

Reactivation of Hepatitis B Virus Infection Associated with Anti-Tumor Necrosis Factor- α Therapy

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Abstract

The use of TNF- α inhibitors, nowadays widely employed as first choice drugs for the therapy of chronic inflammatory diseases such as Rheumatoid Arthritis (RA), Psoriatic Arthritis (PA), and Inflammatory Bowel Diseases (IBD), may be associated to reactivation of HBV infection. In this review we summarized the case reports/series and prospective/retrospective studies focusing on this topic, and analyzed the guidelines of the major scientific societies dealing with this problem. Reactivation may occur mainly in HBV inactive carriers positive for HBsAg; the likelihood of reactivation is lower in HBsAg positive subjects with low DNA level (<2000 UI/L) and rare in HBsAg negative patients. Anti-TNF- α candidate patients should be screened for HBV serum markers. On the basis of HBV serology, it is possible to suggest different therapeutic strategies. In patients with chronic hepatitis B infection it is necessary to start an appropriated antiviral therapy and adequate follow-up. Inactive HBsAg carriers must be treated with HBV prophylactic agents. Patients with resolved hepatitis B should be tightly monitored for elevation of liver enzymes and HBV DNA levels. All HBV negative patients should receive vaccination before starting anti-TNF- α treatment.

Keywords: Tumor Necrosis Factor- α (TNF- α); Hepatitis B Virus (HBV); HBV prophylaxis; HBV reactivation; Anti-TNF- α ; Infliximab (INF); Etanercept (ETA); Adalimumab (ADA); Golimumab (GOL); Certolizumab (CZ)

Introduction

The discovery and subsequent introduction into clinical practice of tumor necrosis factor alpha (TNF- α) blockers in the late 90s' of the past century verged on a "Copernican Revolution" in comparison with the canonical therapeutic strategy of chronic inflammatory systemic diseases such as Rheumatoid Arthritis (RA), Psoriatic Arthritis (PA), Ankylosing Spondylitis (AS) and Inflammatory Bowel Diseases (IBD) and related disorders. The natural course of these diseases and the lives of affected individuals were dramatically improved by these biological drugs. However, since their initial clinical applications, reactivation of latent infections as severe as tuberculosis and hepatitis B was observed in some patients, as a consequence of the systemic immunosuppressive effects (suppressed cell-mediated immunity plus cytokine unbalance between TNF- α and interferon- γ) of TNF- α blockers.

HBV Biology

Hepatitis B Virus (HBV) is a member of Hepadnaviridae (hepatotropic DNA virus) family. Hepadnaviruses have a strong preference for infecting liver cells, but small amounts of hepadnaviral DNA can be found in kidney, pancreas, and mononuclear cells. HBV virions are double-shelled particles, 40 to 42 nm in diameter with an outer lipoprotein envelope that contains three related envelope glycoproteins (or surface antigens). Within the envelope is the viral nucleocapsid, or core. The core contains the viral genome, a relaxed-circular, partially duplex DNA of 3.2 kb, and a polymerase that is responsible for the synthesis of viral DNA in infected cells. DNA sequencing of many isolates of HBV has confirmed the existence of multiple viral genotypes, each with a characteristic geographic distribution [1]. It is classified in 10 different genotypes (A-J). After viral transmission-either perinatal, sexual or percutaneous-the virus enters hepatocytes and its DNA is converted to the covalently closed circular form (cccDNA) in the nucleus of these cells [2,3]. This form of DNA, which serves as the transcriptional template for a number of different viral mRNAs coding for HBV proteins [hepatitis B core

antigen (HBcAg), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), DNA polymerase, HBV X protein (HBx)] has the ability to persist in infected hepatocytes for long periods of time, even after viral clearance (spontaneous or treatment-induced). This persisting hepatic reservoir of HBV DNA is responsible for the viral reactivation during immunosuppressive therapy that occurs in a small proportion of patients with past or resolved HBV infection.

HBV and the Immune System

In adults infected with HBV, following a short period (lasting weeks) when the virus remains hidden from the host immune system, strong innate (involving natural killer (NK) and natural killer T (NKT) cells) and adaptive (mainly through CD8⁺ T cells) immune responses are mounted against infected hepatocytes expressing HBV antigens. Non-cytolytic and cytolytic immune-mediated mechanisms of viral clearance are engaged in this process, including the action of different cytokines such as interferons (IFN- α , IFN- β and IFN- γ), TNF and IL-6. In the majority (>95%) of adults infected with HBV, host immune responses are able to eradicate the virus [4-6]. On initial hepatocyte infection, viral replication leads to the production of various proteins. These foreign proteins undergo intracellular processing and are presented by the HLA class I pathway. Cytotoxic (CD8 α) T lymphocytes bind to the HLA class I complex and with appropriate co-stimulation initiate a robust immune response to the virus [7]. Intrahepatic HBV-specific CD8 T cells are required for rapid viral clearance during acute HBV infection. In addition, other

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reports suggest the existence of dual antiviral functions that overlap temporally during natural acute HBV infection: a primarily non-cytolytic CD8-dependent mechanism that may be mediated by the secretion of cytokines and a primarily cytolytic mechanism that clears the remaining infected cells [8]. These responses involve both major-histocompatibility-complex (MHC) class II-restricted, CD4⁺ helper T cells and MHC class I-restricted, CD8⁺ cytotoxic T lymphocytes. The mechanisms by which cytotoxic T lymphocytes kill liver cells and cause viral clearance have been incisively investigated in transgenic mice that express viral antigens or contain replication competent viral genomes in the liver. It is striking that, in this model, the number of hepatocytes killed by direct engagement between cytotoxic T lymphocytes and their targets is very small and clearly insufficient to account for most of the liver damage. This suggests that much of the injury is due to secondary antigen-nonspecific inflammatory responses that are set in motion by the response of the cytotoxic T lymphocytes [1]. Selected inflammatory cytokines, potentially derived from the HBV-specific T cells and the inflammatory cells that they recruit, might contribute to viral clearance and/or disease pathogenesis by modulating hepatocellular HBV gene expression during naturally acquired infection [9]. A vigorous, multispecific CD4 and CD8 response is associated with viral clearance. In individuals with chronic hepatitis B infection, the HBV specific CD4 and CD8 response is insufficient; and can cause a persistent inflammatory response that is ineffective for hepatitis B virus clearance [10]. Although non-cytolytic inhibition of HBV replication by CD8⁺ T cell-derived antiviral cytokines is sufficient to prevent the production of new virus particles and, therefore, viral spread, complete viral clearance from the liver requires elimination of the cccDNA nuclear episome that serves as the transcriptional template of the virus in infected cells. The immunological response reduces the pool of cccDNA molecules non-cytolytically, probably by eliminating their circular DNA precursors and perhaps by destabilizing them. The second step enhances this process by destroying infected hepatocytes and triggering their turnover. However, despite this multipronged response, traces of cccDNA persist indefinitely in the liver, likely providing a continuous antigenic stimulus that confers lifelong immunity [11].

TNF- α

This cytokine exists in: i. a membrane-bound form that participates in cell-to-cell interactions, activating other effector cells such as neutrophils or macrophages involved in an immune response and also may play a role with its receptor to down-regulate an immune response after a pathogen has been cleared [12]; ii. a soluble form that increases the expression of adhesion molecules, stimulates the release of other cytokines like interleukin-1 (IL-1) and interleukin-6 (IL-6), and can induce apoptosis [13,14]. The physiologic effects of TNF- α are exerted through two receptors (TNFR), TNFR-p⁵⁵ (CD120a) and TNFR-p⁷⁵ (CD120b) [15]. Both receptors are expressed on the membrane of most cells, giving TNF- α diverse biologic effect [14]. As with TNF- α , the two TNFR exist in two forms, i. a membrane-bound receptor, that upon binding activates nuclear factor- κ B (NF κ B), triggering the release of inflammatory cytokines [16]; ii. a soluble form that upon binding attenuates the bioactivity of TNF- α [17]. Increased expression of both forms of TNFR can be found in response to various inflammatory disease states [15,18]. Several studies [19-22] have confirmed that one of the most important roles of TNF- α is the clearance and containment of latent infections. Much evidence has been gained upon introduction of TNF- α inhibitors into clinical practice. For example, a direct consequence of TNF- α inhibition is impaired granuloma formation

due to suppressed cell-mediated immunity: this is the mechanism at the base of the reactivation of latent infections with both *Mycobacterium tuberculosis* (TB) and histoplasmosis [14,23]. An indirect consequence of TNF- α inhibition is the creation of a cytokine imbalance with Interferon (IFN). In fact TNF- α acts synergistically with IFN- γ to eradicate or contain infection by TB and histoplasmosis: IFN γ without TNF- α lacks the potency to successfully contain the initial infection by such organisms.

