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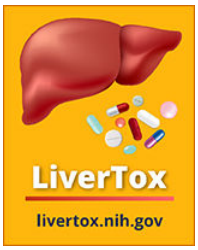

Etanercept

Updated: February 10, 2017.

OVERVIEW

Introduction

Etanercept is an antagonist of tumor necrosis factor alpha (TNFα) which has potent antiinflammatory activity and is used widely in severe forms of rheumatoid arthritis and psoriasis. Etanercept has been linked to rare instances of acute, clinically apparent liver injury.

Background

Etanercept (ee tan' er sept) is a soluble form of the human TNFα receptor which is fused wih the Fc portion of immunoglobulin G. This recombinant fusion protein binds serum TNFα, leading to inhibition of pathways of inflammation and pain mediated by this potent, pro-inflammatory cytokine. Etanercept was approved for use in the United States in 1998 and current indications include moderate to severe rheumatoid arthritis, juvenile idiopathic (rheumatoid) arthritis, ankylosing spondylitis, psoriatic arthritis and severe psoriasis. Unlike infliximab, adalimumab and certolizumab, etanercept has not been shown to be effective in inflammatory bowel disease. Etanercept is considered a disease modifying antirheumatic drug (DMARD) and has been shown to improve symptoms as well as joint and cartilage damage in the inflammatory arthritides. Etanercept is available in 25 mg and in 50 mg/mL prefilled syringes or single use vials under the brand name of Enbrel. The typical dose in adults with rheumatoid arthritis is 50 mg given subcutaneously once or twice weekly. Common side effects include injection site reactions, gastrointestinal upset, rhinitis, rash and fever. TNFα antagonists are also capable of causing immune suppression, resulting in reactivation of microbial infections including tuberculosis and hepatitis B.

Hepatotoxicity

Etanercept has been associated with low rates of serum ALT elevations during therapy that are generally asymptomatic, transient, and do not require dose modifications. There have been isolated reports of clinically apparent liver injury during etanercept therapy, but the frequency has been far less than with infliximab, and several patients with infliximab induced liver injury have been reported to tolerate etanercept without recurrence. Etanercept therapy can be associated with induction of autoantibodies, including antinuclear antibody (ANA) and cases of autoimmune hepatitis, induced or exacerbated by etanercept therapy have been reported. The latency to onset has ranged greatly, from as short as 2 weeks to as long as several years. The pattern of serum enzyme elevations has also varied, both cholestatic and hepatocellular injury being reported. Immunoallergic manifestations such as fever, rash and eosinophilia are rare. Autoimmune phenomena are reported and the injury is reportedly responsive to corticosteroid therapy. How frequently the disease recurs after corticosteroids are discontinued has not been carefully assessed.

Etanercept has been linked to rare cases of reactivation of hepatitis B, although less frequently than infliximab. Reactivation typically occurs in patients who are inactive HBsAg carriers, with normal serum aminotransferase levels and no or only low levels of HBV DNA in serum. The immune suppression caused by the immunomodulatory agent leads to an increase in HBV replication and rise in serum HBV DNA levels. With stopping immune suppression (or between cycles of therapy), restoration of immune function leads to an acute immunological response to the heightened viral replication and a flare of hepatitis, that can be severe and can result in hepatic failure and death. Reactivation in patients with anti-HBc without HBsAg (serologic pattern of previous HBV infection) has not been reported in patients treated with etanercept, but has been reported after therapy with other TNFα antagonists and more commonly with rituximab and after bone marrow transplantation. The anti-TNF inhibitors have little or no effect on hepatitis C virus levels and have been used safely in patients with chronic hepatitis C.

Likelihood score: B (highly likely cause of clinically apparent liver injury).

Mechanism of Injury

The liver injury caused by etanercept is likely due to induction of autoimmunity. While a high proportion of patients develop autoantibodies either de novo or in rising titer, only rarely do persons develop clinically apparent autoimmune conditions, such as lupus-like syndrome or autoimmune hepatitis.

Outcome and Management

The hepatotoxicity of etanercept has largely been mild and self-limiting, although sometimes requiring corticosteroid therapy. No instances of chronic hepatitis or vanishing bile duct syndrome have been reported. Patients who are to start etanercept therapy should be screened for evidence of hepatitis B, and those with preexisting HBsAg should be offered prophylaxis with an oral antiviral agent such as lamivudine, tenofovir or entecavir. Patients who develop an autoimmune hepatitis-like syndrome during etanercept therapy may not recover promptly with stopping the TNFα antagonist and may require corticosteroid therapy. In this event, the dose of the corticosteroid should be kept to a minimum to control the disease and, ultimately, attempts made to withdraw the immune suppression (or decrease to levels used before administration of etanercept). It is unclear whether patients with hepatotoxicity due to etanercept can be safely treated with a monoclonal antibody based TNFα antagonist (such as infliximab, adalimumab or certolizumab); if such therapy is planned, it should be done with caution and biochemical monitoring for liver injury.

References on the hepatotoxicity and safety of the anti-TNF necrosis factor agents are given together at the end of the Overview section on the Tumor Necrosis Factor Antagonists.

Drug Class: Antirheumatic Agents; Dermatologic Agents

Other Drugs in the Subclass, Tumor Necrosis Factor Antagonists: Adalimumab, Certolizumab, Golimumab, Infliximab

CASE REPORT

Case 1. Autoimmune hepatitis arising during etanercept therapy.

[Modified from: Fathalla BM, Goldsmith DP, Pascasio JM, Baldridge A. Development of autoimmune hepatitis in a child with systemic-onset juvenile idiopathic arthritis during therapy with etanercept. J Clin Rheumatol 2008; 14: 297-8. PubMed Citation]

A 9 year old girl with juvenile idiopathic (rheumatoid) arthritis was treated with etanercept and hydroxychloroquine after she had failed to respond to a regimen of methotrexate, low dose prednisone and

nonsteroidal antiinflammatory agents. Her dose of etanercept was increased to 50 mg weekly, which was followed by clinical improvement and allowed for lowering of the prednisone dose. Ten months after starting etanercept, she developed fatigue, abdominal discomfort and jaundice. Examination showed jaundice without fever, rash or signs of chronic liver disease. Laboratory results showed elevations in serum bilirubin (12 mg/dL) and aminotransferase levels (ALT 354 U/L, AST 486 U/L) with normal alkaline phosphatase. Tests for hepatitis A, B and C and Epstein-Barr virus were negative. Serum ANA was positive at 1:640 and SMA at 1:80, while antibodies to dsDNA and liver-kidney microsomal antigen were negative. Serum IgG levels were markedly increased (3637 mg/dL: normal <1600 mg/dL). Abdominal ultrasound was normal except for mild splenomegaly. A liver biopsy was consistent with autoimmune hepatitis with interface hepatitis and lobular necrosis with inflammation. Etanercept and hydroxychloroquine were discontinued, the dose of prednisone was increased to 2 mg/kg/day, and azathioprine was added. Her jaundice resolved and serum aminotransferase levels fell into the normal range and autoantibodies became negative within 8 months of stopping etanercept.

Key Points

Medication:	Etanercept (50 mg once weekly)
Pattern:	Hepatocellular
Severity:	3+ (jaundice, hospitalization)
Latency:	10 months
Recovery:	Within 8 months (on prednisone)
Other medications:	Hydroxychloroquine, prednisone (5 mg daily), naproxen

Comment

A child with juvenile idiopathic arthritis (formerly known as juvenile rheumatoid arthritis) developed clinically apparent autoimmune hepatitis after 10 months of etanercept therapy. While it seems clear that the clinical syndrome was due to autoimmune hepatitis, it is not certain whether the hepatitis was caused by etanercept directly or was a preexisting diathesis that was triggered or merely worsened by the immunomodulatory therapy and reduction in dose of prednisone. The child improved upon stopping etanercept, but the improvement may have been due to the concurrent increase in prednisone dose and addition of azathioprine. Information on long term follow up and whether azathioprine or prednisone could be discontinued (or lowered to previous low levels) might help to resolve these issues. However, the majority of cases of autoimmune hepatitis associated with anti-TNF therapies (and other biologic agents such as the interferons) have appeared to be a triggering of autoimmune hepatitis in a susceptible patient, rather than the de novo induction of an autoimmune hepatitis-like liver injury that then resolves entirely with stopping therapy (as is typical of nitrofurantoin, minocycline or methyldopa). These different interpretations have important implications for the long term management of such patients; i.e. whether long term immune suppression will be required.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Etanercept – Enbrel®

DRUG CLASS

Antirheumatic Agents; Dermatologic Agents

COMPLETE LABELING

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Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Etanercept	185243-69-0	Monoclonal antibody	Not available

ANNOTATED BIBLIOGRAPHY

References updated: 10 February 2017

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999; no mention of the tumor necrosis factor antagonists including etanercept).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents; "the biological immuno-suppressants are largely free from hepatototxicity, with the exception of the TNF alpha antagonists").

