



Tumor Necrosis Factor Antagonists

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OVERVIEW

Tumor necrosis factor (TNF) alpha is a bioactive cytokine that is an important component of the inflammatory and pain pathways. Inhibition of TNF can decrease the inflammatory response, and this approach has been used in therapy of autoimmune conditions, most effectively in inflammatory bowel disease (IBD), rheumatoid arthritis, juvenile idiopathic arthritis (also known as juvenile rheumatoid arthritis), psoriasis, psoriatic arthritis and ankylosing spondylitis. Five anti-TNF antagonists have been developed and introduced into clinical medicine: a mouse-human chimeric monoclonal antibody to TNF (infliximab), two human monoclonal antibodies to TNF (adalimumab and golimumab), a humanized Fab fragment of anti-TNF linked to polyethylene glycol (certolizumab), and a soluble recombinant form of the TNF cellular receptor (etanercept) which, on binding, blocks the activity of TNF. These TNF antagonists have potent activity in several autoimmune diseases marked by excessive production of this proinflammatory cytokine. All five of these agents are approved for use in rheumatoid arthritis and are considered “disease modifying anti-rheumatic drugs” (DMARDs), having been shown to decrease pain, improve function, and ameliorate progressive joint damage in rheumatoid arthritis. The monoclonal antibodies to TNF have also been shown to be effective in psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease. The five agents rarely cause serum aminotransferase elevations, but have been linked to rare instances of clinically apparent, acute liver injury which often resembles autoimmune hepatitis and can be severe or require corticosteroid therapy. TNF antagonists are also immunosuppressive and can lead to reactivation of latent infections such as tuberculosis and hepatitis B. Severe and even fatal instances of reactivation of hepatitis B have been linked to several anti-TNF agents, and routine screening for HBsAg before starting therapy with these agents is recommended. Patients with HBsAg should receive prophylaxis with an oral antiviral agent during therapy with one of the TNF antagonists.

Among the TNF antagonists, infliximab has been most frequently and etanercept least frequently linked to liver injury, including asymptomatic serum aminotransferase elevations, induction of clinically apparent autoimmune hepatitis, and reactivation of hepatitis B. However, infliximab has been most extensively used and studied than the other anti-TNF monoclonal antibodies, and liver injury due to these agents is probably class specific. For these reasons, all five of these agents should be considered potentially hepatotoxic, etanercept perhaps less so than the others.

Drug Class: [Antirheumatic Agents](#); [Gastrointestinal Agents](#); [Psoriasis Agents](#)

References on hepatotoxicity and safety of the tumor necrosis factor antagonists are given together at the end of this Overview section. References to specific agents are also provided in the drug specific sections.

The following links are to individual drug records.

- Adalimumab
- Certolizumab
- Etanercept
- Golimumab
- Infliximab

REFERENCES

References updated: 10 February 2017

Zimmerman HJ. Drugs used to treat rheumatic and musculoskeletal 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 either infliximab or 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 hepatotoxicity, with the exception of the TNF alpha antagonists").

Wallace JL, Sharkey KA. Pharmacotherapy of inflammatory bowel disease. 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).

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354: 1932-9. PubMed PMID: 10622295.

(Controlled trial of infliximab vs placebo for 30 weeks in 428 patients with rheumatoid arthritis receiving methotrexate, found no difference in rates of ALT elevations between the two groups [37% vs 29%] and no cases of clinically apparent liver injury).

Menghini VV, Arora AS. Infliximab-associated reversible cholestatic liver disease. Mayo Clin Proc 2001; 76: 84-6. PubMed PMID: 11155419.

(44 year old woman with Crohn disease developed fatigue 19 days after single infusion of infliximab with subsequent jaundice [bilirubin 7.4 rising to 19.2 mg/dL, ALT 149 U/L, Alk P 55 U/L, ANA weakly positive], liver biopsy showing bland cholestasis and abnormalities resolving within 2 months of stopping: Case 1).

Saleem G, Li SC, MacPherson BR, Cooper SM. Hepatitis with interface inflammation and IgG, IgM, and IgA anti-double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al. Arthritis Rheum 2001; 44: 1966-8. PubMed PMID: 11508453.

(36 year old woman with rheumatoid arthritis developed symptoms shortly after third monthly infusion of infliximab with subsequent jaundice [bilirubin 16.6 mg/dL, ALT 448 U/L] and increase in ANA titer [1:160] with IgG antibodies to dsDNA, improved rapidly with prednisone therapy).

Biancone L, Pavia M, De Vecchio Blanco G, D'Inca R, Castiglione F, De Nigris F, Doldo P, et al. Hepatitis B and C virus infection in Crohn's disease. Inflamm Bowel Dis 2001; 7: 287-94. PubMed PMID: 11720317.

(Among 332 Italian patients with Crohn disease, 7.4% had anti-HCV and 2.1% HBsAg compared to 5.1% and 2.1% of Italian controls; no clear change in hepatitis with therapy of Crohn's in small numbers of cases studied retrospectively).

Day R. Adverse reactions to TNF-alpha inhibitors in rheumatoid arthritis. *Lancet* 2002; 359: 540-1. PubMed PMID: 11867103.

(Editorial on the severe side effects of long term anti-TNF therapy in rheumatoid arthritis focusing upon reactivation of tuberculosis, induction of a lupus-like syndrome and rare instances of cancer; no mention of hepatotoxicity).

Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, et al.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; 359: 1541-9. PubMed PMID: 12047962.

(Randomized trial of infliximab vs placebo in 573 patients with Crohn disease; no mention of hepatotoxicity).

Biancone L, Del Vecchio Blanco G, Pallone F, Castiglione F, Bresci G, Sturniolo G; Italian Group for the Study of the Colon and Rectum. Immunomodulatory drugs in Crohn's disease patients with hepatitis B or C virus infection. *Gastroenterology* 2002; 122: 593-4. PubMed PMID: 11845808.

(Further analysis of 4 patients with Crohn disease and hepatitis B who received immunomodulatory medications; no instances of reactivation).

Michel M, Duvoux C, Hezode C, Cherqui D. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. *J Rheumatol* 2003; 30: 1624-5. PubMed PMID: 12858469.

(Patients with adult Still disease and HBsAg [without HBeAg or HBV DNA] developed fever, rash and severe hepatitis after a second infusion of infliximab [direct bilirubin 14.6 mg/dL, ALT 30 times ULN], progressing to acute liver failure and liver transplant but without detectable HBV DNA; no testing for delta hepatitis).

Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. *Ann Rheum Dis* 2003; 62: 686-7. PubMed PMID: 12810441.

