Letters to the Editor

To the Editor:

We would like to thank Dr. Borman [1] and colleagues for their case presentations illustrating the potentially harmful impact of anti-TNF-agents on the liver. In this case in their ability to induce autoimmune hepatitis (AIH). We have previously shown that infliximab, one of the anti-TNF-drugs, may successfully treat AIH in selected difficult-to-treat cases [2].

It is well known, that autoimmune features may occur during treatment with anti-TNF-agents, especially the emergence of anti-dsDNA-antibodies has been described in up to 30% of the patients [3]. Yet, not all patients who develop autoantibodies will also develop clinical symptoms or disease. Further on, most patients at risk are likely to have a strong genetic background for the development of autoimmune diseases as anti-TNF-agents are primarily used to treat autoimmune diseases. Therefore, it seems necessary to discriminate between de novo autoimmune diseases in genetically prone patients and paradoxical inflammation that may also develop as a consequence of use of these agents. Especially for infliximab, the oldest among the recombinant antibodies (and unlike etanercept as a soluble receptor also binding to cell-bound TNF), a wide number of immunological side effects have been described [4], among others psoriasis-like lesions, lupus like syndrome, systemic lupus erythematoses, (paradoxical) joint inflammation, (de-novo) inflammatory bowel disease, uveitis as well as different forms of vasculitis [5].

Conflict of interest

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References


Meredith A. Borman
Stefan Urbanski
Mark G. Swain*

Faculty of Medicine, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta, Canada
*Corresponding author.

E-mail address: swain@ucalgary.ca

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Also, there are some case reports describing exacerbations of the underlying treated disease when applying anti-TNF-drugs. The potential mechanism of how anti-TNF-drugs induce this paradoxical inflammation is unknown and most likely, there are several phenomena contributing:

1. There is a high likelihood of genetic predisposition in patients developing paradoxical inflammation or de novo autoimmune diseases. Unfortunately, the vast majority of patients with new onset immunological diseases or symptoms (e.g., AIH as described by Borman et al. in this issue) have not been HLA-typed. Most likely, these are individuals with a strong genetic predisposition for AIH (namely, e.g., HLA-DRB1*0301 or HLA-DRB1*0401 positive in the case of new onset or drug-triggered AIH).

2. Anti-TNF may block or decrease production of (immuno-suppressive) glucocorticoids in end-organs and thereby contribute to promotion of inflammation [6]. In an experimental setting, lack of TFN may increase the level of inflammation [7].

3. Anti-TNF-antibodies may bind to cell-bound TNF and thereby induce apoptosis in these cells [10]. Cell death may lead to the release of nucleosome-derived antigens and thereby induce autoantibodies directed against nucleosome autoantigens in patients who are genetically susceptible.

4. The down-regulation of TNF may lead to an upregulation of IL-10 which leads to an activation of (autoreactive) B cells, it may also lead to a general upregulation of a TH2-immune response.

5. It has been noted that the presence of anti-cardiolipin antibodies and bacterial infections have been associated in patients on anti-TNF-drugs. It has been postulated that unmethylated CpG motifs of bacterial antigens can activate CD86-expression, which may lead to IL-6-expression in B cells and synthesis of IFN-gamma, by NKT and TH1 cells. This may then lead to paradoxical inflammation in affected patients [5].

One main question remains unanswered by this and other reports on anti-TNF-induced liver injury: Did these patients really suffer from drug-induced AIH or rather from immune-mediated drug-induced liver injury (DILI) [8]? The presence of fibrosis suggests that these patients most likely have predisposing features (and in the report by Borman and colleagues especially in the latter patient, who had exhibited liver enzyme elevations even before the initiation of infliximab treatment, AIH with low activity cannot be ruled out) and therefore, “true” AIH triggered by infliximab remains more likely. The other question that is not fully understood is why re-exposure to other anti-TNF-drugs in most patients did not lead to a relapse of AIH. Is it because of a different kinetic or route of application of the drug (adalimumab, certolizumab as well as golimumab are administered subcutaneously vs. infliximab, that is infused intravenously) or the different type of antibody (partly or fully humanized vs. soluble receptor)?

In general, the safety profile of the anti-TNF-drugs is acceptable and the risk of liver enzyme elevation for patients on TNF-antagonists is very low [9]. Therefore, anti-TNF-agents remain safe for the vast majority of patients.

For the off-label use in autoimmune hepatitis, it seems important to select patients eligible for this kind of rescue-treatment carefully. Patients receiving this rescue-treatment should have shown failure towards conventional treatment. In addition, disease activity should be confirmed by elevated transaminases and the demonstration of inflammation on liver biopsy. Finally, treatment should be monitored closely.

In future, it may be feasible to individualize treatment even to the point that pre-treatment cytokine levels could be measured in order to make sure, that the patients identified for such treatment truly have a predominant TH1-response.

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References


Christina Weiler-Normann*
Johannes Herkel
Christoph Schramm
Ansgar W. Lohse
Department of Medicine,
University Medical Center Hamburg-Eppendorf,
Martinistrasse 52, 20146 Hamburg,
Germany

*Corresponding author.
E-mail address: cweller@uke.de

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