Wallace JL, Sharkey KA. Pharmacotherpay of inflammatory bowel disesae. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1350-62.

(Textbook of pharmacology and therapeutics).

Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. Ann Rheum Dis 2003; 62: 1078-82. PubMed PMID: 14583571.

(Monitoring of 24 patients with both rheumatoid arthritis and hepatitis C found no overall changes in ALT, AST, Alk P or HCV RNA levels during therapy with etanercept or infliximab over a period of 2-34 months).

Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. Drug Saf 2004; 27: 307-24. PubMed PMID: 15061685.

(Review of safety of anti-TNF agents based on literature and FDA reports found no evidence of worsening of hepatitis C during therapy, but chance of reactivation of hepatitis B, at least by infliximab; no discussion of hepatotoxicity).

Parke FA, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. Arthritis Rheum 2004; 51: 800-4. PubMed PMID: 15478165.

(Among 5 patients with rheumatoid arthritis and HCV infection who were treated with etanercept or infliximab for 8 to 49 months, none had worsening of serum ALT levels and HCV RNA levels were stable or decreased).

Magliocco MA, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. J Am Acad Dermatol 2004; 51: 580-4. PubMed PMID: 15389194.

(Three men, ages 51-54 years, with psoriasis and chronic hepatitis C received etanercept for 3-7 months with no change in serum ALT or AST levels and slight decrease in HCV RNA levels in two).

Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. Ann Rheum Dis 2004; 63 Suppl 2: ii18-ii24. PubMed PMID: 15479865.

(Review of the safety and complications of anti-TNF therapy in patients with concurrent hepatitis B or C or HIV infection).

Zein NN; Etanercept Study Group. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. J Hepatol 2005; 42: 315-22. PubMed PMID: 15791697.

(Controlled trial of adding etanercept to interferon and ribavirin therapy of chronic hepatitis C found similar rates of sustained response [32% vs 42%] and no evidence of worsening of hepatitis during etanercept therapy).

Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. Best Pract Res Clin Rheumatol 2006; 20: 757-90. PubMed PMID: 16979537.

(Extensive review of side effects of use of anti-TNF blockers; in 7 reports on 29 patients with hepatitis C, no flares of disease occurred on infliximab or etanercept; 11 report cases of use in hepatitis B with at least 3 instances of reactivation, one fatal, largely with infliximab and methotrexate).

Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology(Oxford) 2006; 45: 1294-7. PubMed PMID: 16603583.

(Retrospective analysis of 6 patients with chronic hepatitis and inflammatory arthritis treated with anti-TNF agents for 3-39 months, none had rise in ALT or viral levels during therapy, but 3 with hepatitis B were also on lamivudine).

Sánchez Carazo JL, Mahiques Santos L, Oliver Martinez V. Safety of etanercept in psoriasis: a critical review. Drug Saf 2006; 29: 675-85. PubMed PMID: 16872241.

(Review of safety of etanercept focusing upon psoriasis; no discussion of hepatotoxicity).

Wahie S, Alexandroff A, Reynolds NJ. Hepatitis: a rare, but important, complication of infliximab therapy for psoriasis. Clin Exp Dermatol 2006; 31: 460-1. PubMed PMID: 16681606.

(64 year old man with psoriasis developed enzyme elevations [ALT 569 U/L, GGT 77 U/L, bilirubin normal] 1 week after a second infusion of infliximab, which resolved with 4 weeks and did not recur with etanercept therapy).

Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-. therapy: guidelines for clinical approach. J Gastro Hepatol 2006; 31: 1366-71. PubMed PMID: 16911678.

(Review and proposed guidelines for use of anti-TNF therapy in patients with underlying chronic viral hepatitis; recommended screening for HBV and HCV, careful monitoring during therapy and prophylaxis or early intervention with lamivudine in HBsAg-positive patients).

Rokhsar C, Rabhan N, Cohen SR. Etanercept monotherapy for a patient with psoriasis, psoriatic arthritis, and concomitant hepatitis C infection. J Am Acad Dermatol 2006; 54: 361-2. PubMed PMID: 16443079.

(53 year old man with severe psoriasis and hepatic fibrosis caused by methotrexate and hepatitis C responded well to etanercept while HCV RNA levels were unchanged).

Cecchi R, Bartoli L. Psoriasis and hepatitis C treated with anti-TNF alpha therapy (etanercept). Dermatol Online J 2006; 12: 4. PubMed PMID: 17459290.

(45 year old man with psoriasis and hepatitis C was treated with etanercept for 12 months and had no change in serum enzyme or HCV RNA levels).

De Simone C, Paradisi A, Capizzi R, Carbone A, Siciliano M, Amerio PL. Etanercept therapy in two patients with psoriasis and concomitant hepatitis C. J Am Acad Dermatol 2006; 54: 1102-4. PubMed PMID: 16713482.

(Letter in response to Magliocco [2004] reporting two patients with psoriasis and hepatitis C who tolerated 12 months of etanercept therapy with no change in serum tests and slight decrease in HCV RNA levels).

Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. Ann Rheum Dis 2006; 65: 983-9. PubMed PMID: 16627542.

(Review of the problem of reactivation of hepatitis B in patients with rheumatic diseases treated with immunosuppressive agents with recommendations on prevention).

Koike R, Takeuchi T, Eguchi K, Miyasaka N; Japan College of Rheumatology. Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. Mod Rheumatol 2007; 17: 451-8. PubMed PMID: 18084695.

(Review of guidelines for the use of infliximab and etanercept in rheumatoid arthritis; no mention of hepatotoxicity or need to screen for hepatitis B).

Vassilopoulos D, Calabrese LH. Risks of immunosuppressive therapies including biologic agents in patients with rheumatic diseases and co-existing chronic viral infections. Curr Opin Rheumatol 2007; 19: 619-25. PubMed PMID: 17917544.

(Review of use of anti-TNF agents in patients with chronic hepatitis B, C and HIV infection).

Sakellariou GT, Chatzigiannis I. Long-term anti-TNFalpha therapy for ankylosing spondylitis in two patients with chronic HBV infection. Clin Rheumatol 2007; 26: 950-2. PubMed PMID: 16865308.

(Two patients with ankylosing spondylitis and inactive HBsAg carrier state who were treated with infliximab; 43 year old man developed reactivation after 14 weeks [ALT 49 U/L, HBV DNA positive] and was successfully treated with lamivudine; 41 year old man had ALT elevations [85 U/L], but no reactivation even when later switched to etanercept).

GarciíAparicio AM, Rey JR, Sanz AH, Alvarez JS. Successful treatment with etanercept in a patient with hepatotoxicity closely related to infliximab. Clin Rheumatol 2007; 26: 811-3. PubMed PMID: 16550301.

(48 year old man with ankylosing spondylitis developed mild ALT elevations [60 U/L] after second and higher levels [ALT 382 rising to 656 U/L, Alk P 166 U/L, bilirubin 0.6 mg/dL, ANA negative] after third and fourth infusion of infliximab, with no recurrence on switching to etanercept: Case 2).

Linardaki G, Katsarou O, Ioannidou P, Karafoulidou A, Boki K. Effective etanercept treatment for psoriatic arthritis complicating concomitant human immunodeficiency virus and hepatitis C virus infection. J Rheumatol 2007; 34: 1353-5. PubMed PMID: 17552060.

