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Original article

# Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review

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## Abstract

**Objectives.** To identify all of the patients affected by chronic hepatitis C infection treated with TNF-α blockers (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) in order to evaluate the safety profile.

**Methods.** A systematic review of the literature from January 1990 to October 2010.

**Results.** In total, 37 publications with data on 153 patients who were treated with anti-TNF-α agents in the setting of HCV infection were found. The mean anti-TNF-α treatment duration was 11.9 months. Ninety-one patients had RA, 22 had psoriasis, 6 had Crohn's disease and 14 patients had other chronic inflammatory diseases. To date, etanercept is the biological agent that has been most extensively used in the patients with HCV infection, with only one definitely confirmed case of HCV hepatitis worsening and five suspected cases (elevation of transaminases not associated with an increase in the HCV viral load and vice versa) in 110 treated patients. Treatment with this agent resulted in stable levels of liver transaminases and a stable viral load in 74 patients, with an improvement in HCV chronic liver disease in combination with IFN–ribavirin therapy in 29 patients.

**Conclusions.** The safety profile of anti-TNF-α agents in the setting of HCV infection seems to be acceptable, even if differences in the hepatotoxic profile are apparent between different agents. In the absence of long-term and large, controlled clinical trials a definitive statement on the safety of anti-TNF-α therapies in the setting of chronic HCV infection cannot be made.

**Key words:** Hepatitis C, Psoriasis, Rheumatoid arthritis, Inflammatory bowel disease, Ankylosing spondylitis, Vasculitis, Safety, Adalimumab, Etanercept, Infliximab.

CLINICAL SCIENCE

## Introduction

HCV has been the major cause of chronic liver disease worldwide since 1989, with an estimated worldwide prevalence of 2.2% ($1.3 \times 10^9$ HCV-positive persons worldwide), and is the most common blood-borne infection in the USA [1, 2]. Geographical variations in prevalence are well known; low rates of HCV seroprevalence are found in the UK (0.01%), Germany (0.6%), Canada (0.8%), India (0.9%), France (1.1%) and Australia (1.1%) [1–3]. Higher rates have been reported in the USA [with 3.9 million (1.8%) of the population infected], Japan (1.5–2.3%), Italy (2.2%), China (3.2%) and Egypt (22%) [1–3].

HCV infection is implicated in the rising incidence of hepatocellular carcinoma (HCC) in many countries, such as Japan, Spain, France and Italy [1–4]. HCV chronic liver disease accounts for the development of 27% of cases of cirrhosis and 25% of the cases of HCC worldwide [2]. Therefore, prevention of HCV infection remains the key factor for public health intervention, without ignoring the benefits of anti-viral therapy in eradicating the virus and the benefit of avoiding hepatotoxic agents [3].

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Chronic inflammatory diseases such as RA, Crohn's disease (CD), ulcerative colitis (UC), AS, psoriasis and PsA are frequently found in the US and European populations. Considering the psoriasis prevalence of 1–3% in the USA, the estimated prevalence of both psoriasis and HCV occurring simultaneously is 0.02–0.06% in this population (~55 000–150 000 persons in the USA) [5]. For RA, the prevalence in the US population is estimated at 1% [6]. So, the prevalence of both RA and HCV occurring simultaneously is 0.02% between all age groups (~55 000 persons in the USA) [6]. Evidence of HCV infection in patients with CD has an estimated prevalence of 7.4% in Italy, 2.3% in France and 0.79% in Spain [7]. In our daily practice, we face an increasing number of patients concomitantly affected by HCV infection and chronic inflammatory diseases susceptible to be treated with TNF-α blockers.

Treatment of chronic inflammatory conditions such as IBD, RA, AS, PsA and psoriasis in the setting of chronic HCV infection can be quite difficult because many traditional therapies may aggravate hepatitis and increase viraemia [7–13]. On the other hand, anti-HCV therapy, particularly IFN-α, can aggravate or induce psoriasis, PsA, RA, polyarthropathy and IBD (even if there is a lack of definitive evidence regarding IBD) [7–13].

In the past 13 years, anti-TNF-α agents have emerged as an effective therapy for a wide spectrum of chronic inflammatory diseases. Infliximab is a recombinant human–murine chimeric immunoglobulin-G1 (IgG1) antibody that specifically binds both soluble and membrane-bound precursor forms of TNF-α [14]. Actually, infliximab is Food and Drug Administration (FDA) approved for psoriasis, PsA, RA, adult and paediatric CD, AS and UC [14]. Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa TNF receptor linked to the Fc portion of the human IgG1 [15]. Etanercept is FDA approved for RA, polyarticular-course JIA, PsA, AS and adult and paediatric psoriasis [15]. Adalimumab is a human-derived recombinant IgG1 mAb that binds to TNF-α, but not TNF-β and blocks the interaction between soluble TNF-α and cell-surface TNF receptors [16]. Adalimumab is FDA approved for RA, polyarticular-course JIA, adult CD, PsA, AS and psoriasis [16]. Golimumab is a human IgG1K mAb that binds to both the soluble and transmembrane bioactive forms of human TNF-α [17]. Golimumab is actually approved for RA, PsA and AS [17]. Certolizumab pegol is a pegylated Fab-9 fragment of a humanized anti-TNF-α antibody that binds to TNF-α, blocking the interaction with cell surface receptors [18]. Certolizumab is currently approved for RA and CD [18]. Hepatotoxicity during anti-TNF-α therapy is an uncommon side effect that can sometimes be life threatening [19]. In the post-marketing surveillance phase, FDA has reported 134 patients with liver failure associated either with infliximab or etanercept; in particular, FDA has highlighted seven patients in whom other causes of liver failure were excluded and regression of the liver failure occurred after drug suspension [19, 20]. In the current article, we present a systematic literature review that identified patients with HCV infection who were concomitantly treated with anti-TNF-α agents, in order to assess the safety of these treatments.