(59 year old man with rheumatoid arthritis developed hepatitis 18 months after starting infliximab [bilirubin 1.3 mg/dL, ALT 573 U/L], with presence of IgM anti-HBc and increase in serum HBV DNA polymerase activity; resolution in 2 months).

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).

Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, Fischkoff SA, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003; 30: 2563-71. PubMed PMID: 14719195.

(Controlled trial of 24 weeks of adalimumab vs placebo in 636 patients with rheumatoid arthritis; adverse events were similar between the two groups with no differences in mean ALT or AST levels; adalimumab group had higher rates of de novo autoantibody formation [ANA 27% vs 15%, anti-DNA 13% vs 1%]).

Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis

in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48: 35-45. PubMed PMID: 12528101.

(Controlled trial of 24 weeks of adalimumab vs placebo in 271 patients with rheumatoid arthritis found no significant changes in serum ALT levels and no instance of clinically apparent liver injury).

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).

Oniankitan O, Cuvoux C, Challine D, Mallat A, Chevalier X, Pawlotsky J-M, Claudepierre P. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 2004; 31: 107-9. PubMed PMID: 14705228.

(Two patients with rheumatoid arthritis treated for one year with infliximab had no worsening of liver disease; one with hepatitis B was on lamivudine, one with hepatitis C had no change in HCV RNA levels).

Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Fone M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; 53: 1363-5. PubMed PMID: 1536601.

(Among 3 patients with hepatitis B and Crohn disease, 2 developed a severe flare of hepatitis B after 2-3 months of infliximab therapy; the patient who did not suffer reactivation was being treated with lamivudine).

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).

Feletar M, Brockbank JE, Schentag CT, Lapp V, Gladman DD. Treatment of refractory psoriatic arthritis with infliximab: a 12 month observational study of 16 patients. *Ann Rheum Dis* 2004; 63: 156-61. PubMed PMID: 14722204.

(Among 16 patients with psoriasis treated with infliximab, 3 developed asymptomatic ALT elevations [141, 434 and 150 U/L], leading to early discontinuation; all resolved rapidly, 2 were on methotrexate).

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).

Eriksson C, Engstrand S, Sundqvist KG, Rantapää-Dahlqvist S. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. *Ann Rheum Dis* 2005; 64: 403-7. PubMed PMID: 15297281.

(Among 53 patients with rheumatoid arthritis treated with infliximab, ANA titers frequently increased and a proportion of patients developed anti-dsDNA while symptoms improved and rheumatoid factor titers fell).

Anelli MG, Torres DD, Manno C, Scioscia C, Iannone F, Covelli M, Schena FP, et al. Improvement of renal function and disappearance of hepatitis B virus DNA in a patient with rheumatoid arthritis and renal amyloidosis following treatment with infliximab. *Arthritis Rheum* 2005; 52: 2519-20. PubMed PMID: 16052569.

(36 year old woman with rheumatoid arthritis, amyloidosis with presence of HBsAg and anti-HDV in serum was treated successfully with infliximab without reactivation despite lack of antiviral prophylaxis; serum ALT levels, however rose perhaps due to worsening of delta hepatitis).

Germano V, Picchianti Diamanti A, Baccano G, Natale E, Onetti Muda A, Priori R, Valesini G. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. *Ann Rheum Dis* 2005; 64: 1519-20. PubMed PMID: 16162908.

(53 year old woman with psoriasis developed persistent ALT elevations after 6 infusions of infliximab [ALT 234 U/L], with rise in antinuclear and anti-smooth muscle antibodies, liver biopsy showing chronic hepatitis and mild fibrosis, improving with stopping infliximab).

Infliximab: lymphomas and severe hepatitis. *Prescrire Int* 2005; 14: 179. PubMed PMID: 16285074.

(FDA reported 35 cases of severe liver damage due to infliximab including fatal cases of acute liver failure, autoimmune hepatitis and exacerbations of chronic hepatitis B).

Magro F, Pereira P, Carneiro F, Veloso FT. Reactive hepatitis in a patient with Crohn's disease successfully treated with infliximab: does tumor necrosis factor alpha play a role in reactive hepatitis? *Inflamm Bowel Dis* 2005; 11: 88-90. PubMed PMID: 15674127.

(21 year old woman with Crohn disease had elevations in ALT [198 U/L] and Alk P [440 U/L], which improved after infliximab therapy and correlated with disease activity).

Mizuta M, Schuster MG. Cytomegalovirus hepatitis associated with use of anti-tumor necrosis factor-alpha antibody. *Clin Infect Dis* 2005; 40: 1071-2. PubMed PMID: 15825012.

(45 year old woman with Crohn disease developed fever and abnormal liver tests [ALT 282 U/L, Alk P 845 U/L, bilirubin 1.1 mg/dL] and liver biopsy showing changes of cytomegalovirus hepatitis, resolving rapidly with ganciclovir therapy).

Wendling D, Auge B, Bettinger D, Lohse A, Le Huede G, Bresson-Hadni S, Toussirot E, et al. Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthritis. *Ann Rheum Dis* 2005; 64: 788-9. PubMed PMID: 15834064.

(35 year old woman with HBsAg [normal ALT levels and no HBeAg] and ankylosing spondylitis developed rising levels of HBV DNA followed by ALT elevations after starting infliximab therapy and improved on lamivudine therapy).

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).

Ueno Y, Tanaka S, Shimamoto M, Miyataka Y, Hiyama T, Ito M, Kitadai Y, et al. Infliximab therapy for Crohn's disease in a patient with chronic hepatitis B. *Dig Dis Sci* 2005; 50: 163-6. PubMed PMID: 15712655.

(19 year old woman with Crohn disease and HBsAg, developed rise in HBV DNA levels followed by ALT increase after starting infliximab, resolving within 2 months of stopping, without antiviral therapy).

Scheinfeld N. Adalimumab: a review of side effects. *Expert Opin Drug Saf* 2005; 4: 637-41. PubMed PMID: 16011443.

(Review of side effects of adalimumab therapy mentions that it can induce a lupus-like syndrome [~0.1%] and is associated with minor ALT elevations).

Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, Bernstein CN, et al.; CDP870 Crohn's Disease Study Group. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005; 129: 807-18. PubMed PMID: 16143120.

(Preliminary results of a controlled trial of certolizumab in 292 patients with Crohn disease: "Serial hematologic and biochemical measurements did not show the treatment to have any untoward events").

Kaushik VV, Moots RJ. CDP-870 (certolizumab) in rheumatoid arthritis. *Expert Opin Biol Ther* 2005; 5: 601-6. PubMed PMID: 15934837.

(Review of safety and efficacy of certolizumab in rheumatoid arthritis; no serious side effects reported and no mention of hepatotoxicity).

Bratcher JM, Korelitz BI. Toxicity of infliximab in the course of treatment of Crohn's disease. *Expert Opin Drug Saf* 2006; 5: 9-16. PubMed PMID: 16370952.