(45 year old man with HIV-HCV coinfection and psoriasis was successfully treated with etanercept without worsening of hepatitis while on antiretroviral therapy; ALT levels remained normal, but serial HCV RNA levels were not provided).

Marotte H, Fontanges E, Bailly F, Zoulim F, Trepo C, Miossec P. Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus. Rheumatology (Oxford) 2007; 46: 97-9. PubMed PMID: 16720634.

(Among 9 patients with chronic hepatitis C and rheumatologic symptoms treated with etanercept for 3 months, serum ALT levels were stable and HCV RNA [present in 5] did not change).

Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol 2008; 35: 421-4. PubMed PMID: 18203328.

(Five patients with inflammatory arthritis, 3 with HCV, 1 with HBV and 1 with both, were treated with etanercept for 12-23 months; none had change in serum ALT or AST levels; viral levels fluctuated but without a specific pattern).

Thiéfen G, Morelet A, Heurgué, Diebold MD, Eschard JP. Infliximab-induced hepatitis: absence of cross-toxicity with etanercept. Joint Bone Spine 2008; 75: 737-9. PubMed PMID: 18693125.

(48 year old man with ankylosing spondylitis developed rising ALT levels [188 to 393 to 412 U/L] and ANA [1:200 to 1:1600] after 6 infusions of infliximab, which fell to normal 3 months after stopping, and patient was then treated with etanercept for 30 months without changes in ALT levels).

Dominique L. Liver toxicity of TNFalpha antagonists. Joint Bone Spine 2008; 75: 636-8. PubMed PMID: 18952478.

(Editorial in response to Thiefin [2008]).

Farah M, Al Rashidi A, Owen DA, Yoshida EM, Reid GD. Granulomatous hepatitis associated with etanercept therapy. J Rheumatol 2008; 35: 349-51. PubMed PMID: 18260163.

(17 year old woman developed abnormal liver tests without symptoms 4 months after restarting etanercept [bilirubin normal, ALT 162 U/L, Alk P 267 U/L], a biopsy showing granulomas and bile duct injury, improved but did not resolve on stopping etanercept and using ursodiol).

Fathalla BM, Goldsmith DP, Pascasio JM, Baldridge A. Development of autoimmune hepatitis in a child with systemic-onset juvenile idiopathic arthritis during therapy with etanercept. J Clin Rheumatol 2008; 14: 297-8. PubMed PMID: 18824922.

(9 year old girl with juvenile idiopathic [rheumatoid] arthritis developed abdominal pain and jaundice 10 months after starting etanercept [bilirubin 12.0 mg/dL, ALT 354 U/L, GGT 388 U/L, ANA 1:640, IgG 3637 mg/dL], stopping etanercept and starting prednisone and azathioprine led to resolution, normal liver tests and negative ANA: Case 1).

Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, Triolo G, et al.; GISEA Group. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol 2008; 35: 1944-9. PubMed PMID: 18688917.

(Prospective study in 31 patients with rheumatoid arthritis and hepatitis C treated with anti-TNF agents for 7-44 months [adalimumab 3, etanercept 17; infliximab 11]; mean levels of HCV RNA and ALT did not change; fluctuations occurred in a few patients, but no correlation found between changes in viral RNA and ALT levels).

Harada K, Akai Y, Koyama S, Ikenaka Y, Saito Y. A case of autoimmune hepatitis exacerbated by the administration of etanercept in the patient with rheumatoid arthritis. Clin Rheumatol 2008; 27: 1063-6. PubMed PMID: 18563514.

(50 year old woman with rheumatoid arthritis developed abdominal pain 2 weeks after a first injection of etanercept [bilirubin 1.2 mg/dL, ALT 300 U/L, Alk P 488 U/L, ANA 1:1280]; biopsy suggested autoimmune hepatitis and patient responded to prednisone therapy; may have had mild autoimmune hepatitis before starting therapy and also received diclofenac).

Becker H, Willeke P, Domschke W, Gaubitz M. Etanercept tolerance in a patient with previous infliximab-induced hepatitis. Clin Rheumatol 2008; 27: 1597-8. PubMed PMID: 18795397.

(Letter in response to Harada [2008]; 41 year old woman with seronegative rheumatoid arthritis developed elevated enzymes [ALT 1061 U/L, Alk P 244 U/L] after 3 years of infliximab therapy [ANA rising from 1:160 to 1:640], responding to stopping infliximab and prednisone therapy, later tolerating etanercept without ALT elevations and ANA levels falling to baseline).

Leak AM, Rincon-Aznar B. Hepatotoxicity associated with etanercept in psoriatic arthritis. J Rheumatol 2008; 35: 2286-7. PubMed PMID: 19004062.

(50 year old woman with psoriatic arthritis developed jaundice after 2 months of etanercept [50 mg/week] [bilirubin 2.4 mg/dL, ALT ~550 U/L, Alk P ~325 U/L], resolving within 3 months of stopping; but the patient later tolerated a lower dose of etanercept without recurrence of hepatitis, but with persistently borderline high Alk P levels).

Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol 2008; 35: 421-4. PubMed PMID: 18203328.

(Among 2 patients with HBsAg who received etanercept therapy for 12 and 13 months, serum HBV DNA levels rose minimally [from undetectable to 514 and 36 copies/mL] and ALT levels did not change; in 4 patients with hepatitis C treated with etanercept for 13-234 months, HCV RNA levels rose in 3, but ALT levels were only minimally elevated [<2 times ULN]).

Levämpi T, Korpela M, Vuolteenaho K, Moilanen E. Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons leading to discontinuation of the treatment. Rheumatol Int 2008; 28: 261-9. PubMed PMID: 17846778.

(Among 17 patients who stopped anti-TNF therapy because of side effects, none were for hepatotoxicity).

Collazo MH, González JR, Torres EA. Etanercept therapy for psoriasis in a patient with concomitant hepatitis C and liver transplant. P R Health Sci J 2008; 27: 346-7. PubMed PMID: 19069362.

(49 year old man with psoriasis who underwent liver transplantation for liver cancer due to HCV and alcoholic cirrhosis was then treated with etanercept with excellent clinical results: AST levels were stable and HCV RNA levels decreased [from 822 to 1.3 million IU/mL).

Cavazzana I, Ceribelli A, Cattaneo R, Franceschini F. Treatment with etanercept in six patients with chronic hepatitis C infection and systemic autoimmune diseases. Autoimmun Rev 2008; 8: 104-6. PubMed PMID: 19014870.

(Among 6 patients with inflammatory arthritis and anti-HCV who were treated with etanercept, none had worsening of hepatitis and HCV RNA levels changed minimally [174,770 to 348,218 IU/mL]).

Domm S, Cinatl J, Mrowietz U. The impact of treatment with tumour necrosis factor-alpha antagonists on the course of chronic viral infections: a review of the literature. Br J Dermatol 2008; 159: 1217-28. PubMed PMID: 18945310.

(Review of literature on efficacy and safety of TNF antagonists in patients with chronic hepatitis B and C, recommends screening and monitoring).

Cassano N, Vena GA. Etanercept treatment in a hemodialysis patient with severe cyclosporine-resistant psoriasis and hepatitis C virus infection. Int J Dermatol 2008; 47: 980-1. PubMed PMID: 18937672.

(69 year old man on hemodialysis with severe psoriasis and chronic hepatitis C was treated successfully with etanercept without worsening or change in hepatitis C markers or ALT levels).

Boetticher NC, Peine CJ, Kwo P, Abrams GA, Patel T, Aqel B, Boardman L, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology 2008; 135: 1953-60. PubMed PMID: 18848937.

(Controlled trial in 48 patients with moderate-to-severe acute alcoholic hepatitis found a higher 6 month mortality rate with etanercept [58%] than placebo therapy [23%]).

Carroll MB, Bond MI. Use of tumor necrosis factor-alpha inhibitors in patients with chronic hepatitis B infection. Semin Arthritis Rheum 2008; 38: 208-17. PubMed PMID: 18221983.

