

Tuberculosis and viral hepatitis infection in Eastern Europe, Asia, and Latin America: impact of tumor necrosis factor- α inhibitors in clinical practice

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Abstract: Tumor necrosis factor- α (TNF- α) inhibitors are increasingly becoming the standard of care for treating a number of inflammatory diseases. However, treatment with TNF- α inhibitors carries an inherent risk of compromising the immune system, resulting in an increased susceptibility to infections and malignancies. This increased risk of infection is of particular concern in Asia, Eastern Europe, and Latin America where tuberculosis (TB) and viral hepatitis are endemic. In this brief review, we examine the literature and review the impact of TNF- α inhibitors on the incidence and the reactivation of latent disease with respect to TB, hepatitis C infection, and hepatitis B infection. Our findings show that TNF- α inhibitors are generally safe, if used with caution. Patients should be screened prior to the initiation of TNF- α inhibitor treatment and given prophylactic treatment if needed. In addition, patients should be monitored during treatment with TNF- α inhibitors and after treatment has stopped to ensure that infections, if detected, are treated promptly and effectively. Our analysis is consistent with other reports and guidelines.

Keywords: tuberculosis, hepatitis C, hepatitis B, tumor necrosis factor inhibitors, reactivation, risk

Introduction

Tumor necrosis factor- α (TNF- α) inhibitors have been the standard of treatment for several inflammatory, autoimmune diseases including rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, and psoriasis. However, since TNF- α plays an essential role in the host immune system and its defense against infectious diseases, treatment with TNF- α inhibitors may adversely compromise the immune system in these patients and, consequently, increase the risk of developing infections and certain malignancies, particularly lymphoma and lung cancer.¹⁻⁴ Although there are several TNF- α inhibitors currently in use to treat patients with RA, an extensive search in PubMed for publications addressing the use of these agents in patients with risk of tuberculosis (TB) or hepatitis yielded only articles in which etanercept (a human soluble dimeric TNF- α receptor fusion protein),⁵ adalimumab (a fully human monoclonal antibody [mAb] against TNF- α),⁵ or infliximab (a mouse-human chimeric mAb against TNF- α)⁵ was used. Consequently, in this article, we review the impact of treating with only these three TNF- α inhibitors on the incidence of TB and reactivation rate of viral hepatitis and the clinical outcomes in patients.

TB

The global burden of TB continues to be very high.^{6,7} It is estimated that globally, 9 million people developed TB, 1.5 million died from the disease in 2013, and that one-third of the world's population has latent TB.^{6,8} Incidence of TB is high in Asia, Eastern Europe, Latin America, and sub-Saharan Africa, with 56% of cases occurring in Southeast Asia and Western Pacific.^{6,7} Eastern European and Central Asian countries continue to have the highest incidence of multidrug-resistant TB.⁶ In India alone, there are 2.2 million new cases of TB and more than 300,000 deaths each year.⁹

Increased incidence of TB in patients treated with TNF- α inhibitors was first reported for infliximab.¹⁰ Since then, several studies have indicated that the risk for TB is higher in patients treated with TNF- α inhibitors.^{11–21} A biphasic emergence of TB infection among patients with RA using TNF- α inhibitors has been reported due to the reactivation of latent TB infection (LTBI) or new TB infection.²² The reported standardized incidence ratio for etanercept was in the range of 0.4–2.2 compared to 1.7–18.6 for infliximab and 0.9–29.3 for adalimumab.^{14–17} The reported incidence rate per 100,000 patient years was 540 for patients with ankylosing spondylitis treated with infliximab compared to 490 for patients treated with adalimumab; no cases of TB were reported for patients treated with etanercept.¹⁸ These data indicate that in general, the risk of TB infection appears to be higher for patients treated with anti-TNF- α mAbs (infliximab/adalimumab) than for patients treated with TNF- α soluble receptor (etanercept), and among the mAbs, it appears to be higher for patients treated with infliximab than for patients treated with adalimumab (Table 1).^{14–21} Structural and functional disparities between the mAbs and soluble receptor may be the reason for this difference in response.²³