(Review of safety of infliximab for Crohn disease; postmarketing reports of occasional cases of acute liver failure, jaundice, autoimmune hepatitis and cholestasis; single case report of cholestatic hepatitis).

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).

Ierardi E, Della Valle N, Nacchiero MC, De Francesco V, Stoppino G, Panella C. Infliximab single administration followed by acute liver injury. *Inflamm Bowel Dis* 2006; 12: 1089-91. PubMed PMID: 17075352.

(28 year old man with ulcerative colitis developed jaundice 9 days after initial infusion of infliximab [peak bilirubin ~6.5 mg/dL, ALT 4 times ULN], resolving within 6 weeks).

Ierardi E, Della Valle N, Nacchiero MC, De Francesco V, Stoppino G, Panella C. Onset of liver damage after a single administration of infliximab in a patient with refractory ulcerative colitis. *Clin Drug Investig* 2006; 26: 673-6. PubMed PMID: 17163303.

(Authors report same case as described in Inflamm Bowel Dis 2006).

Millonig G, Kern M, Ludwiczek O, Nachbaur K, Vogel W. Subfulminant hepatitis B after infliximab in Crohn's disease: need for HBV-screening? *World J Gastroenterol* 2006; 12: 974-6. PubMed PMID: 16521231.

(50 year old man with Crohn disease developed acute hepatitis 1 month after 3rd infusion of infliximab [bilirubin 2.2 rising to 35 mg/dL, ALT 983 U/L, GGT 109 U/L], found to have HBsAg, IgM anti-HBc, anti-HBe and high levels of HBV DNA, improved rapidly on lamivudine therapy and stopping infliximab; stored serum before therapy was HBsAg positive).

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 Martínez 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).

Soto-Fernández S, González-Carro P, De Pedro-Esteban A, Legaz-Huidobro ML, Pérez-Roldán F, Roncero García Escribano O, Valbuena-González M, et al. [Infliximab-induced hepatitis in a patient with Crohn's disease]. *Gastroenterol Hepatol* 2006; 29: 321-2. Spanish. PubMed PMID: 16733041.

(43 year old woman with Crohn disease developed asymptomatic elevations in ALT [289 U/L] after third infusion of infliximab, resolving rapidly, but more severe recurrence and symptoms upon restarting infusions 6 months later [ALT 1497 U/L, Alk P 71 U/L, bilirubin 0.6 mg/dL], resolving within a few months; all viral and autoimmune markers were negative).

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).

Garcia Aparicio 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).

Hansen RA, Gartlehner G, Powell GE, Sandler RS. Serious adverse events with infliximab: analysis of spontaneously reported adverse events. *Clin Gastroenterol Hepatol* 2007; 5: 729-35. PubMed PMID: 17481964.

(Analysis of 15,763 spontaneous, postmarketing adverse event reports attributed to infliximab found that reports of lymphoma and serious infections were more common than could be expected; no mention of rates of reporting liver injury, jaundice or hepatitis).

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).

Madonia S, Orlando A, Scimeca D, Olivo M, Rossi F, Cottone M. Occult hepatitis B and infliximab-induced HBV reactivation. *Inflamm Bowel Dis* 2007; 13: 508-9. PubMed PMID: 17206687.

(41 year old woman developed acute hepatitis with HBsAg, anti-HBe and HBV DNA after restarting infliximab and prednisone [25 mg/day] for Crohn disease [peak bilirubin 5.5 mg/dL, ALT 10 times ULN], resolving within 2 months with clearance of HBsAg; was known to have been HBsAg negative, but authors suspected HBV reactivation and reverse seroconversion, although anti-HBc and anti-HBs status before therapy was not known).

Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, et al.; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; 357: 228-38. PubMed PMID: 17634458.

(Controlled trial of certolizumab for 26 weeks in 662 adults with Crohn disease; "No clinically significant changes in laboratory values occurred in either study group"; no mention of hepatotoxicity or ALT elevations).

Ozorio G, McGarity B, Bak H, Jordan AS, Lau H, Marshall C. Autoimmune hepatitis following infliximab therapy for ankylosing spondylitis. *Med J Aust* 2007; 187: 524-6. PubMed PMID: 17979620.

(56 year old woman with ankylosing spondylitis developed rising levels of serum enzymes after 3 infusions of infliximab, which was stopped after sixth infusion [bilirubin 5.7 mg/dL, ALT 621 U/L, Alk P 521 U/L, ANA 1:640, SMA 1:2560: all previously negative or normal]; biopsy suggested autoimmune hepatitis, patient improved with prednisolone and stopping infliximab; no follow up beyond 3 months).

Tobon GJ, Cañas C, Jaller JJ, Restrepo JC, Anaya JM. Serious liver disease induced by infliximab. *Clin Rheumatol* 2007; 26: 578-81. PubMed PMID: 16547695.

(Two case reports; 39 and 54 year old women with rheumatoid arthritis developed symptoms after 8 and 17 months of infliximab therapy [bilirubin 15.2 mg/dL and not given, ALT 2560 and 291 U/L, Alk P 840 U/L and not given, ANA 1:640 and 1:160], both were treated with corticosteroids, the first required liver transplant and the second recovered).

Colbert C, Chavarria A, Berkelhammer C. Fulminant hepatic failure in chronic hepatitis B on withdrawal of corticosteroids. Azathioprine and infliximab for Crohn's disease. *Inflamm Bowel Dis* 2007; 13: 1453-4. PubMed PMID: 17600380.

(54 year old man with chronic hepatitis B and Crohn disease developed decompensated cirrhosis while on infliximab and azathioprine; stopping therapy and starting lamivudine was followed by a fatal flare of disease).

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).

Aslanidis S, Vassiliadis T, Pырpasopoulou A, Douloumpakas I, Zamboulis C. Inhibition of TNF alpha does not induce viral reactivation in patients with chronic hepatitis C infection: two cases. *Clin Rheumatol* 2007; 26: 261-4. PubMed PMID: 16924392.

(Two patients, 41 year old man and 47 year old woman with chronic hepatitis C were treated with infliximab for 6 and 13 months and had no change in serum ALT, AST or HCV RNA levels [1 had anti-HCV without HCV RNA before therapy]).

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 Thieffn [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, Baldrige 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).
- García-Simón S, Saliente Callén S, López Avila A, Rabell Iñigo S. [Hepatic cytolysis from infliximab]. *Farm Hosp* 2008; 32: 250-2. Spanish. PubMed PMID: 19128733.
- (32 year old man with psoriasis developed marked but asymptomatic elevations in serum enzymes after third infusion of infliximab [ALT 1,150 U/L, GGT 185 U/L without change in ANA titer], which resolved 5 months after stopping).
- 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).
- Marques M, Magro F, Cardoso H, Carneiro F, Portugal R, Lopes J, Costa Santos C. Infliximab-induced lupus-like syndrome associated with autoimmune hepatitis. *Inflamm Bowel Dis* 2008; 14: 723-5. PubMed PMID: 17929297.