(73 year old woman with rheumatoid arthritis and chronic hepatitis B with high levels of HBV DNA in serum was treated with etanercept and given lamivudine and later adefovir without sustained effects, and later followed on no antiviral therapy with no change in liver histology over a 5 year period).

Zingarelli S, Airò Frassi M, Bazzani C, Scarsi M, Puoti M. Prophylaxis and therapy of HBV infection in 20 patients treated with disease modifying antirheumatic drugs or with biological agents for rheumatic diseases. Reumatismo 2008; 60: 22-7. PubMed PMID: 18432322.

(Retrospective analysis of results of treating 20 HBsAg positive patients with rheumatic conditions using immunosuppressive biologic agents; all patients tolerated therapy well and none had reactivation while on prophylactic antiviral therapy).

Montiel PM, Solis JA, Chirinos JA, a Casis B, Sáchhez F, Rodríguez S. Hepatitis B virus reactivation during therapy with etanercept in an HBsAg-negative and anti-HBs-positive patient. Liver Int 2008; 28: 718-20. PubMed PMID: 18433400.

(73 year old man with ankylosing spondylitis, amyloidosis and anti-HBc without HBsAg in serum was treated with etanercept and prednisone and developed symptomatic hepatitis 14 months later [bilirubin 2.0 mg/dL, ALT 65 U/L, GGT 121 U/L], with appearance of HBsAg and HBV DNA [1507 U/mL], resolving on lamivudine and later restarting etanercept while continuing lamivudine without reactivation).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, 3 were attributed to etanercept, but none to infliximab, adalimumab or certolizumab).

Zingarelli S, Frassi M, Bazzani C, Scarsi M, Puoti M, Airò P. Use of tumor necrosis factor-alpha-blocking agents in hepatitis B virus-positive patients: reports of 3 cases and review of the literature. J Rheumatol 2009; 36: 1188-94. PubMed PMID: 19447932.

(3 patients with rheumatoid arthritis and HBsAg in serum treated with etanercept, infliximab or adalimumab for up to 3 years; 2 with lamivudine prophylaxis did not develop reactivation, 1 without prophylaxis developed mild reactivation at 6 months and was successfully treated with lamivudine; review of literature found reactivation to occur in 12 of 16 patients not given prophylaxis, but only mild rise in HBV DNA in 1 of 7 on lamivudine).

Robinson H, Walker-Bone K. Anti-TNF-alpha therapy for rheumatoid arthritis among patients with chronic hepatitis B infection. Rheumatology (Oxford) 2009; 48: 448-50. PubMed PMID: 19223285.

(63 year old woman with rheumatoid arthritis and inactive hepatitis B treated with various combinations of etanercept, adalimumab, prednisone and methotrexate had no evidence of significant reactivation after 2 years of therapy; on review of literature, authors conclude that prophylaxis is not usually necessary).

Caramaschi P, Bambara LM, Pieropan S, Tinazzi I, Volpe A, Biasi D. Anti-TNFalpha blockers, autoantibodies and autoimmune diseases. Joint Bone Spine 2009; 76: 333-42. PubMed PMID: 19539516.

(Review of frequency of appearance of autoantibodies and autoimmune conditions during anti-TNF therapy).

Carlsen KM, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. Clin Rheumatol 2009; 28: 1001-3. PubMed PMID: 19370307.

(38 year old woman with rheumatoid arthritis developed rising ALT levels after 7 infusions of infliximab [ALT 234 U/L, bilirubin normal, ANA negative], resolving with stopping and no recurrence on switching to etanercept).

Chung SJ, Kim JK, Park MC, Park YB, Lee SK. Reactivation of hepatitis B viral infection in inactive HBsAg carriers following anti-tumor necrosis factor-alpha therapy. J Rheumatol 2009; 36: 2416-20. PubMed PMID: 19797507.

(Among 103 patients with rheumatoid arthritis or psoriasis treated with anti-TNF agents for 15-52 weeks, 8 were HBsAg-positive, but only 1 suffered reactivation; after third infusion with rise in ALT at week 14 peaking at 1054 U/L, HBV DNA 3.1 million copies/mL, entecavir therapy resulted in prompt improvements).

Dufour C, Giacchino R, Ghezzi P, Tonelli R, Ferretti E, Pitto A, Pistoia V, et al. Etanercept as a salvage treatment for refractory aplastic anemia. Pediatr Blood Cancer 2009; 52: 522-5. PubMed PMID: 19061218.

(17 year old man with aplastic anemia and chronic hepatitis C developed mild, transient ALT elevations [peak 176 U/L] during etanercept therapy).

Fairhurst DA, Sheehan-Dare R. Autoimmune hepatitis associated with infliximab in a patient with palmoplantar pustular psoriasis. Clin Exp Dermatol 2009; 34: 421-2. PubMed PMID: 19309375.

(22 year old woman with psoriasis developed rising ALT levels after third infusion of infliximab, peaking at ALT 1663 U/L 55 days after last infusion with rising in ANA [1:40 to 1:640] and a liver biopsy suggestive of autoimmune hepatitis, resolving with prednisone therapy; short follow up and no mention of bilirubin levels).

Kluger N, Girard C, Guillot B, Bessis D. Efficiency and safety of etanercept after acute hepatitis induced by infliximab for psoriasis. Acta Derm Venereol 2009; 89: 332-4. PubMed PMID: 19479148.

(46 year old woman with psoriasis developed rise in ALT [369 U/L] after a fourth infusion of infliximab with negative ANA and bilirubin of 1.5 mg/dL, resolving within 6 weeks of stopping and no recurrence with etanercept).

Li S, Kaur PP, Chan V, Berney S. Use of tumor necrosis factor-alpha (TNF-alpha) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective record review of 11 patients. Clin Rheumatol 2009; 28: 787-91. PubMed PMID: 19291350.

(Retrospective analysis of 11 patients with rheumatoid arthritis and either hepatitis B [n=3] or C [n=8] during 3 to 60 months anti-TNF therapy, 3 had transient minimal ALT elevations [peak levels 51, 73 and 51 U/L], without symptoms or jaundice).

Massarotti M, Marasini B. Successful treatment with etanercept of a patient with psoriatic arthritis after adalimumab-related hepatotoxicity. Int J Immunopathol Pharmacol 2009; 22: 547-9. PubMed PMID: 19505409.

(46 year old man with psoriatic arthritis developed rising ALT levels [19 to 96 to 252 U/L] 2 months after starting adalimumab, with resolution within 2 months of stopping and no recurrence after switching to etanercept).

Wetter DA, Davis MD. Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. Mayo Clin Proc 2009; 84: 979-84. PubMed PMID: 19880688.

(Retrospective analysis of 14 cases of lupus-like syndrome arising during anti-TNF therapy [13 infliximab, 1 adalimumab] over 8 year period; all were ANA positive and most had anti-dsDNA, onset with rash, serositis, fatigue, arthralgias, oral ulcers, but no renal or CNS involvement, all improved on stopping and tolerated other but not the same anti-TNF agent; no hepatic manifestations mentioned).

Rodríguez Gil FJ, Martínez Crespo JJ, García Belmonte D, Nicolás de Prado I, de Prado Serrano R. [Jaundice in a patient treated with etanercept]. Gastroenterol Hepatol 2009; 32: 584-5. Spanish. PubMed PMID: 19523718.

(62 year old woman with primary biliary cirrhosis on ursodiol with mild elevations in Alk P and bilirubin was started on etanercept for psoriasis and 2 months later developed deepening jaundice despite improvements in Alk P and ALT; bilirubin rose gradually to 12.7 mg/dL 5 months after stopping and subsequently fell to baseline as Alk P and ALT levels rose).

Charpin C, Guis S, Colson P, Borentain P, Mattéi JP, Alcaraz P, Balandraud N, et al. Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. Arthritis Res Ther 2009; 11: R179. PubMed PMID: 19941642.