## Methodology

We performed a systematic search of English language databases (PubMed, Embase and Web of Science) from January 1990 until October 2010, using the following keywords and [MESH FORMS]: 'hepatitis C' and/or 'tumor necrosis factor or anti tumor necrosis factor alpha' and/or 'TNF' and/or 'etanercept' and/or 'infliximab' and/or 'adalimumab' and/or 'golimumab' and/or 'certolizumab' and/or 'psoriasis' and/or 'Crohn's disease' and/or 'rheumatoid arthritis' and/or 'psoriatic arthritis' and/or 'ulcerative colitis' and/or 'ankylosing spondylitis' and/or 'liver toxicity'. No exclusion criteria were applied.

## Results

We retrieved 37 publications describing a total of 153 patients (157 cycles of therapy) who were treated with anti-TNF-α agents in the setting of HCV infection, between the years 1999 and 2010 [21–57]. The patients were evaluated for the following variables: disease, comorbidities, HCV genotype, anti-TNF-α treatment (drug, duration and dosage), previous HCV treatment (drug, duration and dosage), concomitant treatments (drug, duration and dosage), liver enzymes (before, during and after anti-TNF-α treatment), HCV viral load (before, during and after anti-TNF-α treatment), histopathological liver reports (before, during and after anti-TNF-α treatment), complications and outcomes.

The mean anti-TNF-α treatment duration in the setting of HCV infection was 11.9 months (range: 1 dose to 60 months) [21–57]. Overall, 91 patients had RA, 7 had PsA, 8 had psoriasis, 8 had both psoriasis and PsA, 6 had CD and 14 were affected by other chronic inflammatory diseases (Table 1). The remaining 19 patients were treated concomitantly with etanercept and IFN-α–ribavirin (IFN–RBV) for HCV liver disease only [21–57]. Of the total patients, 110 were treated with etanercept, 34 with infliximab and 9 with adalimumab [21–57]. Five patients had received two different anti-TNF-α agents sequentially —infliximab and adalimumab (one patient), etanercept and adalimumab (one patient), and etanercept and infliximab (three patients) [29, 34, 37]. We were not able to find reports of patients treated with golimumab or certolizumab in the setting of HCV infection. We decided to separate patients who were affected by different inflammatory conditions in the setting of HCV infection because of the different patterns of comorbidities and hepatotoxicy and also because some subgroups are most often treated with anti-TNF-α agents as monotherapy (psoriasis and PsA), in contrast to patients with RA, IBD, AS and vasculitis, who frequently receive concomitant immunosuppressive therapy.

**Table 1** Numbers of patients treated with anti-TNF-α agents in the setting of HCV infection

| Baseline pathology in association with HCV infection | Patients treated with etanercept | Patients treated with infliximab | Patients treated with adalimumab | Patients treated with infliximab or etanercept | Mean duration of anti-TNF-α therapy | References |
|---|---|---|---|---|---|---|
| RA | 59 | 23 | 8 | 5 | 13.15 months | [22–34] |
| PsA | 6 | 1 | 1 | NA | 9.8 months | [21, 30, 35–37] |
| Psoriasis | 8 | NA | NA | NA | 12 months | [38–42, 55, 56] |
| PsA and psoriasis | 8 | NA | NA | NA | 14.5 months | [39–41, 55, 57] |
| CD | NA | 6 | NA | NA | 15.3 weeks | [46–50] |
| AS | NA | 1 | NA | NA | 13 months | [37] |
| Cryoglobulinaemia | NA | 1 | NA | NA | NA | [50] |
| Vasculitis | NA | 2 | NA | NA | 4 weeks | [51] |
| None | 19 | NA | NA | NA | 24 weeks | [52] |
| HCV-related oligo- and polyarthritis | 9 | NA | NA | NA | 3 months | [53] |
| PM | 1 | NA | NA | NA | 14 months | [30] |

NA: not available.

## Anti-TNF-α therapy for psoriasis in the setting of HCV infection

In the context of psoriatic disease (psoriasis with or without PsA), 22 patients were treated with etanercept, 1 with infliximab and 1 with adalimumab. For detailed information on these patients, see Table 2 [21, 30, 35–45, 55–57]. Regarding anti-HCV treatment, nine patients had received previous IFN or IFN–RBV [21, 35–37, 39, 43, 45, 56], and one patient was treated with IFN and allograft liver transplant [45]. Three patients with psoriasis received concomitant etanercept and IFN–RBV therapy (Table 2) [42, 55]. Other concomitant and potentially hepatotoxic therapies that were administered simultaneously during anti-TNF-α therapy are stated in Table 2.

HCV-related liver disease outcomes during and after anti-TNF-α therapy for psoriasis and PsA were not available in one patient [35]; in one patient who was previously treated with IFN–RBV the HCV viral load and levels of transaminases remained stable during and after treatment with infliximab and then adalimumab [37]. In four patients, improvements in viral load and the levels of transaminases were reported (Table 2) [36, 39, 45], and one of the patients who was concomitantly treated with etanercept and IFN–RBV had complete and sustained viral remission after 6 months of therapy (Table 2). In 17 patients who were treated with etanercept, viral load and/or the levels of transaminases were reported as stable [21, 30, 36–38, 40, 41, 43, 44] (Table 2). In one patient treated with etanercept, viral load increased more than $1 \times \log_{10}$ with stable liver enzymes levels [56].