- (34 year old woman with ulcerative colitis developed symptoms and liver tests abnormalities [ALT 412 U/L, Alk P 152, bilirubin normal, ANA 1:3210, IgG 1840 mg/dL] after fourth infusion of infliximab, biopsy showing changes of autoimmune hepatitis; patient worsened despite stopping infliximab for 5 months, then responded to prednisone).*
- Ojio K, Naganuma M, Ebinuma H, Kunimoto H, Tada S, Ogata H, Iwao Y, et al. Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. *J Gastroenterol* 2008; 43: 397-401. PubMed PMID: 18592158.
- (43 year old woman with Crohn disease and HBsAg developed detectable HBV DNA after fourth infusion of infliximab and flare of hepatitis 6 months later despite therapy with lamivudine, resolving after 3 months; later tolerated infliximab with concurrent lamivudine therapy: Case 3).*
- 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]).*
- Dom 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%]).*
- Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, Kamatani N, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 189-94. PubMed PMID: 17644554.
- (Among 5000 patients treated with infliximab for at least 6 months, 28% developed adverse events [6% serious], including 3.9% with hepatobiliary events [0.04% serious], but no details given).*

Inman RD, Davis JC Jr, Heijde Dv, Diekman L, Sieper J, Kim SI, Mack M, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008; 58: 3402-12. PubMed PMID: 18975305.

(Among 356 patients with ankylosing spondylitis treated with golimumab or placebo for 14 weeks, transient ALT elevations occurred in 6% of golimumab and 2.6% of placebo recipients, and were ≥ 2 times baseline and ≥ 150 U/L in 3% vs 1.3%).

Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009; 60: 2272-83. PubMed PMID: 19644849.

(Among 637 patients with rheumatoid arthritis treated in a randomized controlled trial, responses at 24 weeks were slightly more frequent with the combination [38%] than methotrexate alone [29%] or golimumab alone [33%], but so were ALT elevations [4.4% and 6.3% vs 1.3% and 0%]).

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).

Chalasan 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).

Conde-Taboada A, Muñoz JP, Muñoz LC, López Bran E. Infliximab treatment for severe psoriasis in a patient with active hepatitis B virus infection. *J Am Acad Dermatol* 2009; 60: 1077-80. PubMed PMID: 19467387.

(36 year old man with psoriasis and chronic hepatitis B successfully treated with combination of lamivudine and infliximab with fall of ALT levels [from 349 to 39 U/L] and HBV DNA [$>110,000$ to 1266 copies/mL] after 6 months of treatment, but no further follow up).

Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis* 2009; 68: 1863-9. PubMed PMID: 19147611.

(Among 19,041 patients treated with adalimumab in 36 clinical trials, serious infections occurred in 1-5 patients per year; no discussion of liver toxicity or ALT levels).

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- α (TNF- α) 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).

Murakami A, Tanaka Y, Ueda M, Nagano Y, Kunisaki R, Morimoto M, Enaka M, et al. Hepatocellular carcinoma occurring in a young Crohn's disease patient. *Pathol Int* 2009; 59: 492-6. PubMed PMID: 19563414.

(25 year old man with 12 year history of Crohn disease presented with hepatocellular carcinoma [HCC] without cirrhosis approximately one year after starting infliximab; no other risk factors identified; review of literature identified 7 cases of HCC in patients with Crohn's, mean age 20 years, all had received azathioprine and two infliximab, none had cirrhosis or viral hepatitis).

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).

Shao LM, Chen MY, Cai JT. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. *Aliment Pharmacol Ther* 2009; 29: 605-14. PubMed PMID: 19183161.

(Metaanalysis of safety in 3 controlled trials of certolizumab in 1313 patients with Crohn disease; no increase in serious adverse events except for infections, but no specific data on rates of ALT elevation or liver injury provided).

Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijckens K, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009; 68: 797-804. PubMed PMID: 24431394.

(Controlled trial of methotrexate with or without certolizumab in 619 patients with rheumatoid arthritis; ALT elevations occurred in 5% of patients on methotrexate alone vs 2% on the combination; 5 cases of tuberculosis on certolizumab, but no mention of clinically apparent liver injury).

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, Toussiroit E, Herbein G. Spondyloarthritis 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).

Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, Gaylis N, et al.; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009; 374 (9685): 210-21. PubMed PMID: 19560810.

(Among 461 patients with rheumatoid arthritis in a 14 week randomized controlled trial, 18% on placebo vs 35% and 38% on golimumab [50 or 100 mg monthly]; no mention of ALT elevations or hepatotoxicity).

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in

psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; 60: 976-86. PubMed PMID: 19333944.

(Among 456 patients with psoriatic arthritis treated in a randomized controlled trial for 24 weeks, response rates were 48% and 51% with 50 and 100 mg of golimumab vs 9% with placebo, and rates of adverse events were similar, marked ALT elevations occurring in 0-2% of golimumab- vs 3% of placebo recipients).

Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, et al.; GO-FORWARD Study. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009; 68: 789-96. PubMed PMID: 19066176.

(Among 444 patients with rheumatoid arthritis in a randomized controlled trial, response rates at 14 weeks were 33% with methotrexate alone, 44% with golimumab alone and 56% with the combination, and adverse events were similar in all groups; ALT elevations were not mentioned).

Golimumab (simponi) for inflammatory arthritis. *Med Lett Drugs Ther* 2009; 51 (1316): 55-6. PubMed PMID: 19590489.

(Concise review of the mechanism of action, efficacy and safety of golimumab shortly after its approval for treatment of rheumatoid and psoriatic arthritis in the US).

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).

Mancini S, Amorotti E, Vecchio S, Ponz de Leon M, Roncucci L. Infliximab-related hepatitis: discussion of a case and review of the literature. *Intern Emerg Med* 2010 PubMed PMID: 20107930.

(33 year old man with psoriasis developed fatigue and ALT elevations followed by jaundice after a third infusion of infliximab [bilirubin 3.7 mg/dL, ALT 2132 U/L, Alk P 594 U/L, ANA 1:320 and positive anti-dsDNA], responding to corticosteroids [becoming ANA negative], which were discontinued without relapse).

Smith LS, Nelson M, Dolder CR. Certolizumab pegol: a TNF- α antagonist for the treatment of moderate-to-severe Crohn's disease. *Ann Pharmacother* 2010; 44: 333-42. PubMed PMID: 20118143.

