Reply to: "Treatment of veterans with hepatitis C in the United States Department of Veterans Affairs"

To the Editor:
I would like to thank Dr. Ross.

(1) Dr. Ross does not state how many veterans with HCV are currently receiving care at the Department of Veterans Affairs (VA). In 2008, VHA clinicians cared for over 147,000 veterans with chronic HCV [1]. Treating 4500 patients with HCV in 20 months is only 225 patients per month. The VA is currently treating less than 2% of infected veterans per year with boceprevir and telaprevir. It will take more than fifty years for the VA to treat all of their HCV infected patients. Evidence based care of an infectious disease is cure of the infection not the development of integrated models to address comorbidities. If 98% of patients with a curable infection are not treated each year, the VA's response is inadequate.

(2) The VA does a better job with the human immunodeficiency virus (HIV) treating 78% of veterans [2]. The number of patients on antiviral therapy clearly indicates that HIV is a high priority for the VA while HCV treatment is not.

(3) Telaprevir is not available as a non-formulary drug at the Louisville VA. Boceprevir is on the formulary there.

(4) More than 1800 patients with HCV antibodies have been identified at the Louisville VA over 19 years. They had multiple physicians providing care.

(5) $100 million for antiviral therapy over 20 months is $5 million per month. This is clearly inadequate to treat 147,000 veterans with hepatitis C. This is why legislation should be passed so that all veterans with HCV immediately prequalify for their choice of Medicaid or Medicare. They could then obtain antiviral therapy in the private sector instead of waiting for the VA to treat 2% of them each year. Now, many are trapped in the VA system while their curable infection progresses to liver cancer, liver failure and death.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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[2] http://www.va.gov/opa/publications/factsheets/fs_hiv_aids_treatment.pdf.

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Use of TNFα antagonists in refractory AIH: Revealing the unforeseen

To the Editor:
We read with considerable interest the paper by Weiler-Normann *et al.* in the *Journal of Hepatology* [1], which reported promising results regarding the use of infliximab as a therapeutic option in difficult-to-treat patients with autoimmune hepatitis (AIH). Although the exact role of tumor necrosis factor α (TNFα) in the pathogenesis of AIH has not been elucidated yet, very recently, it has been shown in a mouse model of fatal AIH that TNFα is essential in the induction of AIH through upregulation of hepatic CCL20 expression, which allows migration of dysregulated splenic T cells [2]. As a consequence, the efficacy of anti-TNFα therapy in AIH could have a pathophysiological basis, taking also into account that TNFα is produced in large amounts in the liver, in the context of AIH, by macrophages, $CD8^+$ T cells and possibly Th17 lymphocytes [3]. However, it is already known from the use of anti-TNFα treatment in various autoimmune diseases that anti-TNFα can also be immunogenic, with development of either autoantibodies or true autoimmune diseases, making infliximab a two-edged sword [4].

The induction of AIH is one of the examples of the latter "therapeutic paradox" during anti-TNFα treatment. In fact, the hepatic flare reported in the second patient of the study of Weiler-Normann *et al.* [1] could have been such an effect, especially if it was combined with an IgG increase. Here, we are reporting an additional case of a 30-year old female patient admitted to our department because of infliximab induced AIH, in an attempt to further emphasize the "two-sided" face of anti-TNFα treatment. Our patient had a history of refractory psoriasis treated with infliximab (5 mg/kg at week 0, 2, 6 and then every 8 weeks by intravenous infusion) and presented to our department with an asymptomatic transaminase flare (ALT and AST >10 × upper normal limit), 3 months after starting anti-TNFα therapy. Patient's history and extensive laboratory tests excluded genetic, toxic or viral causes of acute hepatitis. Autoimmune serology revealed anti-nuclear and anti-smooth muscle antibodies positivity (titers 1/640 and 1/320, respectively), with reactivity against F-actin. Serum IgG levels were also elevated (1280 mg/dl before anti-TNFα treatment; 1755 mg/dl at AIH diagnosis; upper normal limit: 1600 mg/dl), while liver biopsy revealed moderate interface hepatitis along with emperipolesis, hepatic rosette formation, drop out necrosis (replacement of dead hepatocytes by inflammatory cells) and lymphoplasmocytic infiltrates in portal tracts extending into the lobule. Taken together, all the above gave a simplified score of 7, confirming the diagnosis of definite AIH [5]. Apart from infliximab withdrawal, the patient was treated after an informed consent, according to our experience and

clinical practice [6], with prednisolone (initial dose 1 mg/kg/day) plus mycophenolate mofetil (2 g/day), resulting in complete remission of AIH within 2 months, as attested by normal transaminases and IgG levels. Prednisolone was discontinued at the 4th month, but 2 months later a biochemical relapse was observed (ALT and AST up to three times the upper normal limit but normal IgG) and again prednisolone was started at a low dose (20 mg/day). At the time of this writing (12 months from initial treatment and 6 months from re-treatment), the patient has complete response under mycophenolate monotherapy (3-month prednisolone off treatment).

This report adds to a small but increasing number of published cases of AIH induced by TNFα blockade, highlighting the dual effects that anti-TNFα therapy might have, particularly in the case of AIH [7,8]. The paradox of anti-TNFα therapy in AIH is mainly attributed to the disruption of the regulatory role of TNFα signaling on the immune system. TNFα blockade interferes with the normal cytotoxic T lymphocyte suppression of self-reactive B-cell population, leading to autoantibody production, a hallmark of AIH diagnosis, although from the pathophysiological point of view the role of autoantibodies in AIH development is obscure. Furthermore, anti-TNFα therapy disrupts the TNFα-mediated apoptosis of activated T lymphocytes resulting in unregulated lymphocyte activation [9].

Moreover, treatment with infliximab predisposes patients to severe infections, as clearly demonstrated by this series of Weiler-Normann *et al.* [1], where 7 out of 11 patients treated with infliximab, had serious bacterial or viral infections. Indeed, the high risk for serious infections is a well-recognized side effect of anti-TNFα therapy in patients with rheumatoid arthritis or inflammatory bowel disease [10]. However, the increased odds ratio might be even more crucial in patients with advanced liver disease (in this series [1], 7 out of 11 patients had histologically confirmed cirrhosis), since the already existing dysregulation of the immune system due to cirrhosis, may further increase the risk of serious infectious complications after anti-TNFα treatment.

Therefore, the induction of autoimmunity along with the possibility of lethal infections constitutes the "dark side" of anti-TNFα therapy in AIH. In our opinion, TNFα blockade could be a therapeutic option for refractory cases of AIH, taking into account its reported efficacy and the potential role of TNFα in the pathogenesis of AIH [2,3]. However, we strongly believe that anti-TNFα treatment for AIH could be a rational option only after alternative regimens with a safer side-effect profile, such as cyclosporine, tacrolimus or mycophenolate mofetil [6] have failed. In any case, the incapability to predict efficiently the "unforeseen complications" of such a treatment, such as the emergence of severe infections or, in particular, the development and/or deterioration of autoimmunity, should be seriously weighted in the final decision of the clinician.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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To the Editor:
We would like to thank Saitis and colleagues [1] for their view on TNFα antagonist use in difficult-to-treat autoimmune hepatitis (AIH) and for the addition of pathophysiological mechanisms, which may explain the effects of this treatment in AIH [2].

There are around 40 case reports in the literature – including the most recent one presented here – that have described the development of AIH or an immune mediated hepatitis after administration of anti-TNFα agents such as infliximab [3], adalimumab [4] and etanercept [5]. Whether the induction of AIH