## HCV-related liver disease outcomes after anti-TNF-α therapy for RA

In the context of RA, 61 patients were treated with etanercept, 24 with infliximab and 8 with adalimumab and in 5 patients, treatment with etanercept or infliximab was reported [22–34]. For detailed information on these patients, see Table 3. In patients with RA, HCV-related liver disease was reported to be stable (stable HCV viral load and/or stable levels of transaminases) in 83 patients, 50 of whom were treated with etanercept [23, 27–32, 34]. Of the remaining 33 patients, 5 were treated with etanercept or infliximab [24], 19 were treated with infliximab [20, 24, 28, 30, 58] and 9 received adalimumab [27, 29, 30]. An improvement in HCV viral load and/or the levels of transaminases was described in two patients with RA who were treated with etanercept [26, 31]; one of these patients was also concomitantly treated with IFN–RBV [26]. Worsening of previous levels of transaminases, without HCV viral load increase was reported in one patient under etanercept and an increase in HCV viral load was described in seven patients who were treated with anti-TNF-α agents; four of these patients were treated with etanercept [22, 32, 33] and three were treated with infliximab [32, 33]. In one patient, described by Pritchard [22], a 12-fold increase in viral load was accompanied by a 3-fold increase in the levels of transaminases, which was reversed after the suspension of etanercept treatment. Li *et al*. [34] described one patient with a 3-fold increase in transaminases and a 4-fold increase in HCV viral load after switching treatment from etanercept to infliximab. Regarding anti-HCV treatment, one patient received previous IFN therapy [31] and another patient received concomitant etanercept and IFN–RBV therapy with sustained virological remission [26] (Table 3). Other concomitant and potentially hepatotoxic therapies that were administered simultaneously during ant-TNF-α therapy are stated in Table 3.

## HCV-related liver disease outcomes after anti-TNF-α therapy for CD and other inflammatory conditions

HCV-related liver disease outcomes during and after treatment with anti-TNF-α agents for other diseases such as CD [46–50], AS [37], cryoglobulinaemia [51], vasculitis [52], HCV-related oligo- and polyarthritis [54] and

**Table 2** Anti-TNF-α therapies in the setting of psoriatic disease and HCV infection: comorbidibities, HCV genotype, previous and concomitant therapies and hepatic outcome

| Study | Disease (number of patients) and comorbidities | HCV genotype | Patients treated with infliximab (mean duration) | Patients treated with etanercept (mean duration) | Patients treated with adalimumab (mean duration) | Previous HCV therapies (number of patients) | Concomitant therapies | Hepatic outcome (number of patients) |
|---|---|---|---|---|---|---|---|---|
| Khanna *et al.* [35] | PsA (1) | NA | 0 | 1 (NA) | 0 | IFN | NA | NA |
| Magliocco *et al.* [37] | PsA (2); PsA and latent TB (1) | NA | 0 | 3 (mean: 5 months) | 0 | IFN–RBV (2); IFN (1) | None | Stable (2), decrease in HCV viral load (1) |
| Rokhsar *et al.* [43] | Psoriasis and PsA (1) | NA | 0 | 1 (12 months) | 0 | NA | MTX | Stable HCV viral load |
| De Simone *et al.* [45] | Psoriasis and PsA (2) | 1, 4 | 0 | 2 (12 months) | 0 | IFN–RBV (1) | None | Stable HCV viral load (2) |
| Aslanidis *et al.* [36] | PsA (1) | 1b | 1 switched to adalimumab (6 months) | 0 | 1 (6 months) | IFN–RBV(1), exacerbation of psoriasis | NA | Stable HCV viral load and levels of liver enzymes (1) during treatment with infliximab and adalimumab |
| Cecchi *et al.* [38] | Psoriasis (1) | 1 | 0 | 1 (12 months) | 0 | None | None | Stable liver disease |
| Linardaki *et al.* [21] | PsA, HIV infection, and haemophilia A (1) | 1b | 0 | 1 (24 months) | 0 | IFN | HAART | Stable levels of liver enzymes and HCV viral load |
| Cavazzana *et al.* [30] | PsA (1) | NA | 0 | 1 (14 months) | 0 | NA | NA | Non-statistically significant increase in HCV viral load |
| Collazo *et al.* [44] | Psoriasis and PsA (1) | NA | 0 | 1 (3 months) | 0 | Allograft liver transplant and IFN | Tacrolimus, MMF or prednisone | Decreased viral load and levels of transaminases |
| Piccolo *et al.* [39] | Psoriasis (1) | 1b | 0 | 1 (11 months) | 0 | IFN | NA | $1 \times \log_{10}$ improvement in HCV viral load and 3-fold decrease in levels of ALT |
| Alcaide *et al.* [40] | Psoriasis and Down's syndrome (1) | 1b | 0 | 1 (6 months) | 0 | None | None | Stable levels of liver enzymes and viral load |
| Prignano *et al.* [41] | Psoriasis (1) | 1 | 0 | 1 (3 months) | 0 | NA | None | Stable disease |
| Behnam *et al.* [42] | Psoriasis (1) | NA | 0 | 1 (14 months) | 0 | None | IFN–RBV | Stable levels of liver enzymes |
| Brunasso *et al.* [55] | Psoriasis (1); psoriasis and PsA (2) | 1b, 2 | 0 | 3 (mean:26.3 months) | 0 | No (3) | IFN–RBV | Stable HCV viral loads and stable levels of liver enzymes (2); complete and sustained viral remission after 6 months (1) |
| Paradisi *et al.* [57] | Psoriasis and PsA (2) | 4,1 | 0 | 2 (mean:12 months) | 0 | None | None | Stable HCV viral load, stable levels of liver enzymes and stable liver biopsy |
| Ventura *et al.* [56] | Psoriasis | 3, 1b | 0 | 2 (mean:12 months) | 0 | IFN with induction of psoriasis (1) | None | Stable HCV viral load, stable levels of liver enzymes (1 patient), $1 \times \log_{10}$ increase in HCV viral load with stable liver enzymes (1 patient) |

ALT: alanine transaminase; HAART: highly active antiretroviral therapy; TB: tuberculosis.