The consequences of new infection or reactivation of LTBI in patients prescribed treatment with TNF- α inhibitors could be extremely harmful or even fatal.²⁴ Thus, it is imperative that patients in TB endemic areas eligible for TNF- α inhibitor therapy are tested for TB/LTBI so that, if needed, appropriate chemoprophylaxis can be administered prior to the initiation of treatment. Patients detected with LTBI when given prophylactic treatment with isoniazid or rifampin/isoniazid prior to TNF- α inhibitor therapy had a low rate of conversion to disease.^{25–29}

Given the potential damaging effect of TB on the patient, the threshold for initiating chemoprophylaxis is understandably low.^{30,31} However, initiating chemoprophylaxis delays critical TB treatment, potentially exacerbating the disease

and adding to costs that may not be affordable in many regions. Chemoprophylaxis also can cause its own adverse events, further negatively affecting the patient's quality of life.³² Testing can be done using either the tuberculin skin test (TST) or the interferon gamma release assay (IGRA). TST is sensitive, specific to TB, and identifies all patients who have been exposed to TB. However, it does not differentiate between individuals with active TB, latent TB, or those immunized against TB with a *Bacillus Calmette–Guérin* (BCG) vaccine.³³ IGRA has increased the detection of LTBI, especially in patients with immunological diseases,^{22,34,35} in countries where the population is universally vaccinated with BCG. However, the sensitivity and specificity of IGRA has not yet been fully verified and its use is not universal.^{29,33,36} Recent studies have shown that using a multistep approach that includes TST, chest X-ray, and IGRA to screen patients who are candidates for TNF- α inhibitor therapy identifies those patients for whom chemoprophylaxis is essential.^{29,37,38} These approaches decreased the number of patients who underwent chemoprophylaxis, thereby enabling more patients to receive the anti-TB treatment earlier. The subsequent incidence of TB was comparable to that in countries where TB is not endemic.^{29,39,40} It is recommended that patients receiving TNF- α inhibitor therapy be screened at least annually for new TB infection or the emergence of LTBI.⁴¹ Serial IGRA monitoring has been shown to be effective in detecting active TB in patients with RA receiving TNF- α inhibitor therapy.²² Prophylactic monitoring of patients and selecting appropriate treatment have subsequently reduced the overall costs of treatment.

Given the potential for very severe consequences due to TB infection or LTBI reactivation in patients receiving TNF- α inhibitor therapy, it is imperative that they be monitored regularly during their treatment to ensure timely treatment for latent or active TB. Care must be taken in the interpretation of TB test results in patients receiving chemoprophylaxis or TNF- α inhibitors, since treatment and the tests themselves can affect subsequent test results.^{42,43} This review confirms earlier findings indicating that TNF- α inhibitors are safe to use with appropriate monitoring even in patients who are immunocompromised and at high risk for TB.

Viral hepatitis C

The global burden of hepatitis C is high, and the prevalence of hepatitis C virus (HCV) infection worldwide is estimated to be 2.8% of the population, ie, >185 million people, with 3–4 million people being newly infected each year.⁴⁴ Prevalence is high (>3.5%) in countries of Central and East Asia, North Africa,