(21 patients with rheumatic conditions who had anti-HBc without HBsAg in serum and were monitored during 7-56 months of therapy with infliximab [4], etanercept [14] or adalimumab [2]; anti-HBs titers decreased minimally and no patient developed HBV DNA or HBsAg or features of reactivation).

Frankel AJ, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF Jr, Gottlieb AB; National Psoriasis Foundation. Treatment of psoriasis in patients with hepatitis C: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2009; 61: 1044-55. PubMed PMID: 19811848.

(Recommend that infliximab and etanercept be considered second line agents in patients with psoriasis and hepatitis C, and conclude that more studies are needed).

Prignano F, Zanieri F, Milani S, Lotti T. Switch from etanercept to efalizumab in a psoriatic patient with HCV infection: a case report. Dermatol Ther 2009; 22: 386-90. PubMed PMID: 19580583.

(40 year old man with severe psoriasis and chronic hepatitis C was treated with etanercept and then efalizumab for six months without worsening of hepatitis or significant change in HCV RNA levels).

Giannitti C, Benucci M, Caporali R, Manganelli S, Bellisai F, Sebastiani GD, Galeazzi M. Efficacy and safety of anti-TNF-alpha therapy combined with cyclosporine A in patients with rheumatoid arthritis and concomitant hepatitis C virus infection. Int J Immunopathol Pharmacol 2009; 22: 543-6. PubMed PMID: 19505408.

(7 patients with rheumatoid arthritis and chronic hepatitis C were treated with cyclosporine and either etanercept or adalimumab and had clinical improvements with no worsening of liver disease, but instead mild decreases in ALT [38 to 26 U/L] and HCV RNA levels [7.1 to 2.3 million IU/mL]).

Wendling D, Di Martino V, Prati C, Toussirot E, Herbein G. Spondyloarthropathy and chronic B hepatitis. Effect of anti-TNF therapy. Joint Bone Spine 2009; 76: 308-11. PubMed PMID: 19346146.

(Four patients with chronic hepatitis B and spondylitis treated with infliximab or etanercept; two who did not receive prophylaxis with lamivudine developed rising HBV DNA levels within a month of starting therapy, which then responded to lamivudine therapy).

Kaiser T, Moessner J, Patel K, McHutchison JG, Tillmann HL. Life threatening liver disease during treatment with monoclonal antibodies. BMJ 2009; 338: b508. PubMed PMID: 19224957.

(66 year old man with psoriasis was treated with efalizumab [anti-CD11a] and then adalimumab [anti-TNF] and 11 days later developed jaundice and severe hepatitis [bilirubin 9.1 rising to 52 mg/dL, ALT 549 U/L, Alk P 131 U/L], with HBsAg being detected and slow but eventual recovery).

Shale MJ, Seow CH, Coffin CS, Kaplan GG, Panaccione R, Ghosh S. Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. Aliment Pharmacol Ther 2010; 31: 20-34. PubMed PMID: 19681818.

(Extensive review of literature on effects of anti-TNF therapies on underlying chronic hepatitis B and C; among 28 HBV-infected patients, reactivation was common in those not on antiviral therapy, more frequent with monoclonal antibodies than etanercept; among 110 HCV-infected patients, little evidence of worsening of disease and in some instances a decrease in HCV RNA levels).

Khokhar OS, Lewis JH. Hepatotoxicity of agents used in the management of inflammatory bowel disease. Dig Dis 2010; 28: 508-18. PubMed PMID: 20926880.

(Review of the hepatotoxicity of drugs used to treat inflammatory bowel disease focusing upon sulfaxalazine, thiopurines, TNF inhibitors, and methotrexate).

Haennig A, Bonnet D, Thebault S, Alric L. Infliximab-induced acute hepatitis during Crohn's disease therapy: absence of cross-toxicity with adalimumab. Gastroenterol Clin Biol 2010; 34: e7-8. PubMed PMID: 20189334.

(46 year old man with Crohn disease developed elevations in ALT [284 and 528 U/L] without Alk P and bilirubin elevations or symptoms after first 3 doses of infliximab, falling to normal in 3 months and not recurring during 6 months of adalimumab therapy).

Cravo M, Silva R, Serrano M. Autoimmune hepatitis induced by infliximab in a patient with Crohn's disease with no relapse after switching to adalimumab. BioDrugs 2010; 24 Suppl 1:25-7. PubMed PMID: 21175232.

(38 year old woman with Crohn disease was on and off infliximab for 8 years, developed abnormal liver tests [bilirubin normal, ALT 191 U/L, ANA 1:640], responding to prednisolone and azathioprine within 12 weeks and later treated with adalimumab without worsening of liver disease, but on long term azathioprine [50 mg/day]).

Katsanos KH, Tsianos VE, Zois CD, Zioga H, Vagias I, Zervou E, Christodoulou DK, et al.; Northwest Greece IBD Study Group. Inflammatory bowel disease and hepatitis B and C in Western Balkans: a referral centre study and review of the literature. J Crohns Colitis 2010; 4: 450-65. PubMed PMID: 21122543.

(Among 482 patients with inflammatory bowel disease, 11 had HBV and 4 HCV, antiviral therapy for which did not worsen the underlying bowel disease).

Which TNF inhibitor for rheumatoid arthritis? Med Lett Drugs Ther 2010; 52 (1338): 38-9. PubMed PMID: 20467356.

(Discussion of the efficacy, safety and costs of the 5 TNF inhibitors approved for use in rheumatoid arthritis states that none have been shown to be more effective than any other and adverse effects are similar, although reactivation of tuberculosis may be less common with etanercept than infliximab).

Brunasso AM, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology (Oxford) 2011; 50: 1700-11. PubMed PMID: 21690185.

(Systematic review of 37 publications on 153 patients with hepatitis C who were treated with anti-TNF agents for an average of 12 months found only one instance of worsening during therapy and no evidence of increases in HCV RNA levels during treatment).

Fotiadou C, Lazaridou E, Ioannides D. Safety of anti-tumour necrosis factor-. agents in psoriasis patients who were chronic hepatitis B carriers: a retrospective report of seven patients and brief review of the literature. J Eur Acad Dermatol Venereol 2011; 25: 471-4. PubMed PMID: 20561122.

(Seven patients with psoriasis and HBsAg carrier state were treated with adalimumab, etanercept or infliximab for 6-24 months with lamivudine prophylaxis and none suffered reactivation, HBV DNA being undetectable or present at low levels).

Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. Clin Rheumatol 2010; 29: 1021-9. PubMed PMID: 20556450.

(Review of literature on anti-TNF therapy in patients with hepatitis B identified 35 cases, 7 cases of reactivation occurred, including 7 of 17 on infliximab but none of 12 on etanercept or 6 on adalimumab; 18 received lamivudine, but only 7 as prophylaxis).

Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, Montecucco C, Sarzi-Puttini P. Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers(hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. Arthritis Care Res (Hoboken) 2010; 62: 749-54. PubMed PMID: 20535784.

(Among 732 patients treated with anti-TNF agents, 5 had HBsAg and were given prophylaxis with lamivudine and 67 had anti-HBc without HBsAg [25 on infliximab, 23 etanercept, 19 adalimumab], none of whom developed HBsAg or reactivation during an average follow up of 3.5 years).

Gandhi RK, Pickup T, Sheth PB. Is etanercept safe for treating plaque psoriasis in a patient with chronic hepatitis C virus infection? Arch Dermatol 2010; 146: 1151-2. PubMed PMID: 20956650.

(58 year old man with severe psoriasis and hepatitis C was treated successfully with etanercept and was reported to become HCV RNA negative during treatment).

Garavaglia MC, Altomare G. Etanercept therapy in patients with psoriasis and concomitant HCV infection. Int J Immunopathol Pharmacol 2010; 23: 965-9. PubMed PMID: 20943071.

(5 patients with psoriasis and chronic hepatitis C were treated with etanercept for up to 2 years; HCV RNA and ALT levels changed minimally in 4 and rose in 1 who was then treated with peginterferon and ribavirin).

Prestinari F, Ferguglia G, Laria G. Etanercept in a patient with severe psoriasis and latent viral hepatic disease and latent tuberculosis. Am J Clin Dermatol 2010; 11 Suppl 1: 57-8. PubMed PMID: 20586514.