**Table 3** Anti-TNF-α therapies in the setting of RA and HCV infection: HCV genotype, previous and concomitant therapies and hepatic outcome

| Study | Disease (number of patients) | HCV genotype (number of patients) | Patients treated with infliximab (mean duration) | Patients treated with etanercept (mean duration) | Patients treated with adalimumab (mean duration) | Previous HCV therapies (number of patients) | Concomitant therapies (number of patients) | Hepatic outcome (number of patients) |
|---|---|---|---|---|---|---|---|---|
| Pritchard [22] | RA (1) | NA | 0 | 1 (2 months) | 0 | NA | NA | 12-fold increase in liver transaminases and 3-fold increase in HCV viraemia, with improvement after etanercept suspension |
| Peterson *et al*. [23] | RA (24) | NA | 3 (mean: 9 months) | 21 (mean: 9 months) | 0 | NA | NSAIDa (17), MTX (3), HCQ + MTX (1) | Stable HCV viral loads and liver enzymes |
| Parke *et al*. [24] | RA (5) | 1b, 1a, 3e, NA (2) | 5 pt with infliximab and or etanercept (mean: 22.2 months) | 5 pt with Infliximab and or etanercept (mean: 22.2 months) | 0 | None | NA | No elevation of amino-transferases, decresaed HCV viral load (1) |
| Oniankitan *et al*. [25] | RA (1) | 1b | 1 (14 weeks) | 0 | 0 | NA | No | Unchanged liver enzymes, viral load and histological damage |
| Niewold *et al*. [26] | RA (1) | NA | 0 | 1 (15 months) | 0 | None | IFN–RBV (1) | Sustained HCV virological response (remission after 12 months) |
| Belisai *et al*. [27] | RA (1), RA + mixed crzoglubuli-naemia (1) | 3a, 2c | 0 | 1 (etanercept + CyA, 12 months) | 1 (adalimumab + CyA, 16 months) | No | CyA (2), CyA + CSs (1) | Stable liver disease (2) |
| Vauloup *et al*. [28] | RA (6) | NA | 5 (mean: 14 weeks) | 1 (14 weeks) | 0 | NA | MTX (6) | Stable liver enzymes and stable HCV viral load |
| Roux *et al*. [29] | RA (3) | NA | 0 | 3 (mean: 20.33 months, 1 patient switch to adalimumab) | 1 (3 months) | NA | MTX (2) | Stable liver enzymes and stable HCV viral load |
| Cavazzana *et al*. [30] | RA (4) | NA | 0 | 4 (14 months) | 0 | NA | HCQ (3), SSZ (1), CSs (3) | Non-statistically significant increase in HCV viral load |

(continued)

**Table 3** Continued

| Study | Disease (number of patients) | HCV genotype (number of patients) | Patients treated with infliximab (mean duration) | Patients treated with etanercept (mean duration) | Patients treated with adalimumab (mean duration) | Previous HCV therapies (number of patients) | Concomitant therapies (number of patients) | Hepatic outcome (number of patients) |
|---|---|---|---|---|---|---|---|---|
| Cansu *et al*. [31] | RA + HCV (3), RA + HCV + HBV (1) | NA | 0 | 4 (mean: 19,75 months) | 0 | 1 (IFN–RBV) | SSZ (1)<br>MTX (1)<br>MTX, SSZ, HCQ (1) | HCV viral load increased (2)<br>HCV viral load decreased (1)<br>HCV viral load stable (1) |
| Ferri *et al*. [32] | RA (31) | NA | 11 (mean: 20 months) | 17 (mean: 20 months) | 3 (mean: 20 months) | None | Prednisone or methylprednisolone (31), MTX (1) | Stable liver enzymes (30), elevated liver enzymes (1 under etanercept)<br>Stable or decreased HCV viral load (28)<br>Increased HCV viral load (2 patients under infliximab and 1 under etanercept) |
| Kaur *et al*. [33] | RA (1) | 1b | 0 | 1 (2 months) | 0 | NA | NA | Increased HCV viral load with stable liver enzymes |
| Li *et al*. [34] | RA (8) | N/A | 3 (mean: 19 months, 2 patients switched to etanercept) | 5 (mean: 19 months, 1 patient switched to infliximab) | 3 (mean: 19 months) | NA | HCQ (3), SSZ (4), MTX (2), none (2) | Stable liver enzymes (7 pt), stable HCV viral load (3), HCV viral load evolution NA (4), increased liver enzymes and HCV viral load (1) after switched etanercept to infliximab |

ALT: alanine transaminase; HAART: highly active antiretroviral therapy; NA: not available; CyA = ciclosporin A.

PM [30] were reported in 20 patients (10 received etanercept and 10 received infliximab). For detailed information on these patients, see Tables 4 and 5. Of these patients, HCV-related liver disease was reported as stable (stable HCV viral load and/or stable levels of transaminases) in 12 patients (two patients were treated with infliximab [47, 48] and 10 patients were treated with etanercept [30, 54]), improved in four patients who were treated with infliximab [46, 48, 50] (including one patient who received concomitant IFN–RBV plus infliximab, who achieved sustained viral remission after 1 year [50]), and was not assessed in one patient who was treated with infliximab [51]. The remaining three patients died, one due to disseminated aspergillosis [49] and two due to severe vasculitis [52], all during infliximab therapy.

Regarding anti-HCV treatment, three patients had received previous IFN therapy or IFN–RBV therapy in the setting of CD and 12 patients in the setting of other chronic inflammatory diseases [36, 46, 49–52, 54] (Tables 4 and 5). Other concomitant and potentially hepatotoxic therapies that were administered simultaneously during ant-TNF-α therapy are stated in Tables 4 and 5.

Zein *et al*. [53] conducted a double-blind, randomized, placebo-controlled trial involving 50 patients who were chronically infected with HCV; the patients received either placebo and IFN–RBV therapy ($n = 25$) or etanercept and IFN–RBV therapy ($n = 19$) for 24 weeks. At Week 24, 63% ($n = 12$) of patients receiving etanercept had negative HCV viral loads compared with 32% ($n = 8$) of the placebo arm ($P = 0.04$) [53]. At Week 72, 42% ($n = 8$) of patients receiving etanercept had a sustained virological and biochemical response compared with 32% ($n = 8$) of patients receiving placebo. The latter difference did not reach statistical significance, but the trial additionally demonstrated that etanercept was not associated with serious toxic effects in HCV-infected patients [53].