(Review of structure, mechanism of action, pharmacology, safety and efficacy of certolizumab focusing upon Crohn disease; no mention of liver injury or ALT elevations).

Lichtenstein GR, Thomsen O~O, Schreiber S, Lawrance IC, Hanauer SB, Bloomfield R, Sandborn WJ; Precise 3 Study Investigators. Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months. *Clin Gastroenterol Hepatol* 2010; 8: 600-9. PubMed PMID: 20117244.

(Among 241 patients with Crohn disease continued on certolizumab for up to 80 weeks, 2 patients developed tuberculosis, 1 a lupus-like syndrome, 16 [11%] ANA and 4 [2%] anti-dsDNA reactivity; no mention of liver injury or ALT elevations).

Sokolove J, Strand V, Greenberg JD, Curtis JR, Kavanaugh A, Kremer JM, Anofrei A, et al; CORRONA Investigators. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 1612-7. PubMed PMID: 20448284.

- (Retrospective analysis of ALT and AST elevations among 6861 patients with rheumatoid arthritis enrolled in a North American database receiving TNF inhibitors followed for an average of 1.5 years with ~1.7 determinations yearly; any elevation of ALT or AST occurred in 5.4% of visits, >2 times ULN in 0.6%, >5 times ULN in 0.1%; rates slightly higher for those on infliximab or when combined with methotrexate and leflunomide).*
- 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 sulfasalazine, thiopurines, TNF inhibitors, and methotrexate).*
- Poulin Y, Thérien G. Drug-induced hepatitis and lupus during infliximab treatment for psoriasis: case report and literature review. *J Cutan Med Surg* 2010; 14: 100-4. PubMed PMID: 20338127.
- (40 year old woman with psoriasis developed raised ALT after 22 weeks of infliximab treatment [5 infusions], with rise in ALT to 136 and then 536 U/L and symptoms of rash, arthralgias and joint swelling, positive ANA [1:60] and liver biopsy showing chronic hepatitis, resolving with 4 weeks of prednisone therapy and no recurrence in subsequent 4 years).*
- 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).*
- Song MS, Lee SB, Sohn S, Oh JH, Yoon KL, Han JW, Kim CH. Infliximab treatment for refractory Kawasaki disease in Korean children. *Korean Circ J* 2010; 40: 334-8. PubMed PMID: 20664742.
- (Among 16 children with Kawasaki disease treated with infliximab, one 4 month old boy developed an acute hepatitis followed by cholecystitis during therapy).*
- Goujon C, Dahel K, Béréd F, Guillot I, Gunera-Saad N, Nicolas JF. Autoimmune hepatitis in two psoriasis patients treated with infliximab. *J Am Acad Dermatol* 2010; 63: e43-4. PubMed PMID: 20633783.
- (Two cases of autoimmune hepatitis during infliximab therapy, 37 and 51 year old men with psoriasis developed symptoms 4-6 weeks after a third infusion [bilirubin 0.8 and 3.2 mg/dL, ALT 1126 and 768 U/L, Alk P 181 and 391 U/L, ANA 1:200 and 1:2560], one resolving upon stopping and one after treatment with ursodiol, corticosteroids and azathioprine).*

Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2010; 62: 917-28. PubMed PMID: 20131276.

(Among 444 patients treated with golimumab with or without methotrexate or placebo and methotrexate, infections were more frequent in those who received golimumab and side effects were more frequent in those who received golimumab and methotrexate; no mention of ALT elevations or hepatotoxicity).

McCluggage LK, Scholtz JM. Golimumab: a tumor necrosis factor alpha inhibitor for the treatment of rheumatoid arthritis. *Ann Pharmacother* 2010; 44: 135-44. PubMed PMID: 20118145.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of golimumab a fully humanized bivalent IgG1 monoclonal antibody to both soluble and transmembrane TNF; most common side effects are nausea and injection site reactions, serious adverse events include tuberculosis and lymphoma; no mention of ALT elevations or hepatotoxicity).

Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, Pazdur J, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis* 2010; 69: 1129-35. PubMed PMID: 20444749.

(Open label continuation of controlled trial of golimumab [Keystone 2009] showed that responses were sustained and adverse events did not increase; no mention of ALT elevations or hepatotoxicity).

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).

Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. *J Rheumatol* 2010; 37: 1096-104. PubMed PMID: 20436075.

(Systematic review of 4 controlled trials in 1231 patients treated with golimumab and 483 with placebo concluded that golimumab was more beneficial than placebo and adverse events rates were similar to those in controls; no mention of ALT elevations or hepatotoxicity).

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).
- Féau S, Causse X, Corondan A, Michenet P, Autret-Leca E. [Acute drug-induced hepatitis during adalimumab and ibuprofen treatment]. *Gastroenterol Clin Biol* 2010; 34: 420-2. French. PubMed PMID: 20494537.
- (61 year old man with rheumatoid arthritis on adalimumab for 15 months and occasional ibuprofen developed hepatitis [bilirubin 2.9 mg/dL, ALT 2491 U/L, Alk P 292 U/L, ANA negative], resolving within 4 months of stopping medications and increasing prednisone dose).
- Adar T, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O. Adalimumab-induced autoimmune hepatitis. *J Clin Gastroenterol* 2010; 44: e20-2. PubMed PMID: 19593165.
- (36 year old woman with psoriasis and Crohn disease developed nausea after starting adalimumab and after 3 months liver tests were abnormal [bilirubin 0.7 mg/dL, ALT 1265 U/L, Alk P 102 U/L, ANA 1:80], resolving within 2 months of stopping therapy and starting prednisone and azathioprine).
- 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 between 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).
- 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).
- Goldfeld DA, Verna EC, Lefkowitz 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).

Doyle A, Forbes G, Kontorinis N. Autoimmune hepatitis during infliximab therapy for Crohn's disease: a case report. *J Crohns Colitis* 2011; 5: 253-5. PubMed PMID: 21575891.

(60 year old man with Crohn disease who did not improve on prednisone and azathioprine therapy developed rising levels of ALT 14 weeks after starting infliximab [bilirubin not given, ALT 1307 U/L, Alk P 272 U/L], which resolved on stopping infliximab and starting prednisone).

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).

Kuroda T, Wada Y, Kobayashi D, Sato H, Murakami S, Nakano M, Narita I. Effect of etanercept and entecavir 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).

Doubrawa E, Ricca RA, Malucelli TO, Pizzol VI, Barros DH, Paiva ES. Use of infliximab in a patient with rheumatoid arthritis and chronic hepatitis B. *Rev Bras Reumatol* 2012; 52: 653-5. PubMed PMID: 22885430.

(56 year old man with rheumatoid arthritis and hepatitis B was treated with tenofovir and lamivudine and then tolerated infliximab without reactivation).

