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- Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort.
- The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab.
- Infliximab dependency is related to decreased surgical rates in adult Crohn's disease patients.
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- Anti-infliximab antibodies are already detectable in most patients with rheumatoid arthritis halfway through an infusion cycle: an open-label pharmacokinetic cohort study.
- Use of biologics in inflammatory bowel disease patients with cirrhosis.
- Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease.
- Vaccination and infection prevention in inflammatory bowel disease.
- A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease.
- Etanercept: An overview of dermatologic adverse events.
Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort.


OBJECTIVES: Data on the frequency of extraintestinal manifestations (EIMs) in Crohn's disease (CD) and ulcerative colitis (UC) and analyses of their risk factors are scarce. We evaluated their prevalence and risk factors in a large nationwide cohort of inflammatory bowel disease (IBD) patients.

METHODS: IBD patients from an adult clinical cohort in Switzerland (Swiss IBD cohort study) were prospectively included. Data from validated physician enrolment questionnaires were analyzed.

RESULTS: A total of 950 patients were included, 580 (61%) with CD (mean age 41 years) and 370 (39%) with UC (mean age 42 years). Of these, 249 (43%) of CD and 113 (31%) of UC patients had one to five EIMs. The following EIMs were found: arthritis (CD 33%, UC 21%), aphthous stomatitis (CD 10%, UC 4%), uveitis (CD 6%, UC 4%), erythema nodosum (CD 6%, UC 3%), ankylosing spondylitis (CD 6%, UC 2%), psoriasis (CD 2%, UC 1%), pyoderma gangrenosum (CD and UC each 2%), and primary sclerosing cholangitis (CD 1%, UC 4%). Multiple logistic regression identified the following risk factors for ongoing EIM in CD: active disease (odds ratio (OR)=1.95, 95% confidence interval (CI)=1.17-3.23, P=0.01), and positive IBD family history (OR=1.77, 95% CI=1.07-2.92, P=0.025). No risk factors were identified in UC patients.

CONCLUSIONS: EIMs are a frequent problem in CD and UC patients. Active disease and positive IBD family history are associated with ongoing EIM in CD patients. Identification of EIM prevalence and associated risk factors may result in increased awareness for this problem and thereby facilitating their diagnosis and therapeutic management.

The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab.


Aliment Pharmacol Ther 2011; 33: 349-357 SUMMARY: Background  Patients treated with infliximab for Crohn's disease (CD) frequently require intensified dosage due to loss of response. There are scant data regarding the efficacy of shortening the dosing interval to 6 weeks. Aims  We sought to investigate the efficacy of a once every 6 weeks' strategy compared with dose-doubling. Methods  This work was a multicentre retrospective study of infliximab-treated CD patients who required dose escalation. The clinical outcome of patients treated by intensification to 5 mg/kg/6 weeks (6-week group) was compared with the outcome of patients whose infliximab was double-dosed (10 mg/kg/8 weeks or 5 mg/kg/4 weeks). Results Ninety-four patients (mean age: 29.8 years) were included in the study, 55 (59%) in the 6-week group and 39 (41%) in the double-dose group. Demographics and disease characteristics were similar between the two groups, although patients with re-emerging symptoms 5-7 weeks postinfusion were more likely to receive 5 mg/kg/6 weeks dosing (OR: 3.4, 95% CI: 1.4-8.8, P < 0.01). Early response to dose-intensification occurred in 69% of patients in the 6-week group and 67% in the double-dose group (P = N.S.). Regained response was maintained for 12 months in 40% compared with 29% of the patients respectively (P = N.S.). Conclusion  In CD patients who lost response to standard infliximab dose, especially when symptoms re-emerge 5-7 weeks postinfusion, shortening the dosing interval to 6 weeks appears to be at least as effective as doubling the dose to 10 mg/kg or halving the infusion intervals to once in 4 weeks.

Infliximab dependency is related to decreased surgical rates in adult Crohn's disease patients.