HBV and TNF- α

T-helper (Th) 1-type cytokines, including IL-2, IFN- γ , and TNF- α , are involved mainly in cell-mediated immunity and play a crucial role in protection from intracellular pathogen. The importance of TNF- α in immunological control of hepatitis was demonstrated by different studies; in 1992 Gilles et al. [24] demonstrated a 70% reduction in the hepatic steady-state content of a 2.1-kb HBV mRNA following administration of a single nontoxic dose of tumor necrosis factor alpha. In 1994 Guidotti et al. [9] demonstrated that in the hamster IL-2, a cytokine for which the hepatocyte lacks receptors, can down-regulate hepatocellular HBV gene expression by an indirect, non-cytopathic process that is mediated by TNF- α . Regulatory effect of IL-2 was virtually completely abolished by prior administration of anti-TNF- α monoclonal antibodies. Hepatic HBV gene expression was also down-regulated by IFN- α and IFN- β administration, but only when they were injected repetitively and at high dose levels. Interestingly, the effect of IFN- β was not counteracted by repetitive injection of a neutralizing dose of anti-TNF- α monoclonal antibodies, suggesting that IFN- α and IFN- β inhibit HBV gene expression by a TNF- α independent pathway [9]. In 1996 Romero et al. [25] used a construct where HBV core/pregenomic (C/P) promoter and associated cis-acting elements were placed upstream of a luciferase-encoding plasmid. This reporter construct was transfected into cytokine-sensitive hepatoma cells which were exposed to stimulated mononuclear cell-conditioned medium or human recombinant cytokines. TNF- α , IFN- γ , and IFN- α each reduced luciferase activity by 40%. Combinations of TNF- α and interferons mimicked the extent of conditioned medium inhibition (80%) [25]. This study suggested the hypothesis that the action of cytokine may aid in viral clearance by suppressing virus production but also leading to diminished viral production and antigen synthesis that may result in persistent infection because of inadequate immune stimulation. Finally, variation between individuals in levels of TNF- α has been attributed to polymorphisms in the TNF- α promoter and their corresponding extended human leukocyte antigen haplotypes. TNF- α promoter polymorphism has been reported to be associated with the development of chronic HBV infection [26,27].

Anti-TNF- α Agents

To date, five TNF- α inhibitors have been approved by the United States Food and Drug Administration (FDA) for treatment of RA: infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), certolizumab (Cimzia), and golimumab (Simponi). INF is a chimeric (human-murine) IgG1 anti-TNF- α antibody that is administered intravenously. It binds with high affinity to soluble and membrane-bound TNF- α and inhibits its effect by blocking TNF- α -receptor interactions. Unlike the other agents, INF is also cytotoxic for TNF-expressing cells [28]. ETA, a soluble TNF-receptor fusion protein, is composed of two dimers, each with an extracellular, ligand-binding portion of the higher-affinity type 2 TNF receptor (p⁷⁵) linked to the Fc portion of human IgG1. This fusion protein binds to both TNF- α and

TNF- β , thereby preventing each from interacting with its respective receptors [17]. ADA is a recombinant humanized monoclonal anti-TNF- α antibody that is administered subcutaneously. It binds to human TNF- α with high affinity and, as a consequence, stops the cytokine from binding to its receptors [28]. CZ pegol is a pegylated humanized Fab fragment of an anti-TNF monoclonal antibody with high affinity for TNF- α . CZ pegol does not contain an Fc portion and therefore does not induce in vitro complement activation, antibody-dependent cellular cytotoxicity, or apoptosis [29]. GOL is a highly stable human IgG1 TNF- α antagonist monoclonal antibody with high affinity and capacity to neutralize human TNF- α . It binds with high affinity and specificity to both soluble and transmembrane forms of TNF- α , thereby neutralizing the biological activity of TNF- α . It is produced by a murine hybridoma cell line with recombinant DNA technology [30].

Prevalence of HBV Infection in the General Population and in Patients Treated with Anti-TNF- α

One third of the world's population has serological evidence of past or present infection with HBV and 350-400 million people are chronic HBsAg carriers [31]. The global prevalence of HBsAg varies greatly and countries can be defined as having a high, intermediate or low prevalence of HBV infection based on a prevalence of HBsAg carriers of >8%, 2% to 7%, or <2%, respectively [32]. In the past, a significantly higher prevalence of HBV infection in IBD patients than in controls has been reported [33], whereas results from recent Italian studies [34,35] show that HBV infection rates in IBD patients are comparable to or even lower than rates among the general Italian population. This trend is confirmed by a Spanish multicenter study [36]. Alike, another study [37] demonstrated that the prevalence of HBV and HCV in a population with polyarthritis suggestive of RA was not greater than the general population in the same geographic area. PA are another group involved in the use of anti-TNF- α therapy. There are no definitive data about association between psoriasis and hepatitis B, but in a recent report from U.S. population psoriasis was not significantly associated with increased HBV [38,39].

Aim of this article is to review the literature reporting i. the clinical studies and cases describing the risk of reactivation of HBV infection in patients undergoing anti-TNF- α treatment, and ii. the management and prophylaxis of HBV reactivation in patients receiving anti-TNF- α agents.

Materials and Methods

A review of the literature published in English, Spanish, Italian or French languages between 2000 and 2014 was performed using PubMed (<http://www.ncbi.nlm.nih.gov/PubMed>) and the Medline database through Ovid (<http://gateway.ovid.com>). Our research screened articles of Adults: 19+ years, using the keywords "tumor necrosis factor" and "hepatitis B" as well as the currently approved FDA TNF- α inhibitors "infliximab", "etanercept", "adalimumab", "golimumab" and "certolizumab". As exclusion criteria we used the terms "lymphoma", "chemoradiotherapy", "leukemia", "rituximab", "tocilizumab". Articles were selected if the titles and/or abstracts suggested the focus on the use of at least one TNF- α blocker in patients with exposure to hepatitis B virus (HBV). We took into account all the case reports and clinical studies with patients treated by anti-TNF- α agents that resulted infected by HBV, we analyzed the principal guidelines connected with use of anti-TNF- α and HBV. Additional articles of interest were selected from the bibliographies of articles retrieved using this search.

Results

Risk of HBV reactivation in patients with chronic HBV infection receiving anti-TNF- α agents

HBV reactivation is defined by: i. reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B [32]; ii. HBeAg or HBsAg negative reverse seroconversion [40]; iii. virological breakthrough defined as a confirmed increase in HBV DNA level of more than 1 log₁₀ IU/ml compared to the nadir (lowest value) HBV DNA level on therapy; it may precede a biochemical breakthrough, characterized by an increase in ALT levels [31]. The clinical course is highly variable, possibly leading to acute, fulminant liver failure. The risk of reactivation is correlated to the virological/serological state of patients. Cases have been reported in HBsAg positive patients, but there have also been cases of patients who are HBsAg negative and only anti-HBc positive. Eleven years have passed since description of the first three cases of HBV reactivation during therapy with anti-TNF- α agents [41-43]. Cases of HBV reactivation in patients treated by anti-TNF- α agents reported in literature are associated to the use of INF, ETA and ADA. There are no case reports of reactivation of HBV with GOL or CZ pegol; however, as these are newer TNF- α antagonists, the risk of reactivation would be expected to be a class effect.