Table I Risk of tuberculosis associated with TNF- α inhibitor treatment

Drug	Study details	Outcomes	Reference
Infliximab	Analysis of reports of TB in the FAERS MedWatch program from 1998 to May 29, 2001 (http://www.fda.gov/cder/aers/)	70 reported cases of TB after treatment with infliximab for a median of 12 weeks; in 48 patients, TB developed after ≤ 3 infusions; 40 patients had extrapulmonary disease	10
Infliximab, adalimumab, both	873 IBD subjects treated with TNF- α inhibitors from January 2001 to December 2013	25 newly developed TB cases; adjusted SIR, 41.7 (95% CI: 25.3–58.0%); 19 patients developed TB within 2–62 months of treatment initiation; treatment with infliximab was a significant predictor of TB ($P=0.033$)	12
Infliximab, adalimumab	Retrospective analysis of serious infections within 6 months of initiation of TNF- α inhibitor therapy	TB occurred in 3/175 patients; none treated with anti-TB chemoprophylaxis prior to treatment with TNF- α inhibitor	13
Infliximab, adalimumab, etanercept	Incidence study and case-control analysis to determine risk of TB in patients treated with TNF- α inhibitor in the French RATIO registry over 3 years	No patient received anti-TB chemoprophylaxis; overall adjusted SIR (95% CI), 12.2 (9.7–15.5%); for infliximab, 18.6 (13.4–25.8%); adalimumab, 29.3 (20.3–42.4%); etanercept, 1.8 (0.7–4.3%); treatment with infliximab or adalimumab versus etanercept was an independent risk factor for TB with OR (95% CI) 13.3 (2.6–69.0%) and 17.1 (3.6–80.6%), respectively	14
Infliximab, adalimumab, etanercept	Review of medical records from 2002 to 2009 among patients with AS treated with other agents ($n=919$) or TNF- α inhibitors ($n=354$) for new cases of TB; reference data from the Korean National Tuberculosis Association	Mean TB incidence rate per 100,000 PY =69.8 in general population versus 308 in AS patients treated with other agents versus 561 in AS patients treated with TNF- α inhibitors. Incidence rates for infliximab, 540; adalimumab, 490; etanercept, 0	18
TNF- α inhibitors	Retrospective analysis of 949 patients treated with TNF- α inhibitors at the Yonsei University Health System from 2005 to 2012 evaluating incidence of active TB between LTBI-positive ($n=256$) and -negative patients ($n=521$)	Active TB incidence rate per 100,000 PY =1,107 in LTBI-positive patients; 490 in LTBI-negative patients	19
TNF- α inhibitors	Literature review of articles published in PubMed from January 2000 to October 2011 and data from China Hospital Knowledge Database; RA and AS patients from Africa, Middle East, and Asia	Risk for active TB and other infections increased in patients receiving TNF- α inhibitors; risk is higher among those treated with monoclonal antibodies versus soluble TNF- α receptor	15
Infliximab, adalimumab, etanercept	ARI of TB was estimated using published SIR from the French RATIO registry and incidence of TB. The NNH for each TNF- α inhibitor and the NNT to reduce 1 TB event using etanercept instead of adalimumab or infliximab were calculated	The ARI of TB with anti-TNF- α therapies in Asian countries is substantially higher than Western Europe and North America. NNH ranges were 8–163 for adalimumab, 126–2,646 for etanercept, and 12–256 for infliximab. The NNT to reduce 1 TB event using etanercept instead of adalimumab ranged from 8 to 173 and using etanercept instead of infliximab from 13 to 283	20
Adalimumab, etanercept	Retrospective cohort study on RA patients treated with TNF- α inhibitors from 2006 to 2008 using data from Taiwan's National Health Insurance claims databases. Primary outcome: active TB; TB risk estimated using Cox's proportional hazard model	Active TB rates per 100,000 PY were 1,411.3 for patients treated with adalimumab and 679.5 for patients treated with etanercept. Patients treated with TNF- α inhibitors had a higher risk of TB (aHR 4.87 [95% CI: 2.14–11.06%])	16

Abbreviations: aHR, adjusted hazard ratio; ARI, absolute risk increase; AS, ankylosing spondylitis; CI, confidence interval; IBD, inflammatory bowel disease; LTBI, latent TB infection; NNH, number needed to harm; NNT, number needed to treat; OR, odds ratio; PY, patient year(s); RA, rheumatoid arthritis; SIR, standardized incidence ratio; TB, tuberculosis; TNF- α , tumor necrosis factor- α .