BACKGROUND: Infliximab dependency in children with Crohn's disease (CD) has recently been described and found to be associated with a decreased surgery rate.
AIM: To assess infliximab dependency of adult CD patients, evaluate the impact on surgery, and search for possible clinical and genetic predictors.

METHODS: Two hundred and forty-five CD patients treated with infliximab were included from Danish and Czech Crohn Colitis Database (1999-2006). Infliximab response was assessed as immediate outcome, 1 month after infliximab start: complete, partial, and no response. Three months outcome, after last intended infusion: prolonged response (maintenance of complete/partial response), infliximab dependency (relapse requiring repeated infusions to regain complete/partial response or need of infliximab >12 months to sustain response).

RESULTS: Forty-seven percent obtained prolonged response, 29% were infliximab dependent and 24% nonresponders. The cumulative probability of surgery 40 months after infliximab start was 20% in prolonged responders, 23% in infliximab-dependent patients and 76% in nonresponders (P<0.001). The cumulative probability of surgery at 40 months in patients on maintenance versus on demand regime was 33 and 31%, respectively (P=0.63). No relevant clinical or genetic predictors were identified.

CONCLUSION: The infliximab dependency response seems to be equivalent to the prolonged response in adult CD patients when comparing surgery rates.

In favour of early surgery in Crohn's disease: A hypothesis to be tested.
Latella G, Caprilli R, Travis S.

No abstract available

Anti-tumor necrosis factor-α antibodies induce regulatory macrophages in an Fc region-dependent manner
Vos AC, Wildenberg ME, Duijvestein M, Verhaar AP, van den Brink GR, Hommes DW.

BACKGROUND & AIMS: Anti-tumor necrosis factor (TNF)α antibodies are effective in treating patients with Crohn's disease whereas soluble TNFα receptors have not shown clinical efficacy; the mechanism that underlies these different effects is not clear. We examined the immunosuppressive effects of different anti-TNFα reagents on activated T cells.

METHODS: We studied the effects of anti-TNFα antibodies infliximab and adalimumab, the soluble TNFα receptor etanercept, the pegylated F(ab') fragment certolizumab, and certolizumab-immunoglobulin (Ig)G on primary activated T cells. T cells were grown in isolation or in a mixed lymphocyte reaction (MLR). Proliferation was measured by (3)H thymidine incorporation and apoptosis was examined using Annexin V labeling and a colorimetric assay for activated caspase-3. Macrophage phenotypes were assayed by flow cytometry and cytokine secretion.

RESULTS: Infliximab and adalimumab reduced T-cell proliferation in an MLR whereas etanercept and certolizumab did not; this effect was lost after Fc receptors were blocked. The infliximab F(ab')2 fragment did not inhibit proliferation whereas certolizumab-IgG did inhibit proliferation. In the MLR, the antibodies against TNF induced formation of a new population of macrophages in an Fc region-dependent manner; these macrophages had an immunosuppressive phenotype because they inhibit proliferation of activated T cells, produce anti-inflammatory cytokines, and express the regulatory macrophage marker CD206.

CONCLUSIONS: Regulatory macrophages have immunosuppressive properties and an important role in wound healing. Antibodies against TNF induce regulatory macrophages in an Fc region-dependent manner. These functions of anti-TNFs might contribute to the resolution of inflammation.

Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease - subgroup results from a placebo-controlled study.
Schreiber S, Lawrance IC, Thomsen OØ, Hanauer SB, Bloomfield R, Sandborn WJ.

BACKGROUND: Treatment options for fistulizing Crohn's disease (CD) are limited.
AIM: To examine whether fistula closure is maintained at week 26 following treatment with certolizumab pegol.