We have divided the results of literature search into: case reports/case series and prospective/retrospective studies; patients were divided in three categories, using the classification proposed by the American Association for the Study of Liver Diseases (AASLD) guidelines [32] in Table 1. We have reported the studies and the cases described in literature in Table 2 and Table 3, respectively.

Here we describe the prospective and retrospective clinical studies summarized in Table 2.

Chung SJ et al. [44] in 2009 conducted a retrospective study on medical records of 103 Korean patients, seen at the Division of Rheumatology, Gangnam Severance Hospital, Seoul, Korea, between January 2006 and September 2008. Of the 103 patients, 8 (3 with RA and 5 with AS) were inactive HBsAg carriers and had normal ALT/AST levels and undetectable HBV DNA, the HBeAg was negative and anti-HBe positive. 4 patients received ETA, 2 INF and 2 ADA. There was only 1 reactivation during INF therapy that responded to interruption of INF and therapy with entecavir.

Charpin C et al. [45] in 2009 studied the safety of TNF- α -blocking agents in rheumatic patients in a prospective study conducted between 2005 and 2006 in France, where patients were screened for HBV markers before the initiation of anti-TNF- α therapy for RA or Spondyloarthritis (SpA); 21 patients with HBV serology indicating spontaneously resolved hepatitis B (HBsAg negative, anti-HBc antibodies positive, \pm anti-HBe antibodies positive) were enrolled. The mean age was 57.7 \pm 2.7 years, 12 patients suffered from RA, 5 from PA, and 4 from SpA; 4 patients were treated with INF, 14 with ETA, and 3 with ADA. No hepatitis B reactivation, as defined by HBsAg or HBV DNA detection, was observed at the end of the study.

In 2010 Caporali et al. [46] reported the results of a prospective study conducted from January 2001 to December 2008. 732 consecutive patients affected by inflammatory arthropathies started treatment with anti-TNF- α at 2 outpatient rheumatologic clinics in Northern Italy and they were all tested for HBV markers. Inclusion criteria: diagnosis of RA, SpA or PA; documented anti-HBc positivity; no evidence of active HBV replication before anti-TNF- α treatment; patients in treatment

Chronic hepatitis B 1. HBsAg-positive >6 months 2. Serum HBV DNA >20,000 IU/mL (10^5 copies/mL). Lower values (2,000-20,000 IU/mL) (10^4 - 10^5 copies/mL) are often seen in HBeAg-negative chronic hepatitis B 3. Persistent or intermittent elevation in ALT/AST levels 4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation	Inactive HBsAg carrier state 1. HBsAg-positive >6 months 2. HBeAg-negative, anti-HBe+ 3. Serum HBV DNA <2,000 IU/mL 4. Persistently normal ALT/AST levels 5. Liver biopsy confirming absence of significant hepatitis	Resolved hepatitis B 1. Previous known history of acute or chronic hepatitis B or presence of anti-HBc \pm anti-HBs 2. HBsAg -negative 3. Undetectable serum HBV DNA 4. Normal ALT levels
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Table 1: AASLD classification of patients exposed to HBV.

First authors of the studies	Number of patients	Patients with chronic hepatitis B		Inactive HBsAg carriers		Patients with resolved hepatitis B	Patients with HBV reactivation
		Proph +	Proph -	Proph +	Proph -		
Chung SJ et al. (44)	8	0	0	0	8 (1)	0	1
Charpin C et al. (45)	21	0	0	0	0	21	0
Caporali R et al. (46)	67	0	0	0	0	67	0
Kim YJ et al. (47)	96	1	7 (1)	0	0	88 (14)	15*
Vassilopoulos D et al. (48)	33	6 (1)	0	8	0	19	1
Lan JL et al. (49)	88	10	8 (5)	0	0	70 (1)	6
Fotiadou C et al (50)	7	0	0	7 (1)	0	0	1
Tamori A et al. (51) [†]	44	2	0	0	0	42	0
Prignano F et al. (52)	11	0	0	0	0	11	0
Urata Y et al. (53)	135	0	0	0	0	135 (7**)	7
Cho YT et al. (54)	7	1	4 (2)	0	2 (1)	0	3
Laurenti R et al. (55)	8	0	0	1	0	7	0
Papa A et al. (34)	23	0	0	1	0	22	0
Biondo MI et al. (56)	20	0	0	0	0	20	0
Ye H et al. (57)	87	4	2 (2)	9	22 (6)	50	8

Footnotes:

Proph \pm : antiviral prophylactic treatment administered or not, respectively; numbers in brackets () indicate cases of reactivation within the HBV state subgroups; * in this study reactivation was defined only by persistent increase of liver enzymes, without taking into account the other reactivation criteria (see Text); [†] in this study three cases of reactivation were observed in patients treated with Methotrexate but not with anti-TNF α ; ** in this study one case of reactivation was observed in patients treated with Methotrexate but not with anti-TNF α

Table 2: Prospective/retrospective studies on patients exposed to HBV and treated with anti-TNF α .

with anti-TNF- α (INF, ETA or ADA). Anti-HBc carriers were prospectively followed up for HBV reactivation (defined as HBsAg appearance and/or detectable HBV DNA in the serum). Seventy two patients identified as anti-HBc carriers (anti-HBc positive 67, anti-HBe positive 21, anti-HBs positive 28) were enrolled but 5 of them were excluded from the study because HBsAg positive; the mean age was 57.36 ± 12.63 years and no patients presented detectable HBV DNA at enrollment. During the study none received prophylaxis but none had HBV reactivation. The majority of patients received also methotrexate (51 patients) and prednisolone (43 patients). No specific data about the five HBsAg positive patients were provided but they were treated with lamivudine before and during anti-TNF- α and apparently had no reactivation.

A retrospective study conducted on medical records from January 2002 to May 2008 was reported by Kim YJ et al. [47] in 2010. The study was carried out at the Hospital for Rheumatic Diseases, Hanyang University, Korea and included all patients that received anti-TNF- α during this period. The mean age was 51.17 ± 13.45 years, the total of patients with anti-HBc were 88. In this study the elevation of aminotransferase was used as the single biomarker of HBV reactivation during therapy with anti-TNF- α (INF, ETA, ADA). Of the 88 patients, 14 had abnormal liver function test, in multiple logistic regression analysis only HBV infection was a significant risk factor for elevation of aminotransferase.

Vassilopoulos D et al. [48] in 2010 conducted a prospective study in an outpatient rheumatology clinic in Greece, with a medium follow-up of 2 years, and controls every 2-3 months. 131 patients were enrolled,

only 33 with previous HBV infection and a rheumatic disease: RA, SpA, PA, IBD-associated, undifferentiated, other. Reactivation was defined as detection of serum HBV DNA in patients with previously undetectable HBV DNA or $>1 \log_{10}$ increase compared with treatment nadir. 19 patients had a resolved HBV infection (HBsAg negative, anti-HBc positive): none underwent prophylaxis, none had a viral reactivation during anti-TNF- α treatment. No available data on the specific anti-TNF- α drugs used in these patients. Eight patients were inactive carriers (HBsAg positive, HBeAg negative, ALT/AST persistently normal, serum HBV DNA <2000 IU/ml/10000 copies/ml, absence of necroinflammation or fibrosis at liver biopsy) all patients were in antiviral prophylaxis, most with lamivudine, and no reactivations. No available data on the specific anti-TNF- α treatment. Six patients had a chronic hepatitis B (HBsAg positive, ALT/AST persistently or intermittently elevated, HBV DNA >2000 IU/10000 copies/ml, moderate necroinflammation or fibrosis at liver biopsy) all in antiviral prophylaxis with one of lamivudine, tenofovir, entecavir, telbivudine. In this group there was 1 reactivation in a patient treated with ETA due to the emergence of a lamivudine-resistant viral strain (YMDD mutant HBV strain) after 3.2 years; he was then switched to tenofovir with gradual normalization of HBV-DNA. In conclusion, all patients with chronic HBV infection (inactive carrier and chronic hepatitis B) underwent antiviral prophylaxis, there was only one reactivation due to a lamivudine-resistant viral strain.