and the Middle East and moderate (1.5–3.5%) in countries of South and Southeast Asia, sub-Saharan Africa, Latin America, and Europe.⁴⁴ It is estimated that 7–9 million people in Latin America are seropositive for HCV, with Grenada, Bolivia, Haiti, Trinidad and Tobago, and El Salvador having the highest

prevalence (>2.5%).^{45,46} Each year, there are >54,000 deaths directly attributable to HCV infection.⁴⁴ As such, it is important to ensure that drugs being administered for concurrent diseases do not activate latent HCV infection and/or make the patient more susceptible to new HCV infection.

For the most part, infection with HCV has been reported to increase the secretion of TNF- α .⁴⁷⁻⁵¹ However, it has also been reported that induced release of TNF- α from monocytes of patients chronically infected with HCV was decreased.⁵² Although there are no large-scale studies to date evaluating the impact of treatment with TNF- α inhibitors on HCV reactivation, several small studies suggest that the risk is low (Table 2).⁵³⁻⁵⁸ In general, the consensus appears to be that as long as prophylactic therapy is used, treatment with TNF- α inhibitors does not significantly increase the risk of HCV reactivation or reinfection.⁵⁹⁻⁶⁴ It has been reported that HCV viral load did not change significantly after 2 years of treatment with TNF- α inhibitors even when specific anti-HCV treatment was not administered.⁶⁵ Based on low level of evidence, the 2015 American College of Rheumatology guidelines to treat patients with RA recommend the use of biological agents concurrent with antiviral therapy in patients simultaneously infected with HCV and the potential use of etanercept to treat RA patients with chronic HCV infection.⁶⁶

Viral hepatitis B

It is estimated that globally, 240–350 million people are chronically infected with hepatitis B virus (HBV); the prevalence is highest in sub-Saharan Africa and East Asia, where 5–15% of the adult population are chronically infected.^{67,68} In the Middle East and the Indian subcontinent, it is estimated that 2–5% of the general population are chronically infected. Other regions with high rates of chronic infection include the

Amazon basin, Central and Eastern Europe, and Alaska.⁶⁷ By comparison, <1% of the population in Western Europe and North America are chronically infected with HBV. More than 600,000 people die each year due to complications from HBV infection, including acute hepatitis, liver cirrhosis, and hepatocellular carcinoma.^{67,69} In animal models of HBV infection, TNF- α produced by HBV-specific cytotoxic T cells inhibits HBV regulation.⁷⁰ It is conceivable, therefore, that inhibiting the TNF- α production may result in adventitious reactivation of HBV. Thus, it is critical that TNF- α inhibitors administered to treat concurrent diseases be evaluated for their potential to cause reactivation of HBV infection and/or make the patient more susceptible to new HBV infection.

Treatment with immunosuppressive agents has been reported to increase the incidence of reactivation of chronic HBV in up to 25% of patients (Table 3).^{64,71-73} HBV reactivation in patients with chronic inactive/resolved HBV infection undergoing immunosuppressive treatment is defined as an increase of $\geq 1 \log_{10}$ IU/mL plus increase in serum HBV-DNA level or the detection of previously undetectable HBV-DNA, and serum alanine aminotransferase (ALT) elevation $>2-3\times$ upper limit of normal. An increase in liver function tests (hepatitis) usually follows viral reactivation.^{74,75} To date, there are no large-scale prospective studies evaluating the risk of HBV reactivation in response to treatment with TNF- α inhibitors. A number of studies reported HBV reactivation,⁷⁶⁻⁸³ whereas some studies reported otherwise.^{53,58,71,84} Even in studies where reactivation was reported, prophylactic

Table 2 Risk of hepatitis C reinfection associated with TNF- α inhibitor treatment