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 guidelines for screening and management).

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).

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- α 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)

Kouba M, Rudolph SE, Hrdlicka P, Zuber MA. [Hepatitis-B reactivation during treatment with tumor necrosis factor- α blocker adalimumab in a patient with psoriasis arthritis]. *Dtsch Med Wochenschr* 2012; 137: 23-6. PubMed PMID: 22180279.

(66 year old man with psoriatic arthritis developed jaundice 3 weeks after starting adalimumab [bilirubin 7.1 mg/dL, ALT 1218 U/L, GGT 169 U/L, HBsAg positive, HBV DNA 46 million IU/mL], with a severe course, but ultimate recovery).

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- α 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).

Kinnunen U, Färkkilä M, Mäkisalo H. A case report: ulcerative colitis, treatment with an antibody against tumor necrosis factor (infliximab), and subsequent liver necrosis. *J Crohns Colitis* 2012; 6: 724-7. PubMed PMID: 22398069.

(46 year old woman with refractory ulcerative colitis developed jaundice 7 weeks after a second injection of infliximab [bilirubin 16.6 mg/dL, ALT 1826 U/L, Alk P 283 U/L, INR 3.2, ANA negative], progressing to acute liver failure and emergency liver transplant).

Smolen JS, Kay J, Landewé RB, Matteson EL, Gaylis N, Wollenhaupt J, Murphy FT, et al. Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: results of a long-term extension of the randomised, double-blind, placebo-controlled GO-AFTER study through week 160. *Ann Rheum Dis* 2012; 71: 1671-9. PubMed PMID: 22459542.

(Among 459 patients with rheumatoid arthritis in a 24 week controlled trial of golimumab, 236 were continued on treatment for up to 160 weeks; listing of adverse events did not mention ALT elevations, hepatotoxicity or reactivation of hepatitis B).

- Kavanaugh A, van der Heijde D, McInnes IB, Mease P, Krueger GG, Gladman DD, Gómez-Reino J, et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis Rheum* 2012; 64: 2504-17. PubMed PMID: 22378566.
- (Open label continuation of controlled trial of golimumab for psoriatic arthritis found that clinical efficacy was maintained through 1 year and adverse events were similar to those reported earlier [Kavanaugh 2009], 3 patients discontinued therapy because of elevated ALT levels, but no new patients had "clinically meaningful" elevations in ALT since the previous report).*
- 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]).*
- Braun J, Deodhar A, Inman RD, van der Heijde D, Mack M, Xu S, Hsu B. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. *Ann Rheum Dis* 2012; 71: 661-7. PubMed PMID: 22012970.
- (Results of extended therapy with golimumab in patients enrolled in a previous controlled trial in ankylosing spondylitis [Inman 2009] found liver enzymes were more commonly elevated in those on 100 vs 50 mg of golimumab [5% vs 0.7%], no patient had concurrent elevation in ALT and bilirubin).*
- Kuwabara H, Fukuda A, Tsuda Y, Shibayama Y. Precore mutant hepatitis B virus-associated fulminant hepatitis during infliximab therapy for rheumatoid arthritis. *Clin Rheumatol* 2013; 32: S47-9. PubMed PMID: 20379839.
- (73 year old woman with rheumatoid arthritis and HBsAg positivity [HBeAg negative, normal ALT] developed fatal reactivation of hepatitis B after a year of infliximab [bilirubin 15.7 mg/dL, ALT 544 U/L, GGT 130 U/L, HBV DNA and IgM anti-HBc positive], progressing to hepatic failure and death 18 days later).*
- Motaparathi K, Stanisis 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).*
- Nakayama S. Autoimmune hepatitis triggered by anti-TNF- α therapy. *Case Rep Med* 2013; 2013: 561748. PubMed PMID: 24082887.
- (52 year old woman with psoriasis developed fatigue 2 months [6 doses] after starting adalimumab [bilirubin not given, ALT 424 U/L, Alk P 723 U/L, ANA 1:160, IgG 1969 mg/dL], with persistence of abnormalities leading to treatment with prednisolone with subsequent prompt improvement).*
- Dang LJ, Lubel JS, Gunatheesan S, Hosking P, Su J. Drug-induced lupus and autoimmune hepatitis secondary to infliximab for psoriasis. *Australas J Dermatol* 2013 May 8. [Epub ahead of print] PubMed PMID: 23651182.
- (Abstract only).*
- Zhang X, Zhang F, Wu D, Bao C, Zhu P, Zhang X, Huang C, et al. Safety of infliximab therapy in rheumatoid arthritis patients with previous exposure to hepatitis B virus. *Int J Rheum Dis* 2013; 16: 408-12. PubMed PMID: 23992260.

(Retrospective analysis of 41 Chinese patients with rheumatoid arthritis and anti-HBc without HBsAg in serum who were treated with infliximab for 26 weeks; they found no significant change in ALT or AST levels and no evidence of reactivation; no mention on HBV DNA levels).

Caussé S, Bouquin R, Wylomanski S, Flamant M, Joubert M, Dréno B, Quéreux G. [Infliximab-induced hepatitis during treatment of vulvar Crohn's disease]. *Ann Dermatol Venereol* 2013; 140: 46-51. French. PubMed PMID: 23328360.

(29 year old woman with Crohn disease developed serum enzyme elevations 10 days after a first injection of infliximab [bilirubin normal, ALT 20 times ULN, Alk P 1.5 times ULN, ANA negative] which persisted for 2 months, but then resolved promptly with prednisone therapy).

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).

Laurenti R, Giovannangeli F, Gubinelli E, Viviano MT, Errico A, Leoni L, Ballanti E, et al. Long-term safety of anti-TNF adalimumab in HBc antibody-positive psoriatic arthritis patients: a retrospective case series of 8 patients. *Clin Dev Immunol* 2013; 2013: 410521. PubMed PMID: 23606869.

(8 patients with psoriasis and either HBsAg [n=1] or anti-HBc alone in serum [n=7] were treated with adalimumab for up to 6 years without evidence for reactivation, although the HBsAg positive patient was given lamivudine prophylaxis).

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 adalimumab [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 injury 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).

Emery P, Fleischmann RM, Doyle MK, Strusberg I, Durez P, Nash P, Amante E, et al. Golimumab, a human anti-tumor necrosis factor monoclonal antibody, injected subcutaneously every 4 weeks in patients with active rheumatoid arthritis who had never taken methotrexate: 1-year and 2-year clinical, radiologic, and physical function findings of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Care Res (Hoboken)* 2013; 65: 1732-42. PubMed PMID: 23861303.