Lan JL, et al. [49] in 2011 reported the results of a retrospective study conducted from January 2006 to June 2009 at Taichung Veterans General Hospital Taiwan, on 88 patients with a large prevalence of women, positive for anti-HBc and affected by RA, treated with

First authors	HBV infection state	Anti-TNF α used	Prophylaxis	Reactivation	Outcome
Madonia S et al. (58)	Resolved Hepatitis B	INF	NO	YES: LMV	GOOD
Montiel PM et al. (59)	Resolved Hepatitis B	ETA	NO	YES: LMV	GOOD
Esteve M et al. (61)	Inactive HBsAg carrier	INF	NO	YES	GOOD
	Inactive HBsAg carrier	INF	NO	YES	HEPATIC FAILURE \rightarrow DEATH
	Inactive HBsAg carrier	INF	YES: LMV	NO	GOOD
Conde-Taboada A. et al. (86)	Chronic hepatitis B	INF	YES: LMV, ENT	NO	GOOD
Kuwabara H et al. (60)	Chronic hepatitis B (HBV DNA baseline value not available)	INF	NO	YES: LMV	FULMINANT HEPATITIS \rightarrow DEATH
Carroll MB et al. (85)	Chronic hepatitis B	ETA	YES: LMV, AFV	YES	CHRONIC HEPATITIS
Michel M et al. (41)	Inactive HBsAg carrier	INF	NO	YES	FULMINANT HEPATITIS \rightarrow LIVER TRANSPLANTATION
Ostuni P et al. (43)	Inactive HBsAg carrier	INF	NO	YES: LMV	GOOD
Wendling D et al. (70)	Inactive HBsAg carrier	INF	NO	YES: LMV	GOOD
Anelli MG et al. (87)	Chronic hepatitis B	INF	NO	NO	GOOD
Wendling D et al. (69)	Inactive HBsAg carrier	INF	NO	YES: LMV	GOOD
	Inactive HBsAg carrier	INF \rightarrow ADA	YES: LMV	NO	GOOD
	Chronic hepatitis B	ETA	NO	YES: LMV	GOOD
	Chronic hepatitis B	ETA	YES: LMV	NO	GOOD
Verhelst X et al. (63)	Unknown \rightarrow Chronic hepatitis B	ADA	NO	YES: LMV, TFV	SUBFULMINANT HEPATITIS \rightarrow GOOD
Roux CH et al. (88)	Inactive HBsAg carrier	ETA \rightarrow ADA	YES: LMV	NO	GOOD
	Inactive HBsAg carrier	ETA	NO: LMV	NO	GOOD
	Inactive HBsAg carrier	INF	YES: LMV	NO	GOOD
Tsuboi H et al. (68)	Unknown \rightarrow Chronic hepatitis B	INF	NO	YES: LMV	GOOD
Robinson H et al. (89)	Inactive HBsAg carrier	ETA \rightarrow ADA	NO	NO	GOOD
Oniankita n O et al. (42)	Resolved hepatitis	INF	NO	NO	GOOD
Nosotti L et al. (90)	Resolved hepatitis	ETA	NO	NO	GOOD
	Resolved hepatitis	ADA	NO	NO	GOOD
	Resolved hepatitis	ETA	NO	NO	GOOD
	Resolved hepatitis	ADA	NO	NO	GOOD
	Resolved hepatitis	ETA	NO	NO	GOOD
	Resolved hepatitis	ADA	NO	NO	GOOD
	Inactive HBsAg carrier	ETA	YES: LMV	NO	GOOD
Ojio K et al. (67)	Inactive HBsAg carrier	INF	NO	YES: LMV	GOOD
Zingarelli S et al. (66)	Inactive HBsAg carrier	ETA	YES: LMV	NO	GOOD
	Inactive HBsAg carrier	INF \rightarrow ETA	YES: LMV	NO	GOOD
	Inactive HBsAg carrier	ADA	NO	YES: LMV	GOOD
Ueno Y et al. (91)	Inactive HBsAg carrier	INF	NO	YES	GOOD
Colbert C, et al. (62)	Chronic hepatitis B (HBV DNA baseline value not available)	INF	NO	YES: LMV	FULMINANT HEPATITIS \rightarrow DEATH
Kaur PP et al. (64)	Inactive HBsAg carrier	ADA \rightarrow ETA	NO	YES: LMV	GOOD
Sakellariou GT et al. (65)	Inactive HBsAg carrier	INF	NO	YES: LMV	GOOD
	Inactive HBsAg carrier	INF \rightarrow ETA	NO	NO	GOOD

Footnotes:

INF: Infliximab; ETA: Etanercept; ADA: Adalimumab; LMV: Lamivudine; TFV: Tenofovir; ENT: Entecavir; AFV: Adefovir

Table 3: Case reports/case series on patients exposed to HBV and treated with anti-TNF- α .

anti-TNF- α therapy. HBV reactivation was defined as a change to a positive HBsAg, serum HBV DNA greater than 10^5 (>2.6 log) copies/ml or a 10 fold rise in HBV DNA. Occult HBV infection was defined as the presence of HBV DNA in blood and/or hepatocyte without a detectable HBsAg, resolved HBV infection was defined as the presence of a past HBV infection with positive HBcAb, but undetectable serum HBV DNA and HBsAg, and normal ALT levels. Of the 88 patients, 18 had positive HBsAg, 12 had HBsAg negative/HBsAb negative status and 58 patients had HBsAg negative/HBsAb positive status before starting anti-TNF- α therapy, the mean age was 50.1 ± 12.0 years. In the group of HBsAg positive only 10 patients received prophylaxis with lamivudine before starting therapy with anti-TNF- α and none experienced a reactivation of HBV, there were 5 reactivations in the other 8 HBsAg positive patients without prophylaxis; all were treated

with lamivudine with complete resolution, after ten months of therapy a patient had a second reactivation for development of lamivudine-resistance. Of these 5 patients, 3 were treated with ADA, 2 with ETA. In the group of patients who were HBsAg negative/anti-HBs negative/anti-HBc positive none received antiviral prophylaxis and there was only one reactivation in the subgroup of 4 patients with detectable viral loads. The patient was in therapy with ETA and responded promptly to lamivudine therapy. In the largest group of 58 anti-HBs positive without prophylaxis none experienced HBV reactivation.

Fotiadou C et al. [50] in 2011 made a retrospective study in a cohort of 7 patients, affected by psoriasis treated with anti-TNF- α (INF, ETA or ADA) and chronic hepatitis B, followed by the first dermatologic clinic of Aristotle University of Thessaloniki, Greece. The mean age was 51 years, all patients were inactive HbsAg positive carriers with

undetectable viral loads and anti-HBc, anti-HBe positive. All these patients received antiviral prophylactic treatment with lamivudine 100 mg/day, which started 2 weeks before the initiation of anti-TNF- α medication and went on during the whole treatment period. One patient receiving INF had an increase of the viral load that reached 600 IU/mL. The authors did not consider this value sufficiently high for the diagnosis of HBV reactivation because under the cutoff value of 2000 IU/mL that defines viral reactivation.

In the same year, Tamori A et al. [51] published a prospective study conducted at Osaka City University Hospital, Japan, from November 2007 through October 2009, in patients with RA and antibodies against HBsAg. A total of 50 (41 females and 9 males) patients were enrolled and tested for HBsAg, HBV DNA and antibodies against HBsAg in serum. All patients with HBV DNA levels >2.1 log copies/ml received 0.5 mg of entecavir per day to prevent HBV reactivation (defined as increase in the HBV DNA level by more than 1.0 log copy/ml as compared with the level at enrollment, or as HBV DNA level >2.1 copies/ml.). The mean age was 59 years, the mean observation period was 23 months and HBV DNA levels were measured every 2-3 months. 5 patients were HBsAg positive, only 3 were treated with entecavir for an HBV DNA level >2.1 copies/ml at enrollment and of these one received INF and one ETA: none had HBV reactivation, whereas the other two patients that were not treated with entecavir and that had not received anti-TNF- α therapy had a reactivation under prednisolone and methotrexate. A total of 45 patients were HBsAg negative; of these, 36 were anti-HBs positive and 9 were only anti-HBc positive. In 42 patients, anti-TNF- α therapy was added to DMARD therapy, including MTX and none experienced HBV reactivation. The only reactivation in this group occurred in an anti-HBs positive patient treated with methotrexate, but not with anti-TNF- α agents.