Drug	Study details	Outcomes	Reference
Adalimumab, etanercept	Retrospective analysis determining the rate of HCV or HBV reinfection in RA patients with prior HCV or HBV infection	No cases of HCV or HBV reactivation in any patients. Increased transaminases observed in slightly over 20% of patients, which was associated with concomitant DMARD use, isoniazid prophylaxis, or alcohol abuse	53
TNF- α inhibitors	Retrospective analysis of viral load and liver enzymes in PsA patients with concurrent HCV infection	In most patients, viral load and liver enzymes remained stable through 12 months of observation	54
Adalimumab, etanercept, infliximab	Evaluation of RA patients with concurrent HCV infection treated with TNF- α inhibitors at standard doses	Patients exhibited improvements in all RA-related disease characteristics and general health with benefits persisting up to 22 months of follow-up. There were no significant changes in viral load or liver enzymes	55
Etanercept	Prospective, open-label evaluation of RA patients with concurrent HCV infection treated with etanercept, methotrexate, or combination of the two drugs	Patients exhibited improvements in all RA-related disease characteristics. There were no significant changes in viral load or liver enzymes in any of the three treatment arms	56
Etanercept, infliximab	Retrospective survey of RA patients with concurrent HCV infection treated with etanercept or infliximab	There were no significant changes in viral load or liver enzymes in response to treatment with TNF- α inhibitors	57
Adalimumab, etanercept	Retrospective analysis of plaque psoriasis patients with concurrent HCV and/or HBV infection	There were no significant changes in viral load or liver enzymes in response to treatment with TNF- α inhibitors	58

Abbreviations: DMARD, disease-modifying antirheumatic drug; HBV, hepatitis B virus; HCV, hepatitis C virus; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF- α , tumor necrosis factor- α .

Table 3 Risk of hepatitis B reinfection associated with TNF- α inhibitor treatment

Drug	Study details	Outcomes	Reference
Adalimumab, etanercept	Retrospective analysis determining the rate of HCV or HBV reinfection in RA patients with prior HCV or HBV infection	No cases of HCV or HBV reactivation in any patients. Increased transaminases observed in slightly over 20% of patients, which was associated with concomitant DMARD use, isoniazid prophylaxis, or alcohol abuse	53
Adalimumab, etanercept, infliximab	Determination of rate of HBV reactivation in patients, with RA or spondyloarthritis previously infected with HBV, treated with one or more TNF- α inhibitors	No cases of reactivation observed	71
TNF- α inhibitors	Retrospective evaluation of HBV reactivation in patients with rheumatic diseases treated with TNF- α inhibitors	Reactivation occurred in 1/8 patients who were inactive HBV surface antigen carriers	76
TNF- α inhibitors	Retrospective review to determine HBV reactivation in RA patients treated with TNF- α inhibitors	There were no cases of HBV reactivation in patients receiving prophylactic antiviral therapy. In patients not receiving antiviral therapy, HBV reactivation occurred in 5/8 (62.5%) patients	77
Adalimumab, etanercept, infliximab	Meta-analysis to measure HBV reactivation in TNF- α inhibitor-treated patients with rheumatic diseases who were occult carriers of HBV	HBV reactivation was observed in 8/468 (1.7%) patients	78
Adalimumab, etanercept, infliximab	Systematic review to evaluate HBV reactivation in TNF- α inhibitor-treated patients with rheumatic diseases who were occult carriers of HBV	HBV reactivation was observed in 15/122 (39.3%) patients	79
TNF- α inhibitors	Systematic analysis to evaluate HBV reactivation in patients who were occult carriers of HBV treated with TNF- α inhibitors	HBV reactivation was reported in 35/89 (39%) patients positive for HBV surface antigen. HBV reactivation was higher in patients previously treated with immunosuppressive agents and lower in those who received antiviral prophylaxis	80
Adalimumab, etanercept	Retrospective analysis of plaque psoriasis patients with concurrent HCV and/or HBV infection	There were no significant changes in viral load or liver enzymes in response to treatment with TNF- α inhibitors	58
TNF- α inhibitors	Prospective study determining HBV reactivation in patients with chronic HBV infection, resolved HBV infection, or vaccinated against HBV	HBV reactivation observed in only one patient due to the emergence of lamivudine-resistant mutant strain of virus. No other incidence of HBV reactivation observed	81
TNF- α inhibitors	Assessment of HBV reactivation in patients with inflammatory arthritis treated with TNF- α inhibitors	HBV reactivation observed in 2/6 patients with chronic HBV infection who received no antiviral prophylaxis, but not in the other four patients who did. In 31 inactive carriers, increase in viral load was observed in 6/22 (27.3%) patients without antiviral prophylaxis, but no increase in the nine patients who received it. No HBV reactivation observed in 50 patients with resolved HBV infection	82
TNF- α inhibitors	Retrospective analysis of HBsAg-positive patients who received DMARDs	HBV reactivation was demonstrated in ~17% of patients receiving immunosuppressive treatment, 12% of patients receiving antiviral prophylaxis, and 24% of patients not receiving antiviral prophylaxis	83
Infliximab	Retrospective analysis of RA patients treated with infliximab with prior exposure to HBV	There was no statistically significant difference in liver enzymes between infliximab-treated patients with prior exposure to HBV and those without such exposure	84

