In a previous issue of *Arthritis Research & Therapy*, James Kobie and colleagues from the University of Rochester provide a detailed analysis of the influence of inflammation and TNF blockade on the humoral immune response to seasonal trivalent influenza vaccines [1]. Their manuscript sheds light on the role of TNF in B and plasma cell function, and gives a partial answer to the important clinical questions of how to handle vaccinations of patients under TNF blockade.

When TNF blockers became available, it first became clear that TNF is essential for fighting intracellular pathogens, such as *Mycobacterium tuberculosis* or *Listeria monocytogenes*. In contrast, and despite the cytokine’s name, TNF blockade has not been shown to play a role in solid tumor formation in general [2]. The two notable exceptions are skin cancers [2] and, in the Wegener’s Granulomatosis Etanercept Trial [3], combination therapy with cyclophosphamide and etanercept. Under both conditions, one would expect DNA strand breaks to be newly induced by UV light and cyclophosphamide, respectively. The inflammatory removal of cells damaged in this way may be impaired under TNF blockade.

The fact that, under TNF blockade, many patients develop anti-nuclear antibodies, antibodies to double-stranded DNA, or antibodies to phospholipids [4,5] has been seen as an argument that blocking TNF fostered the humoral immune response, which chronic TNF exposure would otherwise keep in check [5,6]. Kobie and colleagues [1] now, in a combination of approaches to analyze the effects of seasonal influenza vaccination, back data that the contrary is true, at least for the normal, protective humoral response, in that TNF apparently leads to increased antibody titers [1].

By hemagglutination inhibition assay, pre- and post-vaccination antibody titers to influenza antigens were measured in a large group of 164 patients with rheumatoid arthritis (RA), including 61 under TNF blockade and 70 under methotrexate, and in 97 healthy individuals. While patients treated with TNF blockers, mostly in combination with methotrexate, depending on the exact antigen, reached only approximately half of the normal antibody levels one month after the vaccination, this effect persisted at six months. The effect of methotrexate was similar, but much milder, while untreated RA effectively increased the immune response compared to healthy individuals.

The authors argued that TNF blockade would likely affect memory B cells, given that influenza vaccine responses mostly are secondary immune responses. One month after vaccination, EliSpot assays of a subset of patients indeed demonstrated that the increase in influenza-specific memory B cells was reduced in RA patients under TNF blockade, but not in the other RA patients, and that this effect was even more pronounced at six months. In a smaller subset, IgD CD27+CD38+ plasmablasts of patients under TNF blockade were not as much increased as in healthy individuals after five to seven days, while even more induced in active, untreated RA. Both findings correlated well with each other, and with the resulting humoral immune response.

**Abstract**

Only after biological response modifiers have become available have we begun to understand some of the complex functions of TNF in the human immune system. TNF is clearly essential for fighting intracellular pathogens, but probably not essential for fighting tumors. TNF influence on the humoral immune response, in contrast, has been more complicated to decipher, since TNF blockade is associated with both autoantibody formation and (somewhat) reduced responses to vaccination. Novel data now show that TNF is good for the humoral immune response. Vaccinations still work, however, and should be strongly recommended.
In combination, the data suggest that TNF and/or the cytokine network induced in active RA foster the formation of plasmablasts, while this is clearly reduced under TNF blockade, and, to a lesser degree, also under methotrexate. This also fits well with the fact that plasmablasts are increased in active systemic lupus erythematosus [7], where TNF levels are highly increased [5]. In an alternative explanation, the authors also argue for a potential role of follicular dendritic cells, but the findings they refer to may be related to a specific effect of etanercept, which also blocks lymphotoxin-α, rather than to TNF blockade. After all, lymphotoxin-α, rather than TNF, is known to be essential for the correct formation of lymphoid structures [8].

Having the novel data in view, the increased formation of autoantibodies to chromatin and phospholipids seen under TNF blockade [5], including preformed lgG antibodies [9], probably is more related to these specific autoantigens than to an overall positive influence on plasmablasts, consistent with the model of increased cell death upon TNF withdrawal leading to more antigen presented [9].

Importantly, and of clinical impact, we now know that influenza vaccination responses are indeed somewhat reduced in patients under TNF blockade, but are still protective in most patients, a finding in line with the majority of previous reports [10-14]. While there are slight differences when other vaccinations are in focus, such as that methotrexate, and not TNF blockers, apparently causes the diminished reaction to pneumococcal vaccination [13,15,16], the overall clinical outcome is similar: vaccinations may not work as well, but still work under the combination of TNF blockade and methotrexate, and are very safe in general.

It is important, therefore, not to come to the wrong clinical conclusions with regard to vaccination. Infections are most probably even more dangerous for patients under TNF blockade. The answer, therefore, is certainly not to leave vaccinations out, but to vaccinate more often, more consistently, and everybody with a rheumatic disease [17,18]. Obviously, vaccination before having to initiate a biological response modifier will be the best option.

Abbreviations
RA, rheumatoid arthritis; TNF, tumor necrosis factor.

Competing interests
The author declares that they have no competing interests.

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