Worsening of the HCV vial load and/or elevation of liver enzyme levels and/or histological demonstration of hepatic worsening between the different diseases studied (psoriasis, RA, CD and other chronic inflammatory conditions) was 8.8% (three patients under infliximab and five patients under etanercept) between patients affected by RA and 4.2% (one patient under etanercept) between patients affected by psoriatic disease (psoriasis and/or PsA) ($P = 1.0$, Fisher's exact test). No alterations were reported in patients suffering from CD or other inflammatory conditions (20 patients).

## Discussion

The treatment of severe, chronic inflammatory conditions in the setting of HCV infection remains a difficult therapeutic challenge because of the risk that treatment of the inflammatory condition could aggravate hepatitis and increase viraemia. On the other hand, anti-HCV therapy such as IFN-α can aggravate the underlying disease [9–12]. Aggressive immunosuppression frequently leads to an increase in the levels of HCV viral load and worsening of liver conditions in transplant patients [4]. Many therapies, including MTX and acitretin, have the potential to induce hepatotoxicity [23, 24], meaning that we often face difficult-to-treat patients who require systemic treatments in the setting of chronic HCV infection and TNF-α-blocking agents might represent a valid option for treatment in these patients.

TNF-α is produced by hepatocytes in patients who are chronically infected with HCV and may play a role in regulating viral replication or hepatocyte damage [4, 59–62]. Increased titres of TNF-α have been associated with high levels of transaminases in patients with chronic HCV infection [4]. An imbalance in the numbers of circulating Th1 and Th2 lymphocytes has been implicated in the progression of infection in HCV-infected patients [4]. In patients in whom the acute response to HCV infection is mediated by Th1 lymphocytes, with the predominant production of IFN-γ, the self-limited response against the infection appears to be optimal; in contrast, patients whose response is primarily mediated by a Th2 response become chronically infected [4, 59]. Patients with high titres of TNF-α before treatment with IFN-α respond to a lesser extent than those who have low titres of TNF-α [4, 59].

TNF-α appears to be implicated in a patient's biological resistance to anti-HCV therapy, as demonstrated by Tsai *et al*. [59]. Treatment with IFN increases secretion of the soluble portion of the TNF-α receptor (sTNF-R p55) that naturally inhibits serum TNF-α [59]. It seems that the inhibitory effect of TNF-α on T-cell proliferation and activation is the key factor for resistance to IFN-α therapy. Blockade of TNF may also stimulate the reactivity of peripheral T cells to specific antigens, for example microbial antigens, and increase the anti-HCV effect of IFN-α [4, 59–62].

To date, the vast majority of the literature that supports the use of TNF-α-blocking agents in patients who are chronically infected with HCV comes from case reports and case series (level of evidence 3); only one Phase II, randomized, controlled trial (level of evidence 2 or more) has been published regarding the safety of anti-TNF-α therapies in patients with chronic HCV infection [21–57]. It is worth noting that, to date, controlled clinical trials evaluating the use of anti-TNF-α therapies in conditions as diverse as RA and psoriasis have excluded patients with chronic HCV infection from participation.

The safety profile of anti-TNF-α agents in the setting of HCV infection appears to be acceptable, considering that only two cases of confirmed or probable HCV liver disease worsening among 153 patients treated with anti-TNF-α agents for a mean of 11.9 months, have been reported until now. One case of confirmed HCV liver disease worsening (with hepatic improvement after withdrawal of etanercept) among 110 patients treated with etanercept and one probable case among 34 patients treated with infliximab (case not confirmed by liver biopsy or by suspension of infliximab and improvement of the HCV viral load and transaminases levels) can be found in the literature. In the other five patients, increases in the levels of transaminases did not correspond to increased viral loads and vice versa and liver biopsies were not executed [32, 33, 56]. As shown here, most of

**Table 4** Anti-TNF-α therapies in the setting of CD and HCV infection: HCV genotype, previous and concomitant therapies and hepatic outcome

| Study | Disease (number of patients) | HCV genotype | Patients treated with infliximab (mean duration) | Patients treated with etanercept (mean duration) | Patients treated with adalimumab (mean duration) | Previous HCV therapies | Concomitant therapies (number of patients) | Hepatic outcome (number of patients) |
|---|---|---|---|---|---|---|---|---|
| Campbell *et al*. [46] | CD (1) | NA | 1 (1 dose) | 0 | 0 | IFN | NA | Improvement in HCV viral load and liver enzymes (1) |
| Biancone *et al*. [47] | CD (1) | NA | 1 (6 weeks) | 0 | 0 | NA | NA | Stable levels of liver disease (1) |
| Holtman *et al*. [48] | CD (2) | 1b, 1 | 2 (mean: 3 months) | 0 | 0 | NA | Prednisone, AZA (1) | Improvement in HCV viral load and stable liver enymes (2) |
| Alderson *et al*. [49] | CD (1) | NA | 1 (1 dose) | 0 | 0 | IFN–RBV | Methyprednisolone, AZA | Dead due to disseminated aspergillosis (1) |
| Abdelmalek *et al*. [50] | CD (1) | 1 | 1 (12 months) | 0 | 0 | IFN–RBV | IFN–RBV | Sustained HCV viral remission after 48 weeks (1) |

NA: not available.

**Table 5** Anti-TNF-α therapies in the setting of other chronic inflammatory diseases (autoimmune diseases) and HCV infection: HCV genotype, previous and concomitant therapies and hepatic outcome

| Study | Disease (number of patients) | HCV genotype (number of patients | Patients treated with infliximab (mean duration) | Patients treated with etanercept (mean duration) | Patients treated with adalimumab (mean duration) | Previous HCV therapies (number of patients) | Concomitant therapies | Hepatic outcome |
|---|---|---|---|---|---|---|---|---|
| Bartolucci *et al*. [51] | Mixed HCV associated cryoglobuli-naemia (1) | NA | 1 (NA) | 0 | 0 | IFN | CSs | No improvement in mixed cryoglo-bulinaemia, liver assays NA |
| Chandesris *et al*. [52] | Vasculitis (2) | 1a, 1 | 2 (mean: 4 weeks) | 0 | 0 | IFN–RBV (1) | None | Two deaths due to HCV-related severe vasculitis |
| Aslanidis *et al*. [36] | AS (1) | 3a | 1 (13 months) | 0 | 0 | IFN–RBV (1), induction of AS | NA | Stable HCV viral load and liver enzymes |
| Marotte *et al*. [54] | Oligo- and polyarthritis associated with HCV (9) | 1 (7), 2 (1), NA (1) | 0 | 9 (mean: 3 months) | 0 | IFN- RBV (5), IFN (1), none (3) | None | Stable level enzymes and HCV viral load |
| Cavazzana *et al*. [30] | PM (1) | NA | 0 | 1 (14 months) | 0 | NA | NA | Non-statistical sig-nificant increase in HCV viral load |