Abbreviations: DMARD, disease-modifying antirheumatic drug; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; RA, rheumatoid arthritis; TNF- α , tumor necrosis factor- α .

treatment with an antiviral agent appeared to prevent reactivation.^{77,80–82} Expert opinion indicates that treatment with TNF- α inhibitors is generally safe, with an overall low risk of HBV reactivation in areas of low HBV prevalence.^{59,64,72,85–87}

It is strongly recommended that patients with active or chronic HBV infection be given preemptive antiviral treatment 1–2 weeks prior to, during, and for at least 6 months after stoppage of TNF- α inhibitor treatment to reduce the

risk of HBV reactivation.^{59,64,72,86–89} Furthermore, these same guidelines recommend that patients who have occult HBV infection (HB surface antigen negative, anti-HBc antibody positive, and HBV-DNA positive) or with a history of HBV infection but seronegative at the time of initiation of TNF- α inhibitor therapy should be closely monitored for potential reactivation so that antiviral prophylaxis can be administered in a timely manner.

Discussion

One of the limitations of this review is that data on the effects of treating patients with RA who were at risk for TB or hepatitis infection were available for only three TNF- α inhibitors: etanercept, adalimumab, and infliximab. Consequently, although it would be difficult to draw a general conclusion for the whole class of TNF- α inhibitors, it is expected that other TNF- α inhibitors would behave similarly.

Based on the available information^{56,90–95} and our own clinical practices, our recommendations for how to treat patients with RA who are at risk for infection with TB, hepatitis C, or hepatitis B are summarized in Table 4. For patients with a risk of infection with TB or reactivation of LTBI, we recommend 1) an initial screen with at least TST, preferably followed with an IGRA for those who were immunized with BCG; 2) a minimum prophylactic treatment of 1 month prior to the initiation of treatment with TNF- α inhibitors,

regardless of the prophylactic treatment used since they vary by country; and 3) monitoring regularly, at least once a month. For patients with a high risk of HCV infection, we recommend consultation with a hepatologist to determine whether or not antiviral prophylactic treatment is needed, eg, with cyclosporine A, ribavirin, and/or interferon. For other patients, we recommend treating with a TNF- α inhibitor, preferably one that has the least risk of HCV infection or reactivation, eg, etanercept along with regular monitoring, at least once a month, to determine whether antiviral treatment needs to be initiated. For patients with active or a high risk of HBV infection, we recommend prophylactic antiviral treatment for at least 2 weeks prior to the initiation of treatment with a TNF- α inhibitor and for 6 months following cessation of this treatment. The choice of antiviral treatment should be made in consultation with a hepatologist. For patients with suspected HBV infection, we recommend testing for HBV surface antigen prior to initiating prophylactic antiviral or TNF- α inhibitor treatment. Patients should be monitored throughout the period during which they are receiving TNF- α inhibitor treatment, at least once a month.

