Demyelination after anti-TNF therapy - who is at risk?

Isabelle Williams[1], Holm H Uhlig [1, 2, 3]

[1] Translational Gastroenterology Unit, University of Oxford, Oxford, UK.

[2] Department of Paediatrics, University of Oxford, Oxford, UK.

[3] Oxford NIHR Biomedical Research Centre, Oxford, UK.

Corresponding author

Holm H. Uhlig (holm.uhlig@ndm.ox.ac.uk), Translational Gastroenterology Unit, Experimental Medicine, University of Oxford, John Radcliffe Hospital Oxford, OX3 9DU, UK. Phone: 0044 1865 8 57963

Over 30 years ago, Marc Feldmann, Ravinder Maini and colleagues demonstrated in a preclinical model that anti-tumour necrosis factor (TNF) antibodies reduced IL-1 in the supernatant of synovial cells of Rheumatoid arthritis patients [1]. Since then TNF targeting therapies have been a transformational treatment for patient with a spectrum of immune mediated disorders such as rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, and inflammatory bowel diseases both Crohn's disease and ulcerative colitis [2]. In addition to increased risk of infection and malignancy, blockade of TNF can lead to adverse polarisation of the immune system causing drug induced lupus erythematosus, paradoxical induction of psoriasis-like skin disease, inflammatory bowel disease-like gut inflammation and nervous system demyelination[3]. The molecular mechanisms of those adverse and paradoxical inflammatory responses are largely unclear.

Anti-TNF associated demyelination shows similarities to multiple sclerosis. One important question is therefore whether anti-TNF associated demyelination unmasks a genetic or environmental predisposition to multiple sclerosis. The genetic susceptibility of multiple sclerosis include over 200 genetic loci such as HLA-DRB1 and non-HLA candidate genes such as *TNFRSF1A, TYK2, CD58* or *STAT3* highlighting a complex contribution of the innate and adaptive immune system [4] [5]. Those genetic susceptibility variants suggest a role for haematopoietic cells such as dendritic cells, natural killer cells, T cell and B cells in the disease pathogenesis as well as tissue resident cells such as microglia but interestingly not other cells of the central nervous system such as astrocytes or neurones [4]. In line with such a genetically informed immune pathogenesis is that targeting activated immune cell populations that home into the brain of multiple sclerosis patients has shown efficacy in randomized controlled trials[5]. Those interventions includes interferon-b, dimethyl fumarate, fingolimod as well as several monoclonal antibodies such as anti-α4-integrin, anti-CD52, anti-CD25, and anti-CD20 [5].

The TNF pathway has been linked to demyelination and neuronal inflammation in several ways: The multiple sclerosis risk variant TNFRSF1A rs1800693 causes an alternative splice variant of the TNFR1 that acts as an antagonist [6]. Mutations in TNFRSF1A can lead to TNF receptor–associated

periodic syndrome which features inflammatory demyelination. Use of TNF antagonists worsen symptoms in multiple sclerosis patients [7]. Anti-TNF therapy results in increased risk of demyelination in immune mediated disorders [8]. In light of the severe neurological consequences, it is important to identify strategies to identify those patients at risk of drug induced demyelination and to understand the mechanism, to prevent those being exposed to anti-TNF and to identify effective treatment strategies.

In this issue of JCC, Lin, Green and Hendy et al. set out to identify whether risk factors associated with multiple sclerosis could drive demyelination in response to anti-TNF therapy[9]. This multicentre retrospective study used physician-reported cases of demyelination in patients on anti-TNF therapy for the treatment of inflammatory bowel disease, rheumatoid arthritis, psoriasis and ankylosing spondylitis. Among 66 patients reported, 53 patients with demyelination were classified as likely anti-TNF associated and 48 were recruited for genetic analysis. Those were compared to a control cohort of 1219 patients selected from the personalised anti-TNF therapy in Crohn's disease study (PANTS) study who did not develop symptoms of demyelination. There was rigorous case identification including MRI or electrophysiological evidence, consultant neurologist and neuroradiologist review of each case and assessment of anti-TNF as the likely cause. Phenotypic risk factors for multiple sclerosis including gender, BMI, ethnicity, age and smoking status were investigated which identified female sex as the only shared risk factor. Furthermore, Lin et al. investigated the genetic burden of 43 multiple sclerosis associated risk alleles. The risk of anti-TNF associated demyelination is not associated with genetic risk variant load of multiple sclerosis. This suggests that the anti-TNF induced demyelination does not have the same genetic basis as multiple sclerosis. Indeed, there were clinical differences to multiple sclerosis as 70% of the patients with anti-TNF induced demyelination experienced a clinically isolated syndrome and only two of the 48 cases subsequently being diagnosed with multiple sclerosis during the 3 year follow up period.

Whilst this study supports the view that multiple sclerosis and anti-TNF associated demyelination have a different genetic background, several questions remain. A long-term evaluation will be important to clarify the prognosis of this condition beyond the three year follow up. Unfortunately, this study shows that three quarters of patients with anti-TNF associated demyelination had ongoing neurological problems at follow up of 3 years despite stopping the drug. The symptoms of demyelination do not completely resolve despite treatment with corticosteroids, intravenous immunoglobulin and plasma exchange. It is not clear whether therapies that have been approved more recently for the treatment of multiple sclerosis treatments are effective in anti-TNF induced demyelination. Identification of better treatments is complicated since drug induced demyelination is a rare event and the patient group affected is not homogenous. Indeed, a recent study showed that anti-TNF treatment increases the risk of both inflammatory demyelination and inflammatory non-demyelinating events such as meningoencephalitis and vasculitis [8]. In analogy to the diverse drug induced skin pathology this likely hints to several alternative inflammatory mechanisms in the central nervous system triggered by anti-TNF therapy.

In this respect, studies into anti-TNF induced demyelination face the same problems as may rare disorders that lack a pathway specific biomarker and are further complicated by absence of tissue samples to identify the pathogenic cellular mechanism(s). Study of even larger cohorts of patients, analysis of rare genetic variants, and the search for infective and environmental triggers could prove a helpful strategy to identify risk factors of anti-TNF associated demyelination. Whether the use of machine learning techniques used to predict response to anti-TNF in rheumatoid arthritis patients [10] could help to predict adverse events (or at least detect those at an early stage) in large cohorts of patients needs to be shown.

The identification of TNF targeting therapies is a great example how research into biologic principles of inflammation can lead to impactful translational results. Understanding the challenging adverse

effects of TNF targeting drugs is important for the patients at risk and will similarly provide a fundamental insight how the inflammatory TNF pathway provides host protective immunity and represses auto-inflammatory processes.

Conflict of interest

HHU received research support or consultancy fees from UCB Pharma, Eli Lilly, Pfizer, AbVie, Celgene, OMass Therapeutics and MiroBio.

IW does not report a conflict of interest

Author contribution

IW and HHU contributed equally to the editorial.

Acknowledgment

HHU is funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

1. Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of tnf alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* 1989;**2**:244-7.
2. Neurath MF. Current and emerging therapeutic targets for ibd. *Nat Rev Gastroenterol Hepatol* 2017;**14**:269-78.
3. Shivaji UN, Sharratt CL, Thomas T*, et al.* Review article: Managing the adverse events caused by anti-tnf therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2019;**49**:664-80.
4. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science* 2019;**365**.
5. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet* 2018;**391**:1622-36.
6. Gregory AP, Dendrou CA, Attfield KE*, et al.* Tnf receptor 1 