NA: not available.

the safety data are available from patients who have been treated with etanercept. Zein *et al*. [53] demonstrated that etanercept was not associated with serious toxic effects in patients treated with etanercept and INF–RBV compared with IFN–RBV plus placebo.

Infliximab therapy in the setting of HCV has been reported in 34 patients, with stable liver outcomes cited in 21 patients, improvement in HCV liver conditions in three patients, and complete and sustained viral remission after combination treatment with infliximab and IFN–RBV in one patient [50]. A fatal outcome was reported due to disseminated aspergillosis in one patient, probably related to immunosuppression, and due to severe HCV-related vasculitis in two patients in whom infliximab was not effective in controlling the systemic inflammatory disease [50, 52].

The frequency of liver HCV condition alteration (worsening of the HCV vial load and/or elevation of liver enzyme levels and/or histological demonstration of hepatic worsening) between the different diseases studied (psoriatic disease, RA, CD and other chronic inflammatory conditions), was 8.8% among patients affected by RA and 4.2% among patients affected by psoriatic disease. No alterations were reported in patients suffering from CD or other inflammatory conditions. The difference in the frequency of liver alterations did not reach statistical significance ($P = 1.0$) and can only be a bias related to the small number of patients treated with other diseases different from RA (91 patients with RA *vs* 62 with other different disease), but could also be related to chronic co-medications frequently received by RA patients (MTX, CSs, NSAIDS and AZA) or to a different pattern of hepatic susceptibility. Regarding the susceptibility to hepatic toxicity, RA patients in comparison with psoriasis patients seem to have at least the same or a better tolerability profile to treatment with MTX and a recent study demonstrated that type of disease (RA *vs* psoriasis) had no influence on susceptibility to liver damage [63, 64]. The experience with adalimumab in the setting of HCV infection is restricted to reports of nine patients. All of the studies found a stable level of transaminases and HCV viral loads during treatment [27, 29, 32, 34, 37].

It must be noted that, in 2004, a warning was added to the package insert of infliximab stating that 'severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis, have been reported in postmarketing data in patients receiving [infliximab]. Autoimmune hepatitis has been diagnosed in some of these cases. Some of these cases were fatal or necessitated liver transplantation' [19]. No such FDA warnings of hepatotoxicity have been issued regarding the use of adalimumab, etanercept, golimumab or certolizumab. Of four patients who have been affected by toxic hepatitis induced by infliximab, the absence of cross-toxicity with etanercept has been reported in three patients and the absence of such reactivity after switching to adalimumab has also been reported in one case [65–68]. Interestingly, no hepatoxicity-related events were associated with pre-existing viral hepatitis.

In the absence of long-term, large, controlled clinical trials, a definitive statement regarding the safety of anti-TNF-$\alpha$ therapies in the setting of chronic HCV infection cannot be made [19, 22–57]. A consensus statement of 2008 regarding the use of anti-TNF-$\alpha$ therapies for the treatment of rheumatic diseases in the setting of HCV infection, recommends screening of all patients before TNF-$\alpha$-blocking agent initiation, because the long-term safety of these agents in patients with chronic HCV infection is unknown [69]. But the consensus statement does not provide a clear indication for the use of anti-TNF-$\alpha$ therapies in the setting of chronic HCV infection, nor a clear contraindication and in daily clinical practice physicians continue to use these therapies without a standardized follow-up schedule.

At present, etanercept is the biological agent that has been most frequently used in the clinical setting in patients with a chronic HCV infection. A possible explanation for the use of different biological treatments in the setting of HCV infection may be the different hepatotoxicity profiles (as reported by the FDA) of each agent, the different patterns of clinical use and the fact that more literature supports the use of etanercept in the setting of HCV infection [19].

For prognostic purposes, the liver biopsy is the only reliable method to obtain information regarding fibrosis stage in routine clinical practice [70]. HCV-RNA quantification is useful to monitor virological responses to anti-viral therapy [70]. Normal fluctuations in HCV-RNA load have been reported, with $<1$ log variations when levels are monitored at monthly intervals and with a maximum of three peaks of HCV-RNA increase (defined as $>50\%$ increase) with a median change of 1 log [71]. Aminotransferase and HCV RNA fluctuations are regularly asynchronous and liver histology does not show significant correlation with the replication activity of the virus [71]. Pre-treatment screening for HCV infection should be performed in all candidates for anti-TNF-$\alpha$ therapy, as already proposed by national guidelines from the USA and UK [72, 73]. Consultation with a liver specialist may be appropriate before starting anti-TNF-$\alpha$ therapy [73]. Monitoring of patients eligible for anti-TNF-$\alpha$ therapy in the setting of a chronic HCV infection should be made with pre-treatment liver biopsy, monthly aminotransferase levels and periodic quantitative HCV RNA [70, 71]. A liver biopsy is indicated in cases of sustained increase of aminotransferase levels and HCV viral load ($>1$ log) in order to better quantify any liver damage [70, 71].

HCV chronic hepatitis is a major risk factor for cirrhosis and HCC, and immunosuppression may accelerate this progression. Long-term treatment with anti-TNF-$\alpha$ therapies and long-term evaluation of patient outcomes has not yet been performed with significant numbers of patients who have chronic HCV infections; thus, careful and well-followed schedules should be proposed for patients with HCV infection who require systemic therapy with these agents. Long-term, prospective trials are needed in order to quantify the safety of anti-TNF-$\alpha$ therapies in the setting of chronic HCV infection.