Conclusion

This review confirms earlier findings that TNF- α inhibitors are safe to use with appropriate monitoring and chemoprophylaxis at high risk for TB infection and TB or viral hepatitis reactivation.

Table 4 Treatment recommendations

Infection	Recommendation	Notes
TB/LTBI	<ol style="list-style-type: none"> 1. Screen for latent infection or exposure, eg, via immunization 2. Prophylactic treatment for at least 1 month 3. Choice of TNF-α inhibitor with least risk 4. Regular monitoring of patients for infection or reactivation of LTBI 	<ol style="list-style-type: none"> 1. Screening with at least TST, preferably followed with IGRA for patients previously exposed or immunized with BCG 2. Prophylactic treatment and length will depend on the country 3. Etanercept (most data available) or secukinumab 4. Suspend TNF-α inhibitor treatment if infection discovered; restart TNF-α inhibitor treatment only if infection resolved
HCV	<ol style="list-style-type: none"> 1. Consult with hepatologist if antiviral prophylaxis is needed 2. Choice of TNF-α inhibitor with least risk 3. Regular monitoring of patients for infection or reactivation of HCV 	<ol style="list-style-type: none"> 1. If prophylactic treatment is not used, patient must be monitored more closely 2. Etanercept (most data available) 3. Suspend TNF-α inhibitor treatment if infection discovered; restart TNF-α inhibitor treatment only if infection resolved
HBV	<ol style="list-style-type: none"> 1. Test for HBsAg to determine whether prophylactic antiviral treatment is needed 2. Consult with hepatologist on antiviral prophylactic treatment to be used 3. Prophylactic treatment for at least 2 weeks prior to initiation of TNF-α inhibitor 4. Choice of TNF-α inhibitor with least risk 5. Regular monitoring of all patients at risk for infection or reactivation of HCV 6. Antiviral treatment for at least 6 months after treatment with TNF-α inhibitor stopped 	<ol style="list-style-type: none"> 1. If prophylactic treatment is not used, patient must be monitored more closely 2. Choice of treatment with a single agent or a combination of agents to ensure prevention of infection/reactivation 3. Antiviral prophylactic treatment should be initiated no later than initiation of TNF-α inhibitor treatment 4. Etanercept (most data available) 5. Suspend TNF-α inhibitor treatment if infection discovered; restart TNF-α inhibitor treatment only if infection resolved 6. Consult with hepatologist if longer antiviral treatment is needed after TNF-α inhibitor stopped

Abbreviations: BCG, *Bacillus Calmette–Guérin*; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IGRA, interferon gamma release assay; LTBI, latent tuberculosis infection; TB, tuberculosis; TNF- α , tumor necrosis factor- α ; TST, tuberculin skin test.

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Author contributions

All authors contributed to identifying articles for this review, data analysis, drafting, and critically revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

Y-HC is on the advisory boards of AbbVie, Astellas, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Guigai, Inova Diagnostics, Johnson & Johnson, Lilly, MSD, Novartis, Pfizer, Roche, and ThermoFisher Scientific and has received funding for research and clinical trials from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Guigai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, Sanofi, and UCB. HMDSdC is a consultant for AbbVie, AstraZeneca, Janssen, Novartis, Pfizer, and Roche. UK is a consultant for AbbVie, BMS, MSD, Pfizer, and UCB. LJQL, GS, RP, and RV are employees of Pfizer and own stock in the company. JJJ is on the advisory board of Pfizer. The authors report no other conflicts of interest in this work.

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