Prignano F et al. [52] in 2011 conducted a retrospective study including 300 outpatients with psoriasis receiving anti-TNF- α therapy at the PsoCare Centre, Dermatology Division II, University of Florence, Italy. All data were evaluated at baseline and follow-up at 1, 3 and 6 months during anti-TNF- α therapy. Of these 300 patients, only 11 had HBV serology indicating past HBV infection (HBsAg negative, anti-HBc positive), the mean age was 61 and the anti-TNF- α used was ETA. No viral reactivation was observed in patients with past HBV infection after a mean 7 months duration of anti-TNF- α treatment, none underwent antiviral prophylaxis.

Urata Y et al. [53] in 2011 observed in a prospective study cases of reactivation under therapy with anti-TNF- α and DMARDs. The study was conducted between January 2008 and March 2009 in Japan: patients treated for RA were screened for HBV and were enrolled in the study only if HBsAg was negative. 135 were HBsAg negative and anti-HBs and/or anti-HBc positive. 97 patients were anti-HBs positive, 38 were anti-HBs negative/anti-HBc positive, and 12 were anti-HBs positive/anti-HBc negative. None underwent prophylaxis. The anti-TNF- α used were INF, ETA or ADA. The patients enrolled in the study had all resolved hepatitis B, and there was a total of 7 reactivations, 5 under therapy with anti-TNF- α (ETA), 1 with tocilizumab and 1 with methotrexate. Of these five patients, one had spontaneous HBV DNA normalization, four patients needed entecavir for HBV DNA normalization, and none interrupted therapy with ETA.

Cho YT et al. [54] in 2012 carried out a retrospective study on seven HBV carriers with psoriasis or PA treated with anti-TNF- α agents (ETA or ADA) between 2007 and 2011 at National Taiwan University Hospital, Taiwan. Reactivation of HBV was defined as an increase of the HBV viral load to more than 10-fold of the baseline

level or an absolute HBV viral load of more than 10^9 copies/mL. The patients were followed up from the start of the anti-TNF- α therapy for a mean duration of 28.9 months and were all HBsAg positive and HBeAg negative. They were divided into chronic hepatitis B (anti-HBe positive) and inactive HBsAg carrier state (anti-HBe negative). None of the patients received antiviral prophylaxis except one that was in treatment with entecavir before the institution of anti-TNF- α therapy. Of 7 patients, 3 (in treatment with ETA) had HBV reactivation (2 in chronic hepatitis B group and 1 in the inactive carriers group). Only one was treated with lamivudine, the others did not receive antiviral treatment because of persistently low HBV viral loads. None suspended anti-TNF- α .

Laurenti R et al. [55] in 2013 reported a retrospective study conducted in outpatients' clinics between 2006 and 2010 in Rome, including 8 patients with PA treated with ADA. There were no active carriers (HBsAg positive, HBV DNA >2000 IU/mL), 1 inactive carrier (HBsAg positive, HBV DNA <2000 IU/mL), 1 occult carrier (HBsAg negative, anti-HBc positive), and 6 patients with past HBV infection (HBsAg negative, anti-HBc positive, anti-HBs positive). Only the inactive carrier received antiviral prophylaxis with lamivudine. None had HBV reactivation during therapy with ADA.

A prospective study was conducted by Papa A et al. [34] at Department of Internal Medicine and Gastroenterology, Catholic University of Rome, Italy, between January 2005 and September 2010. The patients (mean age 41.9 ± 13.2 years) had Crohn's disease (CD) or ulcerative colitis (UC) and were screened for HBV and HCV before the initiation of anti-TNF- α . Approximately 70% of the patients were treated with INF, 30% with ADA and 1.7% with CZ pegol. Patients with positive HBV serological markers were classified as: current HBV infection, including patients with chronic HBV infection or patients in an inactive HBsAg carrier state, or past or resolved HBV infection, including carriers of "occult" HBV infection (patients who were anti-HBc positive with or without anti-HBs antibodies). The HBV positive patients were monitored every 3 months for liver function tests and every six months for HBV DNA and viral markers or if alterations in liver function tests values occurred. A total of 301 IBD patients were enrolled in the study but only 23 were positive for HBV, 22 were anti-HBc positive and 1 was HBsAg positive, only this patient received prophylaxis with lamivudine before anti-TNF- α and at least six months after the stop of therapy. Of these HBV positive patients, 65.2% were treated with INF, 30.4% with ADA and 4.3% with CZ and none had HBV reactivation (defined as: HBsAg detection in patients previously negative for HBsAg or HBV DNA detection in patients with previously undetectable viral genome).

Two prospective studies have been reported in 2014. The first one was conducted by Biondo et al. [56] and took place at the Immuno-Rheumatology Institute of the S. Andrea Hospital, La Sapienza University of Rome, between November 2003 and December 2011. All patients affected by chronic inflammatory arthropathies (RA, AS and PsA) were tested for HBV markers before starting anti-TNF- α (ETA, ADA, INF, GOL). Patients fulfilling the criteria to be defined as potential occult carriers were checked every two months for ALT levels and monitored every six months for HBV reactivation (defined as the serum appearance of either HBsAg or HBV DNA). The median age was 63 ± 9.5 , the patients infected with HBV were divided in: HBsAg positive, subdivided in active and inactive carriers (on the basis of HBV DNA levels ≥ 2000 IU/ml and <2000 IU/ml respectively), and HBsAg negative but anti-HBc positive that may be defined as occult carriers. Of the 169 patients, only 20 were HBsAg negative and anti-

HBc positive and HBV DNA negative, and of these 10 were also anti-HBe and 14 anti-HBs positive. None of these patients was treated with antiviral prophylaxis but none had reactivation of HBV during 4 years follow-up.

The second prospective study reported by Ye H et al. [57] was conducted from January 2008 to January 2011 in six centers in China. 87 patients enrolled with HBV and inflammatory arthritis (RA, SpA, and PA) were followed up every 1-3 months until January 2012. HBV reactivation was defined as an increase of serum HBV DNA level by $>1 \log_{10}$ compared with nadir or detection of HBV DNA in patients with previously undetectable HBV DNA. Fifty patients had a resolved HBV infection (HBsAg negative and anti-HBc positive): 8 were anti-HBc positive, 19 anti-HBs and anti-HBc positive, 6 anti-HBs and anti-HBe positive, 2 anti-HBe and anti-HBc positive, 15 anti-HBs anti-HBe and anti-HBc positive. HBV reactivation was not found in none of these 50 patients during follow-up. Six patients were affected by chronic hepatitis B (HBsAg positive, HBV DNA $>10^5$ copies/ml, elevated ALT) and two of these patients did not take antiviral prophylaxis. Both of them received ETA and were found to have HBV reactivation, treated with interruption of ETA and initiation of lamivudine. ALT returned to normal and HBV DNA was below 10^5 copies/ml after about 1 month. Four patients under prophylaxis with lamivudine had no reactivation; 3 were treated with INF, 1 with ETA. 31 patients were inactive carriers (HBsAg positive, HBV DNA $<10^4$ copies/ml, ALT persistently normal). Nine patients who received antiviral prophylaxis before anti-TNF- α agents showed no viral reactivation. Out of the 22 patients who did not receive antiviral prophylaxis, increase of viral load was detected in 6, and in 4 patients ALT levels were elevated to 1.5-8.18 ULN; of these 4 patients, 2 were treated with INF and 2 with ETA. Of these six patients, 3 stopped the anti-TNF- α agents, 1 withdrew from INF and treated with lamivudine, 1 switched from INF to ETA, and 1 continued to use ETA as prescribed after the detection of viral replication. HBV DNA in all cases decreased until no longer detectable, and no signs of flare were found in these patients during follow-up.