METHODS: Patients with draining fistulas at baseline from PRECiSE 2 (n = 108) received open-label induction with certolizumab pegol 400 mg at weeks 0 (baseline), 2 and 4. Response was defined as ≥100-
point decrease from baseline in the Crohn's Disease Activity Index. Nonresponders (50/108) were excluded. At week 6, responders with draining fistulas (N = 58) were randomised to certolizumab pegol 400 mg (n = 28) or placebo (n = 30) every 4 weeks across weeks 8-24. Fistula closure was evaluated throughout the study, with a final assessment at week 26.

RESULTS: The majority of patients (55/58) had perianal fistula. At week 26, 36% of patients in the certolizumab pegol group had 100% fistula closure compared with 17% of patients receiving placebo (P = 0.038). Protocol-defined fistula closure (≥50% closure at two consecutive post-baseline visits ≥3 weeks apart) was not statistically significant (P = 0.069) with 54% and 43% of patients treated with certolizumab pegol and placebo achieving this end point, respectively.

CONCLUSION: Continuous treatment with certolizumab pegol improves the likelihood of sustained perianal fistula closure compared with placebo.


The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited.

BACKGROUND: Infliximab is effective for induction and maintenance of remission in children with moderately to severely active Crohn's disease (CD).
AIM: To evaluate the long-term efficacy of infliximab treatment in paediatric CD.
METHODS: In this observational, multicentre study, all paediatric CD patients in The Netherlands treated with infliximab from October 1992 to November 2009 and with minimal follow-up of 3 months since start of infliximab, were studied.
RESULTS: One hundred and fifty-two CD patients [81M; median age at start of infliximab 15.0 years (IQR 13.1-16.4)] received a median number of 10.5 infliximab infusions (IQR 6-21). Median follow-up after start of infliximab was 25 months (IQR 13-40). Kaplan-Meier analysis showed that the cumulative probability of losing response to infliximab in patients who initially required repeated infusions was 13%, 40% and 50% after 1, 3 and 5 years, respectively. Seventy-four patients (49%) needed dose adjustments, with a median time to any adjustment of 6 months.
CONCLUSIONS: Duration of effect of infliximab is limited as 50% of patients on infliximab maintenance treatment lose their therapeutic response after 5 years. Dose adjustments after start of infliximab are frequently needed to regain therapeutic benefit. These findings emphasise the need for effective, long-term treatment strategies for paediatric CD.


Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab.

Aliment Pharmacol Ther 2011; 33: 340-348 SUMMARY: Background  The long-term efficacy of adalimumab in patients with ulcerative colitis is not well known. Aim  To evaluate the short- and long-term outcomes of adalimumab in ulcerative colitis patients previously treated with infliximab. Methods Patients with active ulcerative colitis were treated with adalimumab after failure of other therapies including infliximab. Short-term clinical response and remission were assessed at weeks 4 and 12. The proportion of patients who continued on adalimumab and the proportion of patients who remained colectomy free were assessed over the long term. Results  Clinical response at weeks 4 and 12 was achieved in 16 (53%) and 18 (60%) patients, respectively, and clinical remission was obtained in 3 (10%) and 8 (27%) patients, respectively. After a mean 48 weeks' follow-up, 15 patients (50%) continued on adalimumab. Six patients (20%) required colectomy. All patients who achieved clinical response at week 12 were colectomy free at long term. Conclusions  Adalimumab was well tolerated and induced durable clinical response in many patients with otherwise medically refractory ulcerative colitis. Patients achieving clinical response at week 12 avoided colectomy over the long term.
Infliximab rescue therapy in steroid-refractory ulcerative colitis: is more really more?
Molnár T, Farkas K, Szepes Z, Nagy F, Wittmann T.

No abstract available

Review article: the role of non-biological drugs in refractory inflammatory bowel disease.
Ng SC, Chan FK, Sung JJ.