(63 year old man with psoriasis, tuberculin positivity and anti-HBc without HBsAg was treated with isoniazid and etanercept without reactivation or appearance of liver injury).

Bordas X, Martín Sala S. [Etanercept and chronic infection by HCV and HBV]. Actas Dermosifiliogr. 2010; 101 Suppl 1: 82-7. Spanish. PubMed PMID: 20492886.

(Review of the safety of antirheumatic agents in patients with chronic viral hepatitis, and case report of 55 year old woman with psoriasis and chronic hepatitis B treated with lamivudine and etanercept with no worsening of liver disease and improvement in psoriasis).

Vassilopoulos D, Apostolopoulou A, Hadziyannis E, Papatheodoridis GV, Manolakopoulos S, Koskinas J, Manesis EK, et al. Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis 2010; 69: 1352-5. PubMed PMID: 20472596.

(Among 131 patients with rheumatic conditions treated with anti-TNF, 14 had HBsAg [all were given prophylactic anti-HBV therapy], 19 had anti-HBs alone [from vaccination] and 19 anti-HBc [from previous infection]; during an average of 2 years of therapy, one patient with HBsAg on lamivudine developed rising titers of HBV DNA successfully treated with tenofovir, while all others had no change in serologic status or ALT levels).

Paradisi A, Caldarola G, Capizzi R, Siciliano M, Annichiarico E, Vecchio FM, Amerio PL, et al. Safety of etanercept in patients with psoriasis and hepatitis C virus assessed by liver histopathology: preliminary data. J Am Acad Dermatol 2010; 62: 1067-9. PubMed PMID: 20466184.

(Two men, ages 43 and 62 years, with severe psoriasis and chronic hepatitis C were treated with etanercept; monitoring of serum ALT and HCV RNA levels and liver histology showed no change during 12 months of therapy).

Kim YJ, Bae SC, Sung YK, Kim TH, Jun JB, Yoo DH, Kim TY, et al. Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha blocker in the treatment of rheumatic diseases. J Rheumatol 2010; 37: 346-50. PubMed PMID: 20008922.

(Among 266 Korean patients with rheumatic conditions receiving anti-TNF therapy, 8 had HBsAg and 88 anti-HBc without HBsAg; 2 of the 8 HBsAg-positive patients developed reactivation and ALT elevations were more common in the anti-HBc-positive group [16%] than the antibody-negative group [6%], but reactivation was not demonstrated and clinical features were not given).

Ventura F, Gomes J, Duarte Mda L, Fernandes JC, Brito C. Efficacy and safety of etanercept in patients with psoriasis and hepatitis C. Eur J Dermatol 2010; 20: 808-9. PubMed PMID: 20923749.

(Two patients; 35 year old man and 47 year old woman with psoriasis and chronic hepatitis C were treated with etanercept with no change in serum ALT [36 to 44 U/L and 40 to 36 U/L], while HCV RNA levels increased in one and decreased in the other).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, none of which were attributed to anti-TNF agents).

Björnsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, Neuhauser M, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology 2010; 51: 2040-8. PubMed PMID: 20512992.

(Among 24 patients with drug induced autoimmune hepatitis seen at the Mayo Clinic betwen 1997 and 2007, implicated agents included minocycline [n=11], nitrofurantoin [n=11], cephalexin [n=1] and "Prometrium" [n=1], none being attributed to an anti-TNF agent).

Goldfeld DA, Verna EC, Lefkowitch J, Swaminath A. Infliximab-induced autoimmune hepatitis with successful switch to adalimumab in a patient with Crohn's disease: the index case. Dig Dis Sci 2011; 56: 3386-8. PubMed PMID: 21597977.

(58 year old woman with Crohn disease developed liver test abnormalities several weeks after starting infliximab [bilirubin normal, ALT ~205 U/L, ANA 1:2560], which resolved on stopping and did not recur on starting adalimumab).

Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Tanaka Y, et al. Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2011; 21: 343-51. PubMed PMID: 21264488.

(Summary of 6 month postmarketing surveillance of 13,894 Japanese patients with rheumatoid arthritis treated with etanercept; adverse events were reported in 31% and were severe in 6.2%, severe reactions including pneumonia and interstitial lung disease; abnormal liver tests were reported in 328 patients [2.4%], which were severe in 15 [0.1%]).

Stine JG, Bass M, Ibrahim D, Khokhar OS, Lewis JH. Dermatologists' awareness of and screening practices for hepatitis B virus infection before initiating tumor necrosis factor-α inhibitor therapy. South Med J 2011; 104: 781-8. PubMed PMID: 22089354.

(Results of email questionnaire sent to 1,000 US dermatologists found that 52% of 62 respondents were aware of guidelines for screening for HBV before using anti-TNF agents, but only 42% routinely screened patients and none of the 62 had ever seen a case of HBV reactivation).

Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, Retamozo S, et al.; BIOGEAS Study Group. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore) 2011; 90: 359-71. PubMed PMID: 22033451.

(Systematic review of literature identified 257 patients with preexisting HBV markers who received anti-TNF therapy, reactivation occurred in 39% of 89 patients with HBsAg [5 had acute liver failure, 4 died], but only 5% of 168 with anti-HBc without HBsAg [1 died]; lamivudine prophylaxis decreased, but did not eliminate reactivation [62% vs 23% in HBsAg carriers).

Brunasso AM, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology (Oxford) 2011; 50: 1700-11. PubMed PMID: 21690185.

(Systematic review of literature identified 153 patients with chronic hepatitis C treated with anti-TNF agents, mostly etanercept, with only 1 with definite worsening of disease on treatment).

Manzano-Alonso ML, Castellano-Tortajada G. Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy. World J Gastroenterol 2011; 17: 1531-7. PubMed PMID: 21472116.

(Review of reactivation of hepatitis B with chemotherapy or immune suppression discusses 11 cases attributed to infliximab and 7 to etanercept).

Aithal GP. Hepatotoxicity related to antirheumatic drugs. Nat Rev Rheumatol 2011; 7: 139-50. PubMed PMID: 21263458.

(Review of liver injury due to antirheumatic drugs discusses ALT elevations caused by anti-TNF agents and autoimmune hepatitis due to infliximab).

Zanni M, Missale G, Santilli D, Di Nuzzo S. Etanercept in the treatment of psoriasis and psoriatic arthritis with concomitant hepatitis C virus infection: clinical and virological study in three patients. Eur J Dermatol 2011; 21: 564-7. PubMed PMID: 21543290.

(Three patients with psoriasis and hepatitis C were treated with etanercept and had good clinical responses without changes in HCV RNA levels, and only one patient [who also had alcoholic liver disease] showed any worsening of serum enzyme levels).

Iwamoto M, Minota S. Successful treatment with very low-dose etanercept in a patient with etanercept-induced liver dysfunction. Rheumatol Int 2011; 31: 561-2. PubMed PMID: 20349067.

(37 year old woman with rheumatoid arthritis developed ALT elevations [peak value 165 U/L] 12 weeks after starting etanercept, 25 mg weekly, which improved on stopping but remained normal on a dose of 12.5 mg every other week).

van Denderen JC, Blom GJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Elevated liver enzymes in patients with ankylosing spondylitis treated with etanercept. Clin Rheumatol 2012; 31: 1677-82. PubMed PMID: 22941219.

(Among 105 patients with ankylosing spondylitis treated with etanercept, 9 developed liver enzyme elevations considered to be due to treatment leading to discontinuation in 2).

Kuroda T, Wada Y, Kobayashi D, Sato H, Murakami S, Nakano M, Narita I. Effect of etanercept and entecavil in a patient with rheumatoid arthritis who is a hepatitis B carrier: a review of the literature. Rheumatol Int 2012 32: 1059-63. PubMed PMID: 20062998.

(48 year old woman with rheumatoid arthritis and inactive hepatitis B was treated with entecavir and etanercept, with good response and no evidence of reactivation of hepatitis B).