Additionally, we found two case reports of reactivation in HBcAb carriers, treated by lamivudine with good outcome [58,59]. We found three cases of death [60-62] and two cases of subfulminant hepatitis in HBsAg positive patients [41,63]. These are described in Table 3.

Management and Prophylaxis of HBV Reactivation in Patients Receiving Anti-TNF- α Agents

As mentioned before, in case of HBV reactivation lamivudine is the agent of choice, determining recovery in most of the cases reported in literature [43,58,59,64-70]. All the available guidelines [32,71,72] recommend an early intervention. The Asian guidelines suggest lamivudine as first choice [71], whereas the American and European guidelines [31,32] do not provide specific indications, but generically recommend the use of nucleot(s)ide analogues in all patients with HBV reactivation in course of immunosuppressive therapy. With regard to prophylaxis of HBV reactivation, a systematic review [73] showed that prophylactic lamivudine reduced the risk of HBV reactivation and HBV-related hepatitis by 79%. In addition, preventive lamivudine might reduce the risk of HBV-related hepatic failure and death in patients who test positive for HBsAg and receive chemotherapy; a meta-analysis [74] supported the same conclusions. Similar information emerged from the studies included in our analysis, but we could not find a systematic review summarizing all the data available from the registries of patients treated with anti-TNF- α agents. All the available guidelines provide recommendations for patients with HBV who

require immunosuppressive therapy, without any specific reference to anti-TNF- α drugs. The American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL), the Asian-Pacific consensus statement on the management of chronic hepatitis B and the European Crohn and Colitis Organization (ECCO) recommend early introduction of nucleot(s)ide analogues for all HBsAg positive patients requiring immunosuppressive therapy. Anti-viral agents should be administered to those patients who exhibit positive HBsAg titres regardless of HBV DNA level. There is a general agreement to start prophylactic treatment 2-4 weeks before the beginning of immunosuppressive agents [32,72,75] to be continued for at least 6-12 months afterwards [32,75]. If immunosuppressive therapy is expected to last longer than 12 months, others nucleot(s)ide analogues with higher barriers to genetic resistance might be preferred. Entecavir and tenofovir are more attractive candidates. Lamivudine resistance commonly develops with prolonged use, and has been detected in up to 20% of patients after 1 year and up to 60% by 5 years [10,31]. The emergence of resistance has also been associated with reactivation in patients on long-term anti-TNF- α therapy [48]. In HBsAg and HBV DNA negative patients (resolved hepatitis) there is not a clear recommendation for prophylaxis, but HBV reactivation may occur. Since this event is infrequent, and information in the patient population receiving anti-TNF- α therapy is limited, routine prophylaxis for these individuals is not recommended. However, these patients should be monitored routinely (1-3 months) [31] for elevation of liver enzymes, as well as for changes in HBV serology and HBV DNA levels [31,32,71,72,76-78]. In seronegative HBV patients vaccination is recommended, especially in patients with high risk of infection (Table 4) [32]. The efficacy of vaccination may be reduced because of treatment with anti-TNF- α , thus serological responses should be measured after the vaccination is completed [76]. Charpin et al. [45] and Vassilopoulos et al. [48] reported a reduction of anti-HBs Ab titres during anti-TNF- α therapy under the level that is commonly considered protective (10 IU/ml). Finally, the American College of Rheumatology recommends avoiding use of biological agents in patients affected by RA with chronic hepatitis B untreated due to contraindications to treatment or intolerable adverse events, and in treated chronic hepatitis B with Child-Pugh class B and higher [79].

Conclusion

Although definitive evidence on the risk of HBV reactivation in anti-TNF- α -treated patients is not available, yet, the analysis of most cases and studies suggests that the subjects at higher risk are those with persistent HBsAg positivity (chronic hepatitis B and inactive HBsAg carrier state), especially without antiviral prophylaxis, whereas in the cohort of patients with resolved hepatitis B the resumption of viral replication is much less frequent. In a previous review, the reactivation rate in HBsAg positive patients was as high as 39%, compared to only 5% in the anti-HBc antibodies positive group [80]. Other risk factors for HBV reactivation are high viral load at baseline (10^5 copies/L) [71], the subtype of chronic HBV infection (genotype B), underlying comorbidities (i.e. solid cancer), use of additional immunosuppressive drugs (i.e. methotrexate), male sex and younger of 40, HCV co-infection [7,72,81,82]. The use of anti-TNF agents appears to be relatively safe in HBsAg negative patients with undetectable HBV DNA. However, reactivations are documented in this subgroup [49,58,59,83] therefore these patients must be monitored, every one to three months according to the individual patient risk and therapeutic regimen (tighter monitoring during concomitant administration of corticosteroids and DMARDs). In HBsAg positive patients, but with HBV DNA <2000 UI/L and normal liver enzymes, the use of anti-

INDIVIDUALS BORN IN AREAS OF HIGH* OR INTERMEDIATE† PREVALENCE RATES FOR HBV INCLUDING IMMIGRANTS AND ADOPTED CHILDREN‡§
All countries of Asia, Africa, South Pacific Island, Eastern Europe (except Hungary)
Middle East (except Cyprus and Israel)

European Mediterranean: Malta and Spain

The Arctic (indigenous populations of Alaska, Canada, and Greenland)

South America: Ecuador, Guyana, Suriname, Venezuela, and Amazon regions of Bolivia, Brazil, Colombia, and Peru

Caribbean: Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, Turks and Caicos

Central America: Guatemala and Honduras

OTHER GROUPS RECOMMENDED FOR SCREENING

U.S. born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (>8%)

Household and sexual contacts of HBsAg-positive persons§

Persons who have ever injected drugs§

Persons with multiple sexual partners or history of sexually transmitted disease§

Men who have sex with men§

Inmates of correctional facilities§

Individuals with chronically elevated ALT or AST§

Individuals infected with HCV or HIV§

Patients undergoing renal dialysis§

All pregnant women

Persons needing immunosuppressive therapy

Footnotes:

*HBsAg prevalence>8%; †HBsAg prevalence 2%-7%; ‡If HBsAg-positive persons are found in the first generation, subsequent generations should be tested; §Those who are seronegative should receive hepatitis B vaccine.

Table 4: Groups at high risk for HBV infection who should be screened prior to anti-TNF therapy (adapted from AASLD practice guidelines updated).

TNF- α agents appears to be relatively safe upon prophylaxis of HBV reactivation. The available data reported in literature do not provide clear indications on the anti-TNF- α agents of choice with regard to the safety in patients exposed to HBV. In older reports, INF was associated to higher risk of HBV reactivation, mainly due to its pharmacological characteristics [84], but several case reports [59,64,69,85-91] and studies [53,57] highlighted reactivations during treatment with ETA; similar results can be found with ADA [49,63,66].

