

Biologic Agents in the Treatment of Rheumatic Diseases with Chronic Viral Infection. Where Are We?



Biologic agents have increased the therapeutic armamentarium against immune-mediated disorders, and particularly rheumatic diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Nevertheless, infectious side effects are a major concern in the use of these biologics, especially anti-tumor necrosis factor (TNF) agents¹. In this context, the use of TNF blockers in patients with chronic viral infection seems hazardous, and represents an unresolved issue².

In this issue of *The Journal*, Zingarelli, *et al*³ report 3 cases of patients with RA positive for HBsAg, in which anti-TNF therapies (etanercept, infliximab then etanercept, adalimumab) under prophylactic use of lamivudine were not associated with hepatitis reactivation, even after anti-TNF discontinuation with prolonged lamivudine therapy.

In one of their cases, an increase in HBV viral load occurred after discontinuation of methotrexate. Methotrexate was reported to induce subfulminant hepatitis B virus reactivation after its withdrawal^{4,5}. This illustrates the interactions of the underlying condition and the associated immunosuppressive therapy that may confuse our interpretation of the responsibility of the biologic agent in viral reactivation.

Irrespective of chronic viral infection, anti-TNF agents may induce immune-mediated hepatitis⁶, with different risk between chimeric antibody and soluble receptor. Although uncommon, this possibility should be kept in mind and ruled out in case of acute hepatitis occurring under TNF blockers.

Anti-TNF should be used with great caution in patients with chronic hepatitis B⁷. Only a few reports are available describing such a situation, as emphasized by Zingarelli, *et al*³, sometimes due to an incomplete screening before starting anti-TNF therapy. This reactivation may occur whatever currently available anti-TNF agent is used, illustrating a class effect of these agents, and the implication of TNF- α and its receptors in the immune-mediated control of viral replication⁸.

It may be important to account for the underlying disease. In RA, there are currently alternative biologic therapeutic options to TNF blockers, but this is not the case in other conditions such as AS. We recently encountered 4 cases of HBsAg-positive patients with AS treated with anti-TNF agents⁹. In 2 cases, HBsAg positivity was a finding of the pretherapeutic screening; in the 2 other cases, chronic viral infection was known before the rheumatic disease began. In 2 cases, lamivudine treatment was initiated after a short-term reactivation (increase in viral load), and in 2 cases antiviral therapy was concomitant to initiation of anti-TNF, with control of the viral disease for a 12–48 month followup. We agree with Zingarelli, *et al*³ about the interest of longterm followup of these patients, even after withdrawal of anti-TNF therapy. Because of their potent antiviral activity associated with a high barrier to resistance, entecavir and tenofovir are the first-line antiviral therapies now recommended in chronic hepatitis B¹⁰. However, the majority of HBV reactivations associated with anti-TNF reported to date were controlled by lamivudine, the first available nucleoside analog efficient against HBV. The literature review in the article by Zingarelli, *et al*³ shows that lamivudine was efficacious if initiated before anti-TNF treatment or in the case of hepatitis reactivation. Nevertheless, acquired resistance commonly occurred after several months of lamivudine therapy¹¹, as in one of our cases⁹ after 42 months and 3 successive anti-TNF agents. The addition of a second antiviral agent (adefovir) despite ongoing anti-TNF therapy led to the subsequent control of viral load in our case. Recently, a HBsAg-positive patient with RA receiving tocilizumab (anti-interleukin 6 receptor antibody) for more than 5 years along with entecavir was reported to have no exacerbation of hepatitis¹². All these cases emphasize the need for tight followup of HBV viral load in HbsAg-positive patients receiving anti-TNF, and biologic treatment in general.

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Surprisingly, few cases of HBsAg-positive carriers treated with anti-TNF without antiviral therapy did not experience HBV reactivation over a 12 month followup period¹³. Conversely, HBV reactivation under anti-TNF has been reported in some HBsAg-negative, HBc and HBs antibody-positive patients, suggesting that occult HBV infection may be exacerbated by anti-TNF¹⁴. Such an event, however, seems uncommon: preliminary results of 34 month followup of 21 HBsAg-negative, HBc and HBs antibody-positive patients with inflammatory rheumatism pattern treated by TNF therapy showed no HBV reactivation¹⁵.

Viral reactivations under anti-TNF are not restricted to HBV¹⁶ or rheumatologic illness³. HBV reactivation under rituximab has been demonstrated, despite antiviral therapy, in hematological conditions^{17,18}, as well as in AS¹⁹. A retrospective study²⁰ reported 64 cases of viral infection in patients receiving rituximab to treat lymphoma; the infection was mainly due to HBV (39%), cytomegalovirus (23%), and varicella zoster virus (9%).