Jansen TL, Mulder CJ. Rheumatology meets hepatology in 2012: a clinician's guideline for TNF inhibitors in hepatitis B/C virus carriers. Expert Opin Biol Ther 2012; 12: 391-3. PubMed PMID: 22413822.

(Review of the problem of hepatitis B and C in patients undergoing anti-TNF therapy, with recommendations on screening and management).

Viganò M, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. Expert Opin Biol Ther 2012; 12: 193-207. PubMed PMID: 22188392.

(Review of the safety of anti-TNF agents in patients with hepatitis B or C and expert opinion gluidelines for screening and management).

Cho YT, Chen CH, Chiu HY, Tsai TF. Use of anti-tumor necrosis factor-α therapy in hepatitis B virus carriers with psoriasis or psoriatic arthritis: a case series in Taiwan. J Dermatol 2012; 39: 269-73. PubMed PMID: 22077677.

(Retrospective analysis of 7 patients with psoriasis and HBsAg in serum who were treated with anti-TNF therapy and were monitored for changes in HBV DNA levels, found HBV reactivation in 3 patients who were then treated and none developed clinically apparent hepatitis).

Grasland A, Sterpu R, Boussoukaya S, Mahe I. Autoimmune hepatitis induced by adalimumab with successful switch to abatacept. Eur J Clin Pharmacol 2012; 68: 895-8. PubMed PMID: 22205272.

(35 year old woman with seronegative arthritis developed rise in ALT [from 18 to 266 U/L, ANA 1:80, SMA 1:320] two months after starting adalimumab, which fell to normal on stopping prednisone therapy and did not recur on starting abatacept).

Sandhu A, Alameel T, Dale CH, Levstik M, Chande N. The safety and efficacy of antitumour necrosis factor-alpha therapy for inflammatory bowel disease in patients post liver transplantation: a case series. Aliment Pharmacol Ther 2012; 36: 159-65. PubMed PMID: 22616981.

(Retrospective analysis of 6 patients who were treated with infliximab for inflammatory bowel disease after liver transplantation, 4 of whom had an excellent clinical response and none of whom developed liver injury or graft rejection).

Vassilopoulos D, Calabrese LH. Management of rheumatic disease with comorbid HBV or HCV infection. Nat Rev Rheumatol 2012; 8: 348-57. PubMed PMID: 22565315.

(Clinical review of chronic hepatitis B and C and the implications in patients with rheumatic disorders with interpretation of virologic markers and recommendations for screening and prophylaxis against HBV during immunosuppressive therapy)

Titos Arcos JC, Hallal H, Robles M, Andrade RJ. Recurrent hepatotoxicity associated with etanercept and adalimumab but not with infliximab in a patient with rheumatoid arthritis. Rev Esp Enferm Dig 2012; 104: 282-4. PubMed PMID: 22662786.

(47 year old woman with rheumatoid arthritis developed liver test abnormalities without symptoms 2 years after starting etanercept [bilirubin not given, ALT 13 times ULN, Alk P 1.7 times ULN], resolving within 3 months of stopping, but recurring on adalimumab but not on infliximab).

Abramson A, Menter A, Perrillo R. Psoriasis, hepatitis B, and the tumor necrosis factor-alpha inhibitory agents: a review and recommendations for management. J Am Acad Dermatol 2012; 67: 1349-61. PubMed PMID: 22727462.

(Review of reactivation of hepatitis b by anti-TNF factors, particularly infliximab, and recommendations on screening).

Di Minno MN, Iervolino S, Peluso R, Russolillo A, Lupoli R, Scarpa R, Di Minno G, et al.; CaRRDS Study Group. Hepatic steatosis and disease activity in subjects with psoriatic arthritis receiving tumor necrosis factor-α blockers. J Rheumatol 2012; 39: 1042-6. PubMed PMID: 22422493.

(Ultrasound assessment of liver fat was done before and after one year of anti-TNF therapy in 48 patients with psoriatic arthritis and 42 untreated controls; worsening of hepatic fat score occurred in 42% of patients, but only 14% of controls and, while worsening did not correlate with methotrexate therapy, it was more frequent in psoriatic patients with active arthritis).

Tanaka E, Urata Y. Risk of hepatitis B reactivation in patients treated with tumor necrosis factor-α inhibitors. Hepatol Res 2012; 42: 333-9. PubMed PMID: 22150950.

(Review of the problem of reactivation of hepatitis B after therapy with anti-TNF agents).

Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One 2012; 7: e30275. PubMed PMID: 22272322.

(Systematic review of 26 controlled trials of anti-TNF agents for rheumatoid arthritis found similar rates of efficacy with different agents, but slightly lower rates of adverse events with etanercept, as measured by rates of discontinuation for adverse events [risk ratio=0.71]).

Motaparthi K, Stanisic V, Van Voorhees AS, Lebwohl MG, Hsu S. From the Medical Board of the National Psoriasis Foundation: Recommendations for screening for hepatitis B infection prior to initiating anti-tumor necrosis factor-alfa inhibitors or other immunosuppressive agents in patients with psoriasis. J Am Acad Dermatol 2013 Nov 9. [Epub ahead of print] PubMed PMID: 24220724.

(Recommendations for screening and monitoring for hepatitis B in patients with psoriasis treated with anti-TNF agents).

Costa L, Caso F, Atteno M, Giannitti C, Spadaro A, Ramonda R, Vezzù M, Del Puente A, et al. Long-term safety of anti-TNF-α in PsA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. Clin Rheumatol 2013 Aug 24. [Epub ahead of print] PubMed PMID: 23975363.

(Among 15 patients with psoriasis and chronic hepatitis C who were treated with anti-TNF agents for 12 months or more at 4 Italian centers, serum ALT levels remained stable or decreased and no patient had evidence of exacerbation of the underlying liver disease).

Ghabril M, Bonkovsky HL, Kum C, Davern T, Hayashi PH, Kleiner DE, Serrano J, et al.; US Drug-Induced Liver Injury Network. Liver injury from tumor necrosis factor-α antagonists: analysis of thirty-four cases. Clin Gastroenterol Hepato 2013; 11: 558-64. PubMed PMID: 23333219.

(Description of 6 cases of acute liver injury due to anti-TNF agents from the US included 5 women [83%], ages 28 to 54 years, onset after 2-52 weeks of treatment with infliximab [n=3], etanercept [n=2] or adalumimab [n=1], ANA present in 3, [peak bilirubin 1.5-34.2 mg/dL, ALT 384-1687 U/L, Alk P 83-1311 U/L], 5 treated with corticosteroids, but all ultimately recovered).

Lin MV, Blonski W, Buchner AM, Reddy KR, Lichtenstein GR. The influence of anti-TNF therapy on the course of chronic hepatitis C virus infection in patients with inflammatory bowel disease. Dig Dis Sci 2013; 58: 1149-56. PubMed PMID: 23179145.

(Among 4,274 patients with inflammatory bowel disease, 37 had concurrent hepatitis C of whom 5 were treated with infliximab, none of whom had an exacerbation of disease, and had stable or decreasing levels of ALT and HCV RNA in serum while on therapy).

Efe C. Drug induced autoimmune hepatitis and TNF-α blocking agents: is there a real relationship? Autoimmun Rev 2013; 1: 337-9. PubMed PMID: 22841985.

(Review of the literature and commentary on anti-TNF induced autoimmune hepatitis indicating that liver injury from these agents is rare, but they can induce ANA reactivity and may trigger autoimmune hepatitis in susceptible patients).

Papa A, Felice C, Marzo M, Andrisani G, Armuzzi A, Covino M, Mocci G, et al. Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-α agents. J Crohns Colitis 2013; 7: 113-9. PubMed PMID: 22464811.

(In a retrospective study of 301 Italian patients with inflammatory bowel disease, 1 had HBsAg [0.3%], 22 had anti-HBc [7%] and 4 had anti-HCV [1.3%], but only one with HCV RNA; but none developed reactivation or liver injury during anti-TNF therapy; the one patient with HBsAg received lamivudine prophylaxis).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver iInjury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, 4 of which were attributed to infliximab and one to etanercept).