**Rheumatology key messages**

- The safety profile of TNF-α blockers in the setting of HCV seems to be acceptable.
- Differences in the hepatotoxic profile are apparent between different agents.
- TNF-α may play a role in regulating viral replication or hepatocyte damage.

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## References


1 Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558–67.

2 Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13:2436–41.

3 Armstrong GL, Wasley A, Simard EP *et al*. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–14.

4 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:ii18–24.

5 Huerta C, Rivero E, Rodríguez LA. Incidence and risk factors for psoriasis in the general population. Arch Dermatol 2007;143:1559–65.

6 Lawrence RC, Hochberg MC, Kelsey JL *et al*. Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. J Rheumatol 1989;16:427–41.

7 Hou JK, Velayos F, Terrault N, Mahadevan U. Viral hepatitis and inflammatory bowel disease. Inflamm Bowel Dis 2010;16:925–32.

8 Ioannou Y, Isenberg DA. Current evidence for the induction of autoimmune rheumatic manifestations by cytokine therapy. Arthritis Rheum 2000;43:1431–42.

9 Ketikoglou I, Karatapanis S, Elefsiniotis I *et al*. Extensive psoriasis induced by pegylated interferon alpha-2b treatment for chronic hepatitis B. Eur J Dermatol 2005;15:107–9.

10 Kartal ED, Colak H, Ozgunes I *et al*. Exacerbation of psoriasis due to peginterferon alpha-2b plus ribavirin treatment of chronic active hepatitis C. Chemotherapy 2005;5:167–9.

11 Citro V, Fristachi R, Tarantino G. Extensive psoriasis induced by pegylated interferon: a case report. J Med Case Reports 2007;17:86.

12 Yurci A, Guven K, Torun E *et al*. Pyoderma gangrenosum and exacerbation of psoriasis resulting from pegylated interferon alpha and ribavirin treatment of chronic hepatitis C. Eur J Gastroenterol Hepatol 2007;19:811–5.

13 Galeazzi M, Bellisai F, Manganelli S *et al*. Cyclosporine A for the treatment of autoimmune disorders in HCV infected patients. Autoimmun Rev 2006;5:493–8.

14 United States FDA. Safety alerts for drugs, biologics medical devices, and dietary supplements. Remicade (infliximab). Washington DC: FDA, 2004. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107702.pdf (29 June 2010, date last accessed).

15 United States FDA. Safety alerts for drugs, biologics medical devices, and dietary supplements. Enbrel (etanercept). Washington DC: FDA, 2004. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/103795_S5109_ENBREL.pdf. (29 June 2010, date last accessed).

16 United States FDA. Safety alerts for drugs, biologics medical devices, and dietary supplements. Humira (adalimumab). Washington DC: FDA, 2004. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125057s110_SumR.pdf (29 June 2010, date last accessed).

17 United States FDA. Safety alerts for drugs, biologics medical devices, and dietary supplements. Golimumab (Simponi). Washington DC: FDA, 2008. http://www.drugs.com/newdrugs/simponi-golimumab-receives-fda-approval-first-once-monthly-anti-tnf-rheumatoid-arthritis-psoriatic-1329.html (18 January 2011, date last accessed).

18 United States FDA. Safety alerts for drugs, biologics medical devices, and dietary supplements. Certolizumab (Cimzia). http://www.medpagetoday.com/Geriatrics/Arthritis/14210. Washington DC: FDA, 2009.

19 United States FDA. Safety alerts for drugs, biologics medical devices, and dietary supplements. Remicade (infliximab). Washington DC: FDA, 2004. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166901.htm (29 June 2010, date last accessed).

20 Mancini S, Amorotti E, Vecchio S *et al*. Infliximab-related hepatitis: discussion of a case and review of the literature. Intern Emerg Med 2010;5:193–200.

21 Linardaki G, Katsarou O, Ioannidou P *et al*. Effective etanercept treatment for psoriatic arthritis complicating concomitant human immunodeficiency virus and hepatitis C virus infection. J Rheumatol 2007;34:1353–5.

22 Pritchard C. Etanercept and hepatitis C. J Clin Rheumatol 1999;5:179.

23 Peterson JR, Hsu FC, Simkin PA *et al*. 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.

24 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.

25 Oniankitan O, Duvoux C, Challine D *et al*. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. J Rheumatol 2004;31:107–9.

26 Niewold TB, Gibofsky A. Concomitant interferon-alpha therapy and tumor necrosis factor alpha inhibition for rheumatoid arthritis and hepatitis C. Arthritis Rheum 2006;54:2335–7.

27 Bellisai F, Giannitti C, Donvito A *et al*. Combination therapy with cyclosporine A and anti-TNF-alpha agents in the treatment of rheumatoid arthritis and concomitant hepatitis C virus infection. Clin Rheumatol 2007;26:1127–9.

28 Vauloup C, Krzysiek R, Greangeot-Keros L *et al*. Effects of tumor necrosis factor antagonist treatment on hepatitis C-related immunological abnormalities. Eur Cytokine Netw 2006;17:290–3.

29 Roux CH, Brocq O, Breuil V *et al*. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology 2006;45:1294–7.

30 Cavazzana I, Ceribelli A, Cattaneo R *et al*. Treatment with etanercept in six patients with chronic hepatitis C infection and systemic autoimmune diseases. Autoimmun Rev 2008;8:104–6.

31 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.

32 Ferri C, Ferraccioli G, Ferrari D *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.

33 Kaur PP, Chan VC, Berney SN. Histological evaluation of liver in two rheumatoid arthritis patients with chronic hepatitis B and C treated with TNF-alpha blockade: case reports. Clin Rheumatol 2008;27:1069–71.