Background Up to one-third of patients with inflammatory bowel disease (IBD) do not respond to, or are intolerant of conventional immunosuppressive drugs. Although biological agents are alternative treatments, they may not be suitable or available to some patients. Aim To review the evidence for use of nonbiological drugs in the treatment of patients with IBD refractory to corticosteroids or thiopurines. Methods A literature search was performed using PubMed for English language publications with predetermined search criteria to identify relevant studies. Results Published evidence from uncontrolled series and controlled clinical trials has been used to produce a practical approach relevant to clinical practice which incorporates the indication, optimal dose, and side effects of various therapies including tacrolimus, methotrexate, thalidomide, thiouanine, mycophenolate mofotil, leucocyte apheresis, nutritional therapy, antibiotics, probiotics, allopurinol, rectal acetarsol and ciclosporin in the treatment of patients with refractory ulcerative colitis and Crohn's disease. Approaches to optimise thiopurine efficacy are also discussed. Conclusions Patients with IBD refractory to corticosteroids or thiopurines may respond to alternative anti-inflammatory chemical molecules, but the evidence base for many of these alternatives is limited and further trials are needed.

Inflamm Bowel Dis. 2011 Feb;17(2):621-32.
Anxiety and depression in patients with inflammatory bowel disease: comparisons with chronic liver disease patients and the general population.
Häuser W, Janke KH, Klump B, Hinz A.

BACKGROUND: Studies on anxiety and depression in inflammatory bowel disease (IBD) yielded inconsistent results. We compared anxiety and depression of patients with Crohn's disease (CD) and ulcerative colitis (UC) controlled for sociodemographic and medical variables with age- and sex-matched controls.
METHODS: In all, 422 IBD patients (50% females, 314 CD, 108 UC) of different settings were compared with 140 age- and sex-matched patients with chronic liver diseases (CLD) of a tertiary care center and with 422 age- and sex-matched persons of a representative sample of the general German population (GP). Anxiety and depression and probable mental disorder were assessed by the German version of the Hospital Anxiety and Depression Scale. Comparisons between CD and UC were adjusted for medical (disease activity, number of IBD-associated diseases) and sociodemographic factors (age, gender, marital status).
RESULTS: CD and UC patients did not differ in the levels of anxiety and depression or in the frequency of a probable mental disorder. The levels of anxiety and depression of IBD patients with active disease were higher than that of the GP, but not of the IBD patients in remission. The depression score of the CLD sample was higher than that of the IBD sample (P<0.001), but not the anxiety score. Mental disorders were more frequent in IBD patients with slight (27.7%) and moderate/severe disease activity (49.3%) compared to GP (10.4%) (P<0.001), but not in IBD patients in remission (11.3%).
CONCLUSIONS: Patients with active IBD should be screened for anxiety and depression.

Adalimumab for the treatment of fistulas in patients with Crohn's disease.
Fine SN.

No abstract available

Literature Update Immunology – Period 1-31 January 2011
Long-term monitoring of infliximab therapy for perianal fistulizing Crohn's disease by using magnetic resonance imaging.

BACKGROUND & AIMS: Magnetic resonance imaging (MRI) is used to assess the outcome of infliximab (IFX) therapy in patients with perianal fistulizing Crohn's disease (pfCD). However, few long-term data are available about its efficacy.

METHODS: We assessed 59 patients with pfCD by MRI and clinical evaluation at baseline. Treated patients then received paired clinical and MRI examinations for a median time period of 36 (11-53.3) weeks. Short-, mid-, and long-term effects of therapy, as well as the ability of MRI to predict treatment outcome and need for surgery, were evaluated.

RESULTS: Compared with the baseline MRI, the short-term follow-up MRI (n = 29) revealed a reduced number of fistula tracks in 13.8% and in the inflammatory activity in 55.2% of patients, respectively; mid-term MRI (n = 25) in 56% and in 52%, respectively; and long-term MRI (n = 13) in 15.4% and in 31%, respectively. Improvement of pfCD based on MRI results coincided with clinical improvement in 54.7% of the patients. Short-term and mid-term (but not long-term) MRI showed a significant decrease in the activity score. Therapy outcome was worse among patients with persisting fistulas (P = .01), collections (P = .009), and rectal wall involvement (P = .01) in the final MRI. Patients with single-branched fistulas (P < .0001) and collections (P = .006) in their baseline MRI were more likely to undergo surgery.