References

- Ganem D, Prince AM (2004) Hepatitis B virus infection-natural history and clinical consequences. *N Engl J Med* 350: 1118-1129.
- Dienstag JL (2008) Hepatitis B virus infection. *N Engl J Med* 359: 1486-1500.
- Liang TJ (2009) Hepatitis B: the virus and disease. *Hepatology* 49: S13-21.
- Chisari FV, Isogawa M, Wieland SF (2010) Pathogenesis of hepatitis B virus infection. *Pathol Biol (Paris)* 58: 258-266.
- Hösel M, Quasdorff M, Wiegmann K, Webb D, Zedler U, et al. (2009) Not interferon, but interleukin-6 controls early gene expression in hepatitis B virus infection. *Hepatology* 50: 1773-1782.
- Puro R, Schneider RJ (2007) Tumor necrosis factor activates a conserved innate antiviral response to hepatitis B virus that destabilizes nucleocapsids and reduces nuclear viral DNA. *J Virol* 81: 7351-7362.
- Rehermann B (2000) Intrahepatic T cells in hepatitis B: viral control versus liver cell injury. *J Exp Med* 191: 1263-1268.
- Thimme R, Wieland S, Steiger C, Ghayeb J, Reimann KA, et al. (2003) CD8(+) T cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection. *J Virol* 77: 68-76.
- Guidotti LG, Guilhot S, Chisari FV (1994) Interleukin-2 and alpha/beta interferon down-regulate hepatitis B virus gene expression in vivo by tumor necrosis factor-dependent and -independent pathways. *J Virol* 68: 1265-1270.
- Liaw YF, Chu CM (2009) Hepatitis B virus infection. *Lancet* 373: 582-592.
- Wieland SF, Spangenberg HC, Thimme R, Purcell RH, Chisari FV (2004) Expansion and contraction of the hepatitis B virus transcriptional template in infected chimpanzees. *Proc Natl Acad Sci U S A* 101: 2129-2134.
- Kroesen S, Widmer AF, Tyndall A, Hasler P (2003) Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. *Rheumatology (Oxford)* 42: 617-621.
- Choy EH, Panayi GS (2001) Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 344: 907-916.
- Giles JT, Bathon JM (2004) Serious infections associated with anticytokine therapies in the rheumatic diseases. *J Intensive Care Med* 19: 320-334.
- Fang JW, Shen WW, Meager A, Lau JY (1996) Activation of the tumor necrosis factor-alpha system in the liver in chronic hepatitis B virus infection. *Am J Gastroenterol* 91: 748-753.
- Karin M (2006) Nuclear factor-kappaB in cancer development and progression. *Nature* 441: 431-436.
- Olsen NJ, Stein CM (2004) New drugs for rheumatoid arthritis. *N Engl J Med* 350: 2167-2179.
- Marinos G, Naoumov NV, Rossol S, Torre F, Wong PY, et al. (1995) Tumor necrosis factor receptors in patients with chronic hepatitis B virus infection. *Gastroenterology* 108: 1453-1463.
- Rothe J, Lesslauer W, Lötscher H, Lang Y, Koebel P, et al. (1993) Mice lacking the tumour necrosis factor receptor 1 are resistant to TNF-mediated toxicity but highly susceptible to infection by *Listeria monocytogenes*. *Nature* 364: 798-802.
- Moore TA, Lau HY, Cogen AL, Standiford TJ (2005) Defective innate antibacterial host responses during murine *Klebsiella pneumoniae* bacteremia: tumor necrosis factor (TNF) receptor 1 deficiency versus therapy with anti-TNF-alpha. *Clin Infect Dis* 41 Suppl 3: S213-217.
- Deepe GS Jr (2005) Modulation of infection with *Histoplasma capsulatum* by inhibition of tumor necrosis factor-alpha activity. *Clin Infect Dis* 41 Suppl 3: S204-207.
- Tufariello JM, Chan J, Flynn JL (2003) Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection. *Lancet Infect Dis* 3: 578-590.
- Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, et al. (2001) Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 345: 1098-1104.
- Gilles PN, Fey G, Chisari FV (1992) Tumor necrosis factor alpha negatively regulates hepatitis B virus gene expression in transgenic mice. *J Virol* 66: 3955-3960.
- Romero R, Lavine JE (1996) Cytokine inhibition of the hepatitis B virus core promoter. *Hepatology* 23: 17-23.
- Wilson AG, Symons JA, McDowell TL, McDewitt HO, Duff GW (1997) Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci U S A* 94: 3195-3199.
- Cheong JY, Cho SW, Hwang IL, Yoon SK, Lee JH, et al. (2006) Association between chronic hepatitis B virus infection and interleukin-10, tumor necrosis factor-alpha gene promoter polymorphisms. *J Gastroenterol Hepatol* 21: 1163-1169.
- Scott DL, Kingsley GH (2006) Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med* 355: 704-712.
- Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, et al. (2007) Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 357: 228-238.