(Extended results of continuing golimumab in patients with rheumatoid arthritis enrolled in a controlled trial [Emery 2009] mentions serious adverse events of active tuberculosis in 11 patients, malignancies in 14; no mention of ALT elevations, hepatotoxicity or reactivation of hepatitis B).

Keystone EC, Genovese MC, Hall S, Miranda PC, Bae SC, Palmer W, Wu Z, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-FORWARD study extension. *J Rheumatol* 2013; 40: 1097-103. PubMed PMID: 23678153.

(Further follow up on 392 patients with rheumatoid arthritis treated in a controlled trial of golimumab [Keystone 2009], who continued on either 50 or 100 mg of golimumab for 2 years mentions severe adverse events of serious infections [7%], tuberculosis [0.5%] and one patient who died of hepatic failure after "a complicated hospitalization including severe intraabdominal hemorrhage following liver biopsy").

Kavanaugh A, McInnes IB, Mease PJ, Krueger GG, Gladman DD, van der Heijde D, Mudivarthy S, et al. Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. *Ann Rheum Dis* 2013; 72: 1777-85. PubMed PMID: 23161902.

(Further follow up on 394 patients with psoriatic arthritis [Kavanaugh 2009] who were continued on golimumab [50 or 100 mg monthly] for up to 2 years, among whom 5 discontinued therapy because of raised ALT levels and 4 for raised AST levels; no mention of clinically apparent liver injury or reactivation of hepatitis B).

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).

Rowe BW, Gala-Lopez B, Tomlinson C, Girgis S, Shapiro JA. Fulminant hepatic failure necessitating transplantation following the initiation of infliximab therapy: a cautionary tale times two. *Transpl Int.* 2013; 26: e110-e112. PubMed PMID: 24047326.

(40 year old woman with lupus developed jaundice 4 months after starting infliximab [bilirubin 15.3 mg/dL, AST 292 U/L, Alk P 195 U/L, INR 2.6] with progressive liver failure requiring liver transplantation; 51 year old woman with ulcerative colitis developed fever and jaundice 5 months after starting infliximab [bilirubin 5.7 rising to 38.2 mg/dL, AST 568 U/L, Alk P 527 U/L, INR 2.5]).

Colina F, Molero A, Casís B, Martínez-Montiel P. Infliximab-related hepatitis: a case study and literature review. *Dig Dis Sci* 2013; 58: 3362-7. PubMed PMID: 23645381.

(52 year old woman with ulcerative colitis developed enzyme elevations without jaundice after 4 infusions of infliximab [bilirubin 0.6 mg/dL, ALT 683 U/L, Alk P 218 U/L, ANA positive], biopsy showing inflammation with plasma cells and eosinophils, resolving with high dose prednisone therapy).

Latus J, Klein R, Koetter I, Schwab M, Fritz P, Kimmel M, Alscher MD, Braun N. Cholestatic liver disease after rituximab and adalimumab and the possible role of cross-reacting antibodies to Fab 2 fragments. *PLoS One* 2013; 8: e78856. PubMed PMID: 24244376.

(Testing of serum from a patient treated with rituximab, immune globulin and adalimumab who developed ascite and "liver enzyme elevations," identified antibodies to Fab fragments that cross-reacted to both rituximab and adalimumab).

Kim E, Bressler B, Schaeffer DF, Yoshida EM. Severe cholestasis due to adalimumab in a Crohn's disease patient. *World J Hepatol* 2013; 5: 592-5. PubMed PMID: 24179620.

(39 year old woman with Crohn disease developed jaundice 7 months after starting adalimumab and azathioprine [200 mg daily] for more than 3 years [bilirubin 9.7 mg/dL, ALT 15 U/L, Alk P 183 U/L, INR 1.8], resolving with 10 weeks of stopping both).

Nakayama S. Autoimmune Hepatitis Triggered by Anti-TNF- α Therapy. *Case Rep Med* 2013; 2013: 561748. PubMed PMID: 24082887.

(52 year old woman with psoriasis developed fatigue 2 months after starting adalimumab [bilirubin not given, ALT 224 U/L, Alk P 723 U/L, ANA 1:160], biopsy showing interface hepatitis, resolving within 2 months of prednisolone therapy).

Parekh R, Kaur N. Liver injury secondary to anti-TNF-alpha therapy in inflammatory bowel disease: a case series and review of the literature. *Case Rep Gastrointest Med* 2014; 2014: 956463. PubMed PMID: 24707412.

(49, 39 and 19 year old women developed liver enzyme elevations without jaundice 18, 3 and 1 months after starting infliximab [n=2] or adalimumab [n=1] therapy [peak ALT 104, 300 and 84 U/L; Alk P 518, 77 and 527 U/L], resolving in all after stopping; 1 later tolerated switching from infliximab to adalimumab).

Rösner S, Schad A, Kittner J, Rahman F, Wörns MA, Schuchmann M, Galle PR, Schattenberg JM. [Drug-induced liver injury with an autoimmune phenotype following anti-TNF Therapy - presentation of cases and review of literature]. *Z Gastroenterol* 2014; 52: 58-63. German. PubMed PMID: 24420801.

(Three patients with psoriasis developed liver enzyme elevations 1 to 7 months after starting adalimumab, all with ANA positivity, 2 responding to corticosteroids and one resolving just with stopping therapy).

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).

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).

Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, et al.; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; 146: 96-109. PubMed PMID: 23770005.

(Among 464 patients with ulcerative colitis who achieved a clinical response during induction therapy and who were then treated with either 50 or 100 mg of golimumab or placebo, clinical responses were maintained in 47-50% of patients on golimumab vs 31% on placebo; 4 patients developed tuberculosis, 1 of whom died; no mention of ALT elevations or hepatotoxicity).

Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, et al.; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; 146: 85-95. PubMed PMID: 23735746.

(Among 1064 adults with active ulcerative colitis given induction therapy, rates of response were 51-55% on golimumab vs 30% on placebo, and adverse events [through week 6] were similar; no mention of ALT elevations or hepatotoxicity).

Combe B, Dasgupta B, Louw I, Pal S, Wollenhaupt J, Zerbinski CA, Beaulieu AD, et al.; GO-MORE Investigators. Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study. *Ann Rheum Dis* 2014; 73: 1477-86. PubMed PMID: 23740226.

(Among 3366 patients with rheumatoid arthritis treated with golimumab in an open label study, the most common clinically significant abnormal laboratory event was elevation in liver aminotransferase levels, but no specific rates given).

Golimumab (Simponi) for ulcerative colitis. *Med Lett Drugs Ther* 2014; 56 (1439): 25-6. PubMed PMID: 24691148.

(Concise review of the mechanism of action, efficacy, safety and costs of golimumab therapy of ulcerative colitis shortly after its approval for this indication in the US, mentions the risk of reactivation of tuberculosis and hepatitis B with all anti-TNF agents).