CONCLUSIONS: MRI is a useful technique for evaluation of pfCD during the first year of follow-up. In the long-term, the MRI improvement coincides with clinical and endoscopic response to IFX in 50% of the patients.


Abstract Objective: Assess long-term effects of maintenance infliximab therapy in children with moderately-to-severely active Crohn's disease. Research design and methods: One hundred twelve patients with a Pediatric Crohn's Disease Activity Index (PCDAI) score >30 received infliximab 5 mg/kg at weeks 0, 2, and 6 in the REACH study. Patients considered responders at week 10 were randomized to infliximab 5 mg/kg every 8 (q8w) or 12 (q12w) weeks. Patients who completed treatment through week 46, and who the investigator believed would benefit from continued treatment, could enter the open-label extension (OLE) and receive up to three additional years of infliximab. No hypothesis testing was performed. Clinical trial registration: www.clinicaltrials.gov , identifier: NCT0020767. Results: Sixty children entered the OLE: 33, 12, and 15 patients were receiving infliximab 5 mg/kg q8w, 5 mg/kg q12w, and 10 mg/kg q8w, respectively, at extension entry. Patients receiving infliximab for up to 3 years during the OLE maintained clinical benefit, with approximately 80% of patients consistently having no to mild disease activity per the physician's global assessment and very good to fair health in the past 2 weeks per the patient and parent/guardian global assessments. Patients with ≥1-year delay in bone age at baseline trended toward improvement in height during the OLE. Respiratory system disorders, most commonly upper respiratory infections, were the most prevalent adverse events reported; six (10%) patients had serious infections. Conclusions: Among children with moderately-to-severely active Crohn's disease who received infliximab for 46 weeks in REACH and then for up to 3 additional years in the REACH OLE, infliximab was effective in maintaining clinical benefit and was generally well-tolerated.

The role of endoscopic imaging of the small bowel in clinical practice.
Leighton JA.

Enteroscopy, defined as direct visualization of the small bowel (SB) with the use of a fiberoptic or wireless endoscope, has progressed considerably over the past several years. Technological advancements in the field have facilitated endoscopic evaluation of the SB. This comprehensive clinical review summarizes the latest modalities available to aid gastroenterologists in exploring the SB for evaluation of obscure gastrointestinal bleeding, tumors, inflammatory bowel disease, and celiac disease. Previous physical
limitations in equipment that made a complete evaluation of the SB difficult have all but disappeared with the advent of capsule endoscopy, balloon-assisted enteroscopy, and spiral enteroscopy.

Gut. 2011 Jan 5. [Epub ahead of print]

**Adalimumab for Infliximab dependency induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial.**

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


**Treatment of acute ulcerative colitis with infliximab, a retrospective study from three Danish hospitals.**
Mortensen C, Caspersen S, Christensen NL, Svenningsen L, Thorsgaard N, Christensen LA, Bendtsen F.

BACKGROUND: In acute steroid-refractory ulcerative colitis, rescue therapy with infliximab has become a therapeutic option in patients facing colectomy. Data on efficacy and safety in this setting are sparse. METHODS: Patients with ulcerative colitis and acute and severe steroid-refractory disease, who were given infliximab as rescue therapy, were identified by a review of patients' records and databases of infliximab-treated patients. Data on patient background, concomitant medication, endoscopic and laboratory results, clinical activity and adverse events were collected. RESULTS: Fifty-six patients, all admitted because of high disease activity of short duration, and failing high-dose glucocorticoid treatment, received infliximab treatment and were followed up for a median of 538 days (range 2-1769). Colectomy was avoided in 61% of cases. No fatalities were observed. Concomitant medication at the end of follow-up indicated a low number of relapses in patients without colectomies. CONCLUSIONS: Our results show a lasting benefit of infliximab rescue therapy in 61% of patients with acute, steroid-refractory ulcerative colitis, a low incidence of late colectomies, and low frequency of steroid use in patients who avoided colectomy. High levels of C-reactive protein on admittance and at the first infliximab infusion were associated with colectomy. Our study adds to the growing experience of infliximab treatment of patients with acute, steroid-refractory ulcerative colitis.