30. Shealy DJ, Cai A, Staquet K, Baker A, Lacy ER, et al. (2010) Characterization of golimumab, a human monoclonal antibody specific for human tumor necrosis factor β . *MAbs* 2.
31. European Association For The Study Of The Liver (2012) EASL Clinical Practice Guidelines: management of chronic hepatitis B virus infection. *Journal of Hepatology* 57: 167–185.
32. Lok AS, McMahon BJ (2009) Chronic hepatitis B: update 2009. *Hepatology* 50: 661-662.
33. Biancone L, Pavia M, Del Vecchio Blanco G, D'Inca R, Castiglione F, et al. (2001) Hepatitis B and C virus infection in Crohn's disease. *Inflamm Bowel Dis* 7: 287-294.
34. Papa A, Felice C, Marzo M, Andrisani G, Armuzzi A, et al. (2013) Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor- β agents. *J Crohns Colitis* 7: 113-119.
35. Fabris P, Baldo V, Baldovin T, Bellotto E, Rassu M, et al. (2008) Changing epidemiology of HCV and HBV infections in Northern Italy: a survey in the general population. *J Clin Gastroenterol* 42: 527-532.
36. Loras C, Saro C, Gonzalez-Huix F, Mínguez M, Merino O, et al. (2009) Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *Am J Gastroenterol* 104: 57-63.
37. Guennoc X, Narbonne V, Jousse-Joulin S, Devauchelle-Pensec V, Dougados M, et al. (2009) Is screening for hepatitis B and hepatitis C useful in patients with recent-onset polyarthritis? The ESPOIR cohort study. *J Rheumatol* 36: 1407-1413.
38. Kanada KN, Schupp CW, Armstrong AW (2013) Association between psoriasis and viral infections in the United States: focusing on hepatitis B, hepatitis C and human immunodeficiency virus. *J Eur Acad Dermatol Venereol* 27: 1312-1316.
39. Tsai TF, Wang TS, Hung ST, Tsai PI, Schenkel B, et al. (2011) Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. *J Dermatol Sci* 63: 40-46.
40. Hoofnagle JH (2009) Reactivation of hepatitis B. *Hepatology* 49: S156-165.
41. Michel M, Duvoux C, Hezode C, Cherqui D (2003) Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. *J Rheumatol* 30: 1624-1625.
42. Oniankitan O, Duvoux C, Challine D, Mallat A, Chevalier X, et al. (2004) Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 31: 107-109.
43. Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S (2003) Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. *Ann Rheum Dis* 62: 686-687.
44. Chung SJ, Kim JK, Park MC, Park YB, Lee SK (2009) Reactivation of hepatitis B viral infection in inactive HBsAg carriers following anti-tumor necrosis factor- α therapy. *J Rheumatol* 36: 2416-2420.
45. Charpin C, Guis S, Colson P, Borentain P, Mattéi JP, et al. (2009) 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* 11: R179.
46. Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, et al. (2010) Safety of Tumor Necrosis Factor A Blockers in Hepatitis B Virus Occult Carriers (Hepatitis B Surface Antigen Negative/Anti-Hepatitis B Core Antigen Positive) With Rheumatic Diseases. *Arthritis Care & Research* 62: 749–754.
47. Kim YJ, Bae SC, Sung YK, Kim TH, Jun JB, et al. (2010) Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor- α blocker in the treatment of rheumatic diseases. *J Rheumatol* 37: 346-350.
48. Vassilopoulos D, Apostolopoulou A, Hadziyannis E, Papatheodoridis GV, Manolakopoulos S, et al. (2010) Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis* 69: 1352-1355.
49. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, et al. (2011) Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor α therapy. *Ann Rheum Dis* 70: 1719-1725.
50. Fotiadou C, Lazaridou E, Ioannides D (2011) Safety of anti-tumor necrosis factor- α 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* 25: 471-474.
51. Tamori A, Koike T, Goto H, Wakitani S, Tada M, et al. (2011) Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. *J Gastroenterol* 46: 556-564.
52. Prignano F, Ricceri F, Pescitelli L, Zanieri F, Lotti T (2011) Tumour necrosis factor- β antagonists in patients with concurrent psoriasis and hepatitis B or hepatitis C: a retrospective analysis of 17 patients. *Br J Dermatol* 164: 645-647.
53. Urata Y, Uesato R, Tanaka D, Kowatari K, Nitobe T, et al. (2011) Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. *Mod Rheumatol* 21: 16-23.
54. Cho YT, Chen CH, Chiu HY, Tsai TF (2012) Use of anti-tumor necrosis factor- β therapy in hepatitis B virus carriers with psoriasis or psoriatic arthritis: a case series in Taiwan. *J Dermatol* 39: 269-273.
55. Laurenti R, Giovannangeli F, Gubellini E, Viviano MT, Errico A, et al. (2013) 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: 410521.
56. Biondo MI, Germano V, Pietrosanti M, Canzoni M, Marignani M, et al. (2014) Lack of hepatitis B virus reactivation after anti-tumor necrosis factor α agents therapy in antibody to hepatitis B core antigen positive/hepatitis B surface antigen negative subjects with chronic inflammatory arthropathies. *Eur J Intern Med*. S0953-6205
57. Ye H, Zhang XW, Mu R, Fang LK, Gu JR, et al. (2014) Anti-TNF therapy in patients with HBV infection—analysis of 87 patients with inflammatory arthritis. *Clin Rheumatol* 33: 119-123.
58. Madonia S, Orlando A, Scimeca D, Olivo M, Rossi F, et al. (2007) Occult hepatitis B and infliximab-induced HBV reactivation. *Inflamm Bowel Dis* 13: 508-509.
59. Montiel PM, Solis JA, Chirinos JA, Casis B, Sánchez F, et al. (2008) Hepatitis B virus reactivation during therapy with etanercept in an HBsAg-negative and anti-HBs-positive patient. *Liver Int* 28: 718-720.
60. Kuwabara H, Fukuda A, Tsuda Y, Shibayama Y (2013) Precore mutant hepatitis B virus-associated fulminant hepatitis during infliximab therapy for rheumatoid arthritis. *Clin Rheumatol* 32 Suppl 1: S47-49.
61. Esteve M, Saro C, González-Huix F, Suarez F, Forné M, et al. (2004) Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 53: 1363-1365.
62. Colbert C, Chavarria A, Berkelhammer C (2007) Fulminant hepatic failure in chronic hepatitis B on withdrawal of corticosteroids, azathioprine and infliximab for Crohn's disease. *Inflamm Bowel Dis* 13: 1453-1454.
63. Verhelst X, Orlent H, Colle I, Geerts A, De Vos M, et al. (2010) Subfulminant hepatitis B during treatment with adalimumab in a patient with rheumatoid arthritis and chronic hepatitis B. *Eur J Gastroenterol Hepatol* 22: 494-499.
64. Kaur PP1, Chan VC, Berney SN (2008) Histological evaluation of liver in two rheumatoid arthritis patients with chronic hepatitis B and C treated with TNF- α blockade: case reports. *Clin Rheumatol* 27: 1069-1071.
65. Sakellariou GT, Chatzigiannis I (2007) Long-term anti-TNF α therapy for ankylosing spondylitis in two patients with chronic HBV infection. *Clin Rheumatol* 26: 950-952.
66. Zingarelli S, Frassi M, Bazzani C, Scarsi M, Puoti M, et al. (2009) Use of tumor necrosis factor- α -blocking agents in hepatitis B virus-positive patients: reports of 3 cases and review of the literature. *J Rheumatol* 36: 1188-1194.
67. Ojio K, Naganuma M, Ebinuma H, Kunimoto H, Tada S, et al. (2008) Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. *J Gastroenterol* 43: 397-401.
68. Tsuboi H, Tsujii A, Nampei A, Yoshihara H, Kawano K, et al. (2011) A patient with rheumatoid arthritis treated with tocilizumab together with lamivudine prophylaxis after remission of infliximab-reactivated hepatitis B. *Mod Rheumatol* 21: 701-705.
69. Wendling D, Di Martino V, Prati C, Toussiot E, Herbein G (2009) Spondyloarthropathy and chronic B hepatitis. Effect of anti-TNF therapy. *Joint Bone Spine* 76: 308-311.

70. Wendling D, Auge B, Bettinger D, Lohse A, Le Huede G, et al. (2005) Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthritis. *Ann Rheum Dis* 64: 788-789.
71. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, et al. (2008) Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatology* 47: 263-283.
72. Ding T, Ledingham J, Luqmani R, Westlake S, Hyrich K, et al. (2010) BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. *Rheumatology (Oxford)* 49: 2217-2219.
73. Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, et al. (2008) Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 148: 519-528.
74. Katz LH, Fraser A, Gafter-Gvili A, Leibovici L, Tur-Kaspa R (2008) Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis. *J Viral Hepat* 15: 89-102.
75. Marzano A, Angelucci E, Andreone P, Brunetto M, Bruno R, et al. (2007) Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis* 39: 397-408.
76. Nordgaard-Lassen I, Dahlerup JF, Belard E, Gerstoft J, Kjeldsen J, et al. (2012) Guidelines for screening, prophylaxis and critical information prior to initiating anti-TNF- α treatment. *Dan Med J* 59: C4480.
77. Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, et al. (2014) Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 8: 443-468.
78. Orlando A, Armuzzi A, Papi C, Annese V, Ardizzone S, et al. (2011) The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: The use of tumor necrosis factor- α antagonist therapy in Inflammatory Bowel Disease. *Digestive and Liver Disease* 43:1-20
79. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, et al. (2012) 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 64: 625-639.
80. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, et al. (2011) Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine (Baltimore)* 90: 359-371.
81. Motaparthy K, Stanicic V, Van Voorhees AS, Lebwohl MG, Hsu S et al. (2014) From the Medical Board of the National Psoriasis Foundation: Recommendations for screening for hepatitis B infection prior to initiating antitumor necrosis factor- α inhibitors or other immunosuppressive agents in patients with psoriasis. *J Am Acad Dermatol* 7:178-186
82. Chu CM, Liaw YF (2007) Predictive factors for reactivation of hepatitis B following hepatitis B e antigen seroconversion in chronic hepatitis B. *Gastroenterology* 133: 1458-1465.
83. Mori S (2011) Past hepatitis B virus infection in rheumatoid arthritis patients receiving biological and/or nonbiological disease-modifying antirheumatic drugs. *Mod Rheumatol* 21: 621-627.
84. Carroll MB, Forcione MA (2010) Use of tumor necrosis factor α inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol* 29: 1021-1029.
85. Carroll MB, Bond MI (2008) Use of tumor necrosis factor- α inhibitors in patients with chronic hepatitis B infection. *Semin Arthritis Rheum* 38: 208-217.
86. Conde-Taboada A, Muñoz JP, Muñoz LC, López-Bran E (2009) Infliximab treatment for severe psoriasis in a patient with active hepatitis B virus infection. *J Am Acad Dermatol* 60: 1077-1080.
87. Anelli MG, Torres DD, Manno C, Scioscia C, Iannone F, et al. (2005) 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.* 52(8):2519-20
88. Roux CH, Brocq O, Breuil V, Albert C, Euler-Ziegler L (2006) Safety of anti-TNF- α therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. *Rheumatology (Oxford)* 45: 1294-1297.
89. Robinson H, Walker-Bone K (2009) Anti-TNF- α therapy for rheumatoid arthritis among patients with chronic hepatitis B infection. *Rheumatology (Oxford)* 48: 448-450.
90. Nosotti L, Francesconi F, Izzi S, Berardesca E, Morrone A, et al. (2010) Safety of antitumor necrosis factor- α therapy in psoriatic patients with hepatitis B virus infection. *Br J Dermatol* 162: 1408-1410.
91. Ueno Y, Tanaka S, Shimamoto M, Miyanaka Y, Hiyama T, et al. (2005) Infliximab therapy for Crohn's disease in a patient with chronic hepatitis B. *Dig Dis Sci* 50: 163-166.