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

35 Khanna MA, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. J Dermatolog Treat 2003;14:229–32.

36 Aslanidis S, Vassiliadis T, Pyrpasopoulou A *et al*. Inhibition of TNFalpha does not induce viral reactivation in patients with chronic hepatitis C infection: two cases. Clin Rheumatol 2007;26:261–4.

37 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.

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

39 Piccolo D, Di Cesare A, Fargnoli MC *et al*. Effective control of psoriasis by etanercept in a patient with HCV-related diseases. Eur J Dermatol 2008;18:459–60.

40 Alcaide AJ, Barrera MV, Habicheyn S *et al*. Safety of etanercept therapy in a patient with psoriasis, Down's syndrome and concomitant hepatitis C virus infection. J Eur Acad Dermatol Venereol 2008;22:1514–16.

41 Prignano F, Zanieri F, Milani S *et al*. Switch from etanercept to efalizumab in a psoriatic patient with HCV infection: a case report. Dermatol Ther 2009;22:386–90.

42 Behnam SE, Hindiyeh R, Fife DJ *et al*. Etanercept as prophylactic psoriatic therapy before interferon-alpha and ribavirin treatment for active hepatitis C infection. Clin Exp Dermatol 2010;35:397–8.

43 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.

44 Collazo MH, Gonzàlez 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.

45 De Simone C, Paradisi A, Capizzi R *et al*. Etanercept therapy in two patients with psoriasis and concomitant hepatitis C. J Am Acad Dermatol 2006;54:1102–4.

46 Campbell S, Ghosh S. Infliximab treatment for Crohn's disease in the presence of chronic hepatitis C infection. Eur J Gastroenterol Hepatol 2001;13:191–2.

47 Biancone L, Del Vecchio Blanco G *et al*. Immunomodulatory drugs in Crohn's disease patients with hepatitis B or C virus infection. Gastroenterology 2002; 122:593–4.

48 Holtmann MH, Galle PR, Neurath MF. Treatment of patients with Crohn's disease and concomitant chronic hepatitis C with a chimeric monoclonal antibody to TNF. Am J Gastroenterol 2003;98:504–5.

49 Alderson JW, Van Dinter TG Jr, Opatowsky MJ *et al*. Disseminated aspergillosis following infliximab therapy in an immunosuppressed patient with Crohn's disease and chronic hepatitis C: a case study and review of the literature. Med Gen Med 2005;7:7.

50 Abdelmalek MF, Liu C, Valentine JF. Successful treatment of chronic hepatitis C with pegylated interferon, ribavirin, and infliximab in a patient with Crohn's disease. Am J Gastroenterol 2007;102:1333–4.

51 Bartolucci P, Ramanoelina J, Cohen P *et al*. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology 2002;41:1126–32.

52 Chandesris MO, Gayet S, Schleinitz N *et al*. Infliximab in the treatment of refractory vasculitis secondary to hepatitis C-associated mixed cryoglobulinaemia. Rheumatology 2004;43:532–3.

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

54 Marotte H, Fontanges E, Bailly F *et al*. Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus. Rheumatology 2007;46:97–99.

55 Brunasso AM, Delfino C, Gulia A *et al*. Safety of anti-tumor necrosis factor agents in patients with chronic hepatitis C infection. Adv Psor Inflamm Skin Dis 2010;2:17–24.

56 Ventura F, Gomes J, Duarte MD *et al*. Efficacy and safety of etanercept in patients with psoriasis and hepatitis C. Eur J Dermatol 2010;20:808–9.

57 Paradisi A, Caldarola G, Capizzi R *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.

58 Haennig A, Bonnet D, Thebault S *et al*. Infliximab-induced acute hepatitis during Crohn's disease therapy: absence of cross-toxicity with adalimumab. Gastroenterol Clin Biol 2010;34:e7–8.

59 Tsai SL, Liaw YF, Chen MH *et al*. Detection of type 2-like T-helper cells in hepatitis C virus infection: implications for hepatitis C virus chronicity. Hepatology 1997;25: 449–58.

60 Berg L, Lampa J, Rogberg S *et al*. Increased peripheral T cell reactivity to microbial antigens and collagen type II in rheumatoid arthritis after treatment with soluble TNF-alpha receptors. Ann Rheum Dis 2001;60:133–9.

61 Arase Y, Ikeda K, Chayama K *et al*. Fluctuation patterns of HCV-RNA serum level in patients with chronic hepatitis C. J Gastroenterol 2000;35:221–5.

62 Gonzalez-Amaro R, Garcia-Monzon C, Garcia-Buey L *et al*. Induction of tumor necrosis factor alpha production by human hepatocytes in chronic viral hepatitis. J Exp Med 1994;179:841–8.

63 Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. Clin Drug Investig 2006;26:55–62.

64 Amital H, Arnson Y, Chodick G *et al*. Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology 2009; 48:1107–10.

65 Kluger N, Girard C, Guillot B *et al*. Efficiency and safety of etanercept after acute hepatitis induced by infliximab for psoriasis. Acta Derm Venereol 2009;89:332–4.

66 Thiéfin G, Morelet A, Heurgué A *et al*. Infliximab-induced hepatitis: absence of cross-toxicity with etanercept. Joint Bone Spine 2008;75:737–9.

67 García Aparicio AM, Rey JR, Sanz AH *et al*. Successful treatment with etanercept in a patient with hepatotoxicity closely related to infliximab. Clin Rheumatol 2007;26: 811–13.

68 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.

69 Furst DE, Keystone EC, Kirkham B *et al*. Updated consensus statement on biological agents for the treatment of rheumatic diseases 2008. Ann Rheum Dis 2008;67:iii2–25.

70 Ghany MG, Strader DB, Thomas DL *et al*. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–74.

71 Pontisso P, Bellati G, Brunetto M *et al*. Hepatitis C virus RNA profiles in chronically infected individuals: do they relate to disease activity? Hepatology 1999;29: 585–9.

72 Menter A, Gottlieb A, Feldman SR *et al*. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826–50.

73 Smith CH, Anstey AV, Barker JN *et al*. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol 2009;161:987–1019.