronegative RA controls receiving DMARDs, adjusting for age, sex and baseline co-morbidity. Results. At baseline, the mean (s.d.) DAS-28 was 6.4 (5.6). Of the patients, 70.3% were EULAR responders at 12 months. At 6 months, older patients [adjusted odds ratio (OR) 0.97 per year; 95% CI 0.95, 0.99], females (adjusted OR 0.51; 95% CI 0.34, 0.78) and patients on corticosteroids (adjusted OR 0.45; 95% CI 0.28, 0.72) were less likely to achieve a EULAR response. Over 1776.2 person-years of follow-up (median 3.07 per person), the IRR of SAEs compared with controls was not increased (0.9; 95% CI 0.8, 1.3). Conclusions. Anti-TNF therapies have a good response rate in PsA, and have an adverse event profile similar to that seen in a control cohort of patients with seronegative arthritis receiving DMARD therapy.

Clin Dermatol. 2010 Jan-Feb;28(1):88-92.
Malignancy concerns with psoriasis treatments using phototherapy, methotrexate, cyclosporin, and biologics: facts and controversies.
Naldi L.

Cancer is one of the several comorbidities that have been linked with psoriasis. Not surprisingly, tumors associated with well-documented risk factors for the dermatosis, such as smoking and obesity, have been found with increased incidence in psoriatic patients. They include lung, kidney, and colon cancers. For unknown reasons, the risk of lymphoma is also increased in psoriatic patients. Despite several difficulties with documenting risks, some systemic treatments for psoriasis have been linked with an increased risk of selected cancers. The best-documented association is nonmelanoma skin cancer with psoralen plus ultraviolet A therapy and cyclosporin. More recently, an increased risk of cancer has been a concern with newly introduced biologic agents. The documentation of such a purported increased risk requires long-term follow-up of treated patients.

Semin Arthritis Rheum. 2009 Jan 14.
Sarcoidosis Appearing During Anti-Tumor Necrosis Factor alpha Therapy: A New "Class Effect" Paradoxical Phenomenon. Two Case Reports and Literature Review.
Massara A, Cavazzini L, La Corte R, Trotta F.

OBJECTIVES: To report 2 cases of sarcoidosis that developed during treatment with tumor necrosis factor alpha (TNFalpha) antagonists, infliximab and adalimumab, used for inflammatory rheumatic disease and to review previously reported cases. METHODS: We describe 2 patients, the first with psoriatic arthritis, the second with rheumatoid arthritis, who developed noncaseating granulomas of the lungs consistent with sarcoidosis while being treated with anti-TNFalpha drugs. A retrospective review of the literature was performed using the PubMed database. RESULTS: In our patients sarcoidosis developed after 2 years of continuous treatment with infliximab and adalimumab. Both patients presented with low-grade fever, chest pain, and dyspnea. The diagnosis of sarcoidosis was established by the typical well-formed noncaseating granulomas on transbronchial biopsy, after excluding all other granulomatous conditions. Following withdrawal of anti-TNFalpha agents and a brief course of steroids, the clinical picture resolved. Thirteen additional cases of sarcoidosis that developed after anti-TNFalpha treatment have been reported, and in 9 of these the causative agent was etanercept. CONCLUSIONS: The development of sarcoidosis during treatment with TNFalpha antagonists represents a rare and paradoxical adverse event. The occurrence of sarcoidosis with all 3 available agents suggests a new "class effect" probably linked to a cytokine disequilibrium in patients receiving anti-TNFalpha treatment.

Arthritis Research & Therapy 2010, 12:103 (21 January 2010)
When rheumatology meets hepatology: are anti-TNFs safe in hepatitis B virus carriers?
Jansen TL

Over the past decades, more effective and less toxic biologicals in our battle against autoimmune chronic inflammation of RA and SpA have revolutionized rheumatology. What if one has previously had an infection of the liver? Hepatitis B virus carriers clearly present a challenge for clinicians. If HBV serology suggests a carrier state then anti-TNF appears to be safe during a limited period of 3 years in 21 patients according to Charpin et al. Now studies are needed with longer follow-up particularly in patients with low antibody titres (antiHBc). In a 3 year period however, about 30% of French patients developed significant lowering of antibody titres which may become relevant during longterm follow-up. Charpin et al. are the first to reveal promising data on the relative safety of anti-TNFs in a small series of hepatitis B carriers up to three years.