Pompili M, Biolato M, Miele L, Grieco A. Tumor necrosis factor-α inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol 2013; 19: 7867-73. PubMed PMID: 24307780.

(Review of literature on effects of anti-TNF agents in patients with chronic hepatitis C [153 on etanercept, 40 infliximab and 23 adalimumab] for an average of 1 year found only 5 patients with ALT elevations above 3 times ULN, 9 with >1 log IU/mL increase in HCV RNA levels, and 3 withdrawn for this reason).

Nanau RM, Neuman MG. Safety of anti-tumor necrosis factor therapies in arthritis patients. J Pharm Pharm Sci 2014; 17: 324-61. PubMed PMID: 25224347.

(Extensive review of adverse events associated with anti-TNF agents including immune related events).

Li Z, Xiao S, Ren J, Zhang Y, Tu C, Ji F. Hepatotoxicity due to etanercept abated after dose reduction in a patient with pustular psoriasis and without compromised efficacy. Rev Esp Enferm Dig 2014; 106: 492-3. PubMed PMID: 25490172.

(26 year old man with psoriasis developed ALT elevations [305 U/L] 3 weeks after starting etanercept [50 mg weekly], yet levels remained normal after he recovered despite treatment with a lower dose [25 mg weekly]).

Feuerstein JD, Cheifetz AS. Miscellaneous adverse events with biologic agents (excludes infection and malignancy). Gastroenterol Clin North Am 2014; 43: 543-63. PubMed PMID: 25110258.

(Extensive review of side effects of anti-TNF agents mentions drug induced autoimmune hepatitis as a rare complication, for which reason episodic monitoring of liver tests is warranted).

Di Nuzzo S, Boccaletti V, Fantini C, Cortelazzi C, Missale G, Fabrizi G, Lotti T, et al. Are anti-TNF-α agents safe for treating psoriasis in hepatitis C virus patients with advanced liver disease? case reports and review of the literature. Dermatology 2015 Oct 8. [Epub ahead of print] PubMed PMID: 26444967.

(2 cases: 61 and 50 year old men with psoriatic arthritis and chronic hepatitis C and cirrhosis were treated successfully with etanercept, but developed hepatocellular cancer after 21 and 58 months of therapy).

Iannone F, La Montagna G, Bagnato G, Gremese E, Giardina A, Lapadula G. Safety of etanercept and methotrexate in patients with rheumatoid arthritis and hepatitis C virus infection: a multicenter randomized clinical trial. J Rheumatol 2014; 41: 286-92. PubMed PMID: 24429167.

(Among 29 patients with rheumatoid arthritis and chronic hepatitis C monitored carefully during 54 weeks of etanercept and methotrexate therapy, serum ALT, AST and HCV RNA levels did not change significantly and no patient stopped therapy because of worsening liver disease).

Rossi RE, Parisi I, Despott EJ, Burroughs AK, O'Beirne J, Conte D, Hamilton MI, Murray CD. Anti-tumour necrosis factor agent and liver injury: literature review, recommendations for management. World J Gastroenterol 2014; 20: 17352-9. PubMed PMID: 5516646.

(Review of the literature on liver injury during anti-TNF therapy stresses that most ALT elevations are mild-to-moderate and self-limiting even with continuation of therapy).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, the most common implicated agents being nimesulide [n=53: 30%], cyproterone [n=18], nitrofurantoin [n=17], antituberculosis drugs [n=13] and flutamide [n=12: 7%]; but none were attributed to a TNF antagonist).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 6 cases were attributed to TNF antagonists: 1 to adalimumab, 2 etanercept and 3 infliximab).

Bauer H, Luxembourger C, Gottenberg JE, Fournier S, Abravanel F, Cantagrel A, Chatelus E, et al.; Club Rhumatismes et Inflammation, a section of the French Society of Rheumatology. Outcome of hepatitis E virus infection in patients with inflammatory arthritides treated with immunosuppressants: a French retrospective multicenter study. Medicine (Baltimore) 2015; 94: e675. PubMed PMID: 25860212.

(Survey of French physicians treating patients with rheumatic diseases identified 23 patients who developed acute hepatitis E while being treated with immunosuppressive regimens [10 on anti-TNF, 4 rituximab, 2 abatacept, 2 tocilizumab and 16 receiving methotrexate, 4 leflunomide and 1 cyclosporine]; all recovered and cleared HEV RNA, some after reduction in immunosuppression and 5 with ribavirin therapy).

Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? Hepatology 2015; 61: 703-11. PubMed PMID: 25412906.

(Review of the pathogenesis, clinical course, treatment and prevention of HBV reactivation in patients receiving immunosuppressive or anticancer therapies, with particular focus on rituximab and ofatumumab).

Capkin E, Karkucak M, Cosar AM, Ak E, Karaca A, Gokmen F, Budak BS, Tosun M. Treatment of ankylosing spondylitis with TNF inhibitors does not have adverse effect on results of liver function tests: a longitudinal study. Int J Rheum Dis 2015; 18: 548-52. PubMed PMID: 24612551.

(Among 94 patients with ankylosing spondylitis treated with infliximab [n=28], adalimumab [n=32] or etanercept [n=34], there was no change in mean ALT levels after 3 and 6 months of therapy).

Petríková J, Jarčuška P, Svajdler M, Pella D, Macejová Z. Autoimmune hepatitis triggered by adalimumab and allergic reactions after various anti-TNFα therapy agents in a patient with rheumatoid arthritis. Isr Med Assoc J 2015; 17: 256-8. PubMed PMID: 26040057.

(33 year old woman with rheumatoid arthritis developed fatigue after 3 doses of adalimumab [bilirubin not given, ALT 888 U/L, Alk P 348 U/L, ANA positive], biopsy showing interface hepatitis, resolving with prednisolone; later having allergic reactions to etanercept and certolizumab, but responding to anakinra).

Rodrigues S, Lopes S, Magro F, Cardoso H, Horta e Vale AM, Marques M, Mariz E, et al. Autoimmune hepatitis and anti-tumor necrosis factor alpha therapy: A single center report of 8 cases. World J Gastroenterol 2015; 21: 7584-8. PubMed PMID: 26140007.

(Among more than 600 patients treated with anti-TNF agents over a 7 year period, 8 developed autoimmune hepatitis [7 on infliximab, 1 adalimumab]; 3 men, 5 women, most with ANA, 2 symptomatic, no mention of jaundice; all responding to corticosteroids, 2 requiring long term therapy).

Björnsson ES, Gunnarsson BI, Gröndal G, Jonasson JG, Einarsdottir R, Ludviksson BR, Gudbjörnsson B, Olafsson S. Risk of drug-induced liver injury from tumor necrosis factor antagonists. Clin Gastroenterol Hepatol 2015; 13: 602-8. PubMed PMID: 25131534.

(Among 11 cases of liver injury from anti-TNF agents identified over a 5 year period in Iceland, 9 were due to infliximab [among 1076 patients treated=1:120], 1 adalimumab [270 treated] and 1 etanercept [430 treated]; 8 women, 3 men; latency 1 to 6 months; 5 were jaundiced [peak bilirubin 0.6-7.6 mg/dL, ALT 169-1658 U/L, Alk P 71-916 U/L], 8 hepatocellular, 2 cholestatic and 1 mixed injury; 8 had ANA, 5 were treated with corticosteroids [only 1 long term], 8 were switched to another anti-TNF agent without recurrence).

Chiu YM, Tang CH, Hung ST, Yang YW, Fang CH, Lin HY. A real-world risk analysis of biological treatment (adalimumab and etanercept) in a country with a high prevalence of tuberculosis and chronic liver disease: a nationwide population-based study. Scand J Rheumatol 2016: 1-5. [Epub ahead of print] PubMed PMID: 27766916.

(Nationwide population based data on use of adalimumab [n=4049] and etanercept [n=5117] between 2007 and 2011, identified higher rates of serious hepatic events for adalimumab vs etanercept [0.75 vs 0.39 per 100 person years] as well as higher rates of tuberculosis [1.62 vs 0.57 per 100 person-years]).