**Mucosal gene expression signatures that predict response of ulcerative colitis to infliximab.**
Watson AJ, Tremelling M.

No abstract available
Safety


No abstract available


No abstract available


The antitumor necrosis factor (TNF-alpha) drugs are increasingly used in treating skin diseases such as psoriasis. TNF-alpha is a proinflammatory cytokine with a key role in the pathogenesis of psoriasis but also in host defence against bacterial pathogens, especially against those that multiply inside host cells. The effectiveness of anti-TNF-alpha in the treatment of psoriasis is now widely recognized and has led to their increasingly wide use. Although these drugs are considered relatively safe, their use is associated with an increased incidence of serious infections even in patients treated. Have been described above numerous cases of tuberculosis but has also observed an increased incidence of granulomatous infections by intracellular bacteria such as Legionella pneumophila required. Infections due to this biotic agent, if not diagnosed early, are potentially fatal. We report the case of a patient, heavy smoker, suffering from severe skin psoriasis who after starting treatment with infliximab developed a pneumonia caused by Legionella pneumophila. Our aim is to draw the attention of specialists on increasing risk of granulomatous infections by intracellular agents in patients being treated with anti TNF-alpha.


Background and aims Few studies have been conducted addressing the safety of thiopurine treatment in pregnant women with inflammatory bowel disease (IBD). The aim of this study was to evaluate the pregnancy outcome of women with IBD who have been exposed to thiopurines. Methods 215 pregnancies in 204 women were registered and documented in the CESAME cohort between May 2004 and October 2007. Physicians documented the following information from the women: last menstrual date, delivery term, details of pregnancy outcome, prematurity, birth weight and height, congenital abnormalities, medication history during each trimester, smoking history and alcohol ingestion. Data were compared between three groups: women exposed to thiopurines (group A), women receiving a drug other than thiopurines (group B) and women not receiving any medication (group C). Results Mean age at pregnancy was 28.3 years. 75.7% of the women had Crohn's disease and 21.8% had ulcerative colitis, with a mean disease duration of 6.8 years at inclusion. Of the 215 pregnancies, there were 138 births (142 newborns), and the mean birth weight was 3135g. There were 86 pregnancies in group A, 84 in group B and 45 in group C. Interrupted pregnancies occurred in 36% of patients enrolled in group A, 33% of patients enrolled in group B, and 40% of patients enrolled in group C; congenital abnormalities arose in 3.6% of group A cases and 7.1% of group B cases. No significant differences were found between the three groups in overall pregnancy outcome. Conclusions The results
obtained from this cohort indicate that thiopurine use during pregnancy is not associated with increased risks, including congenital abnormalities.

The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept.
Jamnitski A, Bartelds GM, Nurmohamed MT, van Schouwenburg PA, van Schaardenburg D, Stapel SO, Dijkmans BA, Aarden L, Wolbink GJ.

OBJECTIVE: /st> The aim of this study was to test the hypothesis that the reason for non-response (caused by immunogenicity or not) to a first tumour necrosis factor (TNF) inhibitor defines whether a second TNF inhibitor will be effective.

METHODS: /st> This cohort study consisted of 292 consecutive patients with rheumatoid arthritis (RA), all treated with etanercept. A total of 89 patients (30%) were treated previously with infliximab or adalimumab (‘switchers’), and the remaining 203 (70%) were anti-TNF naïve. All switchers were divided into two groups: with and without antibodies against the previous biological. Differences in clinical response to etanercept between switchers with and without antibodies and patients who were anti-TNF naïve were assessed after 28 weeks of treatment using changes in Disease Activity Score in 28 joints (DAS28).