An expert group of the French Society for Rheumatology recommends serological testing for HBV before starting rituximab. In case of HBV infection, advice from a hepatologist must be obtained before making treatment decisions²¹.

Obviously, the situation is not unequivocal, and practical guidelines based upon case records as proposed in the article³ are useful for current practice, since prospective randomized studies in these at-risk patients would probably not be performed.

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REFERENCES

- Patkar NM, Teng GG, Curtis JR, et al. Association of infections and tuberculosis with anti-tumor necrosis factor alpha therapy. *Curr Opin Rheumatol* 2008;20:320-6.
- Wendling D, Herbein G. TNF-alpha antagonist therapy in patients with joint disease and chronic viral infection. *Joint Bone Spine* 2007;74:407-9.
- Zingarelli S, Frassi M, Bazzani C, et al. Use of tumor necrosis alpha-blocking agents use in hepatitis B virus-positive patients. Reports of 3 cases and review of the literature. *J Rheumatol* 2009;36:1188-94.
- Narvaez J, Rodriguez-Moreno J, Martinez-Aguila MD, Clavaguera MT. Severe hepatitis linked to B virus infection after withdrawal of low dose methotrexate therapy. *J Rheumatol* 1998;25:2037-8.
- Ito S, Nakazono K, Murazawa A, et al. Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient. *Arthritis Rheum* 2001;44:339-42.
- Thieffin G, Morelet A, Heurugué A, et al. Infliximab-induced hepatitis: Absence of cross-toxicity with etanercept. *Joint Bone Spine* 2008;75:737-9.
- Pham T, Claudepierre P, Deprez X, et al; Club Rhumatismes et Inflammation, French Society of Rheumatology. Anti-TNF alpha therapy and safety monitoring. Clinical tool guide elaborated by the Club Rhumatismes et Inflammations (CRI), section of the French Society of Rheumatology (Société Française de Rhumatologie, SFR). *Joint Bone Spine* 2005;72 Suppl 1:S1-S8.
- Herbein G, O'Brien WA. Tumor necrosis factor (TNF)-alpha and TNF receptors in viral pathogenesis. *Proc Soc Exp Biol Med* 2000;223:241-57.
- Wendling D, Di Martino V, Prati C, et al. Spondyloarthropathy and chronic B hepatitis. Effect of anti-TNF therapy. *Joint Bone Spine*; doi:10.1016/j.jbspin.2008
- European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol* 2009;50:227-42.
- Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology* 1999;30:1302-6.
- Nagashima T, Minota S. Long-term tocilizumab therapy in a patient with rheumatoid arthritis and chronic hepatitis B. *Rheumatology* 2008;47:1838-40.
- Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. *J Rheumatol* 2008;35:421-4.
- Montiel PM, Solis JA, Chirinos JA, et al. Hepatitis B virus reactivation during therapy with etanercept in an HBsAg-negative and anti-HBs-positive patient. *Liver Int* 2008;28:718-20.
- Charpin CH, Guis S, Colson P, et al. A monitoring of patients with hepatitis B serological pattern indicating past infection and treated by TNF alpha inhibitor for inflammatory rheumatism: preliminary results [abstract]. *Arthritis Rheum* 2008;58 Suppl:S558.
- Wendling D, Streit G, Toussier E, Prati C. Herpes zoster during anti TNF treated chronic arthritis. *Joint Bone Spine* 2008;75:540-3.
- Khaled Y, Hanbali A. Hepatitis B virus reactivation in a case of Waldenstrom's macroglobulinemia treated with chemotherapy and rituximab despite adefovir prophylaxis. *Am J Hematol* 2007;82:688.
- Yang SH, Kuo SH. Reactivation of hepatitis B virus during rituximab treatment of a patient with follicular lymphoma. *Ann Hematol* 2008;87:325-7.
- Rodriguez-Escalera C, Fernández-Nebro A. The use of rituximab to treat a patient with ankylosing spondylitis and hepatitis B. *Rheumatology* 2008;47:1732-3.
- Aksoy S, Harputuoglu H, Kilickap S, et al. Rituximab related viral infections in lymphoma patients. *Leuk Lymphoma* 2007;48:1307-12.
- Pham T, Fautrel B, Gottenberg JE, et al; Rheumatic Diseases and Inflammation Group (Club Rhumatismes et Inflammation, CRI) of the French Society for Rheumatology (Société Française de Rhumatologie, SFR). Rituximab (MabThera) therapy and safety management. Clinical tool guide. *Joint Bone Spine* 2008;75 Suppl 1:S1-99.

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