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: 25516646.

(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).

Olfa H, Aroua G, Wissem M, Wafa BM, Hichem L, Nabil BC, Fethia B, et al. [Fulminant acute hepatitis B after infliximab treatment in Crohn's disease]. *Tunis Med* 2014; 92: 349-50. French. PubMed PMID: 25504398.

(23 year old Tunisian man with Crohn disease developed fever and fatigue 5 weeks after the 7th infusion of infliximab [ALT 70 times ULN, bilirubin and Ak P not given, prothrombin index 30%, HBsAg and IgM anti-HBc positive], with progressive liver failure, coma and death within 10 days of presentation; testing before treatment indicated that he was negative for anti-HBc suggesting acute hepatitis B rather than HBV reactivation as the cause).

Yilmaz B, Roach EC, Koklu S. Infliximab leading to autoimmune hepatitis: an increasingly recognized side effect. *Dig Dis Sci* 2014; 59: 2602-3. PubMed PMID: 25146841.

(39 year old woman with ankylosing spondylitis developed enzyme elevations after a fourth infusion of infliximab [ALT 500-600 U/L, bilirubin and Alk P not given], responding rapidly to prednisolone and azathioprine therapy; no mention of long term outcome).

Bonacini M, Ghabril M, Bonkovsky HL. Hepatotoxicity of anti-TNF agents. *Dig Dis Sci* 2014; 59: 1070-1. PubMed PMID: 24652111.

(Letter in response to Colina [2013] mentioning results from their 6 cases and literature review [Ghabril 2013]).

Carvalho J, Mendes S, Sofia C. Infliximab induced liver injury in Crohn's disease: a challenging diagnosis. *J Crohns Colitis* 2014; 8: 436-7. PubMed PMID: 24291019.

(24 year old man with Crohn disease developed liver enzyme elevations after a second infusion of infliximab [bilirubin not given, ALT 211 U/L, Alk P 388 U/L], biopsy showing chronic hepatitis and cholestasis, improving slowly after switching to adalimumab).

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]).

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).

Chalasan 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).

Shelton E, Chaudrey K, Sauk J, Khalili H, Masia R, Nguyen DD, Yajnik V, et al. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; 41: 972-9. PubMed PMID: 25756190.

(Among 1753 patients with inflammatory bowel disease receiving anti-TNF therapies between 2009 and 2013, 102 developed ALT elevations, but half could be attributed to another cause and the 48 attributed to infliximab [45 of 1170: 3%] or adalimumab [3 of 575: 0.5%], 34 patients [71%] recovering despite continuation of therapy, 4 stopping therapy and 10 switching to an alternative agent without suffering recurrence).

Kay J, Fleischmann R, Keystone E, Hsia EC, Hsu B, Mack M, Goldstein N, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. *Ann Rheum Dis* 2015; 74: 538-46. PubMed PMID: 24344160.

(Analysis of 3 year results from extension studies of 5 controlled trials of golimumab in inflammatory arthritis discusses long term adverse events of serious infections, tuberculosis, opportunistic infections, demyelination syndromes and lymphoma, but not ALT elevations, hepatotoxicity or reactivation of hepatitis B).

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-TNF α 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).

Shelton E, Chaudrey K, Sauk J, Khalili H, Masia R, Nguyen DD, Yajnik V, Ananthakrishnan AN. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; 41: 972-9. PubMed PMID: 25756190.

(Among 1753 patients with inflammatory bowel disease treated with anti-TNF agents, 102 [6%] developed ALT elevations, but half could be attributed to other causes; among 48 with suspected anti-TNF injury [45 infliximab, 3 adalimumab], 34 resolved spontaneously and were able to continue therapy, 10 switched to another agent without recurrence, 4 were treated with corticosteroids).

Cetkovska P, Lomicova I, Mukensnabl P, Kroes AC. Anti-tumour necrosis factor treatment of severe psoriasis complicated by Epstein-Barr Virus hepatitis and subsequently by chronic hepatitis. *Dermatol Ther* 2015; 28: 369-72. PubMed PMID: 26278774.

(38 year old woman with ulcerative colitis developed liver injury after 5th dose of infliximab [bilirubin 20.6 mg/dL, ALT 600 U/L, Alk P 180 U/L, ANA positive, EBV viremia], resolving with valganciclovir therapy, later tolerating adalimumab).

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).

Parra RS, Feitosa MR, Machado VF, Ramalho LN, da Rocha JJ, Feres O. Infliximab-associated fulminant hepatic failure in ulcerative colitis: a case report. *J Med Case Rep* 2015; 9: 249. PubMed PMID: 26518665.

(38 year old with ulcerative colitis developed liver injury after 5 doses of infliximab [ALT 408 U/L] with progression to liver failure requiring liver transplantatoin [bilirubin 23.4 mg/dL, ALT 2177 U/L, Alk P not given, INR 4.1], no mention of ANA or corticosteroid 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).

Chalasanani 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 [0.7%] were attributed to a tumor necrosis factor antagonist, including 3 to infliximab, 2 etanercept and 1 adalimumab, but none to certolizumab or golimumab).

Cheng FK, Bridges EE, Betteridge JD. Drug-induced liver injury from initial dose of infliximab. *Mil Med* 2015; 180: e723-4. PubMed PMID: 26032391.

(27 year old man with ulcerative colitis developed ALT elevations within days of first infusion of infliximab [ALT 213 U/L, bilirubin and Alk P not given], with rapid resolution and recurrence within days of a second infusion [ALT 474 U/L]).

Mostamand S, Schroeder S, Schenkein J, Miloh T. Infliximab associated immunomediated hepatitis in children with iInflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2016 Jan 29. [Epub ahead of print] PubMed PMID: 26835903.

(2 children, boy age 12 and girl age 15 with ulcerative colitis developed liver test abnormalities 4 to 5 months after starting infliximab [bilirubin 0.5 and not given, ALT 234 and 260 U/L, GGT not given and 117 U/L, both ANA negative], liver biopsies showing inflammation and necrosis, resolving within 1-3 months of stopping infliximab).

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]).

Parisi I, O'Beirne J, Rossi RE, Tsochatzis E, Manousou P, Theocharidou E, et al. Elevated liver enzymes in inflammatory bowel disease: the role and safety of infliximab. *Eur J Gastroenterol Hepatol* 2016; 28: 786-91. PubMed PMID: 27015138.

(In a retrospective analysis of liver test abnormalities in 305 patients with inflammatory bowel disease followed between 2008 and 2013, ALT elevations arose in 36% of patients, only slightly more commonly in those on infliximab [n=176: 39%] than on other agents [n=129: 33%], most elevations being mild and resolving spontaneously).