RESULTS: /st> After 28 weeks of treatment, response to etanercept did not differ between patients who were anti-TNF naïve and switchers with anti-drug antibodies (ΔDAS28=2.1±1.3 vs ΔDAS28=2.0±1.3; p=0.743). In contrast, switchers without anti-drug antibodies had a diminished response to etanercept treatment compared to patients who were TNF naïve (ΔDAS28=1.2±1.3 vs ΔDAS28=2.1±1.3; p=0.001) and switchers with antibodies (ΔDAS28=1.2±1.3 vs ΔDAS28=2.0±1.3; p=0.017).

CONCLUSION: /st> Patients with RA with an immunogenic response against a first TNF-blocking agent had a better clinical response to a subsequent TNF blocker compared to patients with RA without anti-drug antibodies. Hence, determining immunogenicity can be helpful in deciding in which patient switching could be beneficial and can be part of a personalised treatment regimen.

Severe neutropenia following infliximab treatment in a child with ulcerative colitis.

No abstract available

Anti-infliximab antibodies are already detectable in most patients with rheumatoid arthritis halfway through an infusion cycle: an open-label pharmacokinetic cohort study.

OBJECTIVE: This study in patients with rheumatoid arthritis (RA) treated with infliximab describes prospectively the course of (anti)infliximab levels within an infusion cycle to assess at what moment patients develop low/no infliximab trough levels and/or detectable anti-infliximab levels.

METHODS: Infliximab treated RA patients were included in this descriptive open-label cohort study. During one infusion cycle (anti-)infliximab levels and disease activity scores were assessed just before and one hour after infusion, and subsequently at 50%, 75% and at the end of the infusion cycle (pre-infusion).

RESULTS: 27 patients were included. The median infliximab levels decreased from 77.0 mg/l (p25-p75: 65-89) one hour after the infusion to pre-infusion levels of 0.0 mg/l (p25-p75: 0.0-3.1). In 7 (26%) patients pre-infusion anti-infliximab antibodies were detected; these antibodies were already present halfway through the infusion cycle in 5 of the 7 individuals. Patients with detectable pre-infusion anti-infliximab antibodies have significantly more often low/no infliximab levels (< 1 mg/l) halfway trough the infusion cycle (in 5/7 patients) compared to patients without detectable pre-infusion anti-infliximab antibodies (0/20 patients, p<0.001).

CONCLUSION: Most anti-infliximab forming patients have detectable anti-infliximab antibodies halfway through an infusion cycle, which implies that these patients are exposed to nontherapeutical infliximab levels during more than half of their infusion cycle. As none of the patients without anti-
infliximab antibodies had no/low-infliximab levels halfway through the infusion cycle, the presence of pre-infusion anti-infliximab antibodies seems a sensitive and specific predictor for no/low infliximab-levels.

Use of biologics in inflammatory bowel disease patients with cirrhosis.
Dhere T.
No abstract available

Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease.

BACKGROUND & AIMS: Few data are available on effects of biologic therapies in patients more than 65 years old with inflammatory bowel disease (IBD). We evaluated the risk and benefits of therapy with tumor necrosis factor (TNF) inhibitors in these patients.
METHODS: We collected data from patients with IBD treated with infliximab (n = 2475) and adalimumab (n = 604) from 2000 to 2009 at 16 tertiary centers. Ninety-five patients (3%) were more than 65 years old (52 men; 37 with ulcerative colitis and 58 with Crohn's disease; 78 treated with infliximab and 17 with adalimumab). The control group comprised 190 patients 65 years old or younger who were treated with both biologics and 190 patients older than 65 years who were treated with other drugs. The primary end points were severe infection, cancer, or death.
RESULTS: Among patients more than 65 years old who received infliximab and adalimumab, 11% developed severe infections, 3% developed neoplasms, and 10% died. No variable was associated with severe infection or death. Among control patients more than 65 years old, 0.5% developed severe infections, 2% developed cancer, and 2% died. Among control patients less than 65 years old, 2.6% developed severe infections, none developed tumors, and 1% died.
CONCLUSIONS: Patients older than 65 years treated with TNF inhibitors for IBD have a high rate of severe infections and mortality compared with younger patients or patients of the same age that did not receive these therapeutics. The effects of anti-TNF agents in older patients with IBD should be more thoroughly investigated, because these patients have higher mortality related to hospitalization than younger patients.

Vaccination and infection prevention in inflammatory bowel disease.
Vermeire S, Van Assche G, Rutgeerts P.

The current medical therapy used in Crohn's disease and ulcerative colitis comprises drugs that interfere with immune response and therefore caution is needed for infectious side effects, and where possible, strategies to prevent their occurrence should be undertaken. Last year, international consensus guidelines on this topic were published by the European Crohn's and Colitis Organisation.

A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease.
Katlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, Sampat S, Mendizabal M, Lin MV, Lichtenstein GR.

BACKGROUND & AIMS: Hepatosplenic T-cell lymphoma (HSTCL) is a rare and usually fatal lymphoma that primarily affects men younger than 35 years old. Treatment of patients with inflammatory bowel disease (IBD) using antibodies to tumor necrosis factor (anti-TNFs) and thiopurines has been associated with HSTCL. We investigated the medications, duration of therapy, and ages of patients associated with HSTCL.
METHODS: We collected and analyzed data on the association between HSTCL, and anti-TNF and thiopurine therapies in patients with IBD from published reports and the MedWatch reporting system of the US Food and Drug Administration.
RESULTS: Of 36 patients with HSTCL, 20 received therapy with infliximab and a thiopurine and 16 received a thiopurine as monotherapy for IBD. Four patients who had been treated with infliximab and a thiopurine also received adalimumab. One of these patients had been given infliximab, adalimumab, and natalizumab. Of 31 patients of known gender, only 2 were female. Twenty-seven of the 30 patients of known age were younger than 35 years old.
CONCLUSIONS: Most patients with HSTCL who received long-term therapy (at least 2 y) with thiopurines for IBD were men younger than 35 years old. There were no reported cases of HSTCL in patients with IBD who received only anti-TNF therapy. Physicians should consider giving thiopurines and anti-TNF agents to young male patients with IBD only in cases in which a clear benefit is expected, such as in early stage disease in untreated patients or possibly in very severe cases.

EtanerceptAn Overview of Dermatologic Adverse Events
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Objectives  To provide a comprehensive overview of dermatologic adverse events of etanercept described in the literature (including all study types, case reports, and surveys) and to present information on the occurrence, severity, treatment, and course of these adverse events.
Data Sources  MEDLINE and EMBASE.
Study Selection  All reports on individual patients who developed a dermatologic adverse event associated with systemic etanercept treatment for any indication in any type of original article were included.
Data Extraction  All data were independently extracted by 2 reviewers. Disagreements were resolved by consensus. All articles included (except for case reports/case series) were assessed regarding level of evidence.
Data Synthesis  In 126 included study reports, a total of 72 separate specific dermatologic adverse events of etanercept were mentioned. In 101 case reports/case series, 153 individual patients with approximately 65 different specific diagnoses (eg, not rash) were reported.
Conclusions  Etanercept is associated with a wide variety of dermatologic adverse events, many of which were described in study reports, but case reports also described numerous exceptional cases. Although the adverse events are usually mild, some reactions are serious and even potentially life threatening. Therefore, all drug-associated cutaneous abnormalities should be carefully evaluated. Diagnostic steps do not deviate from the norm in these patients, but management of the dermatologic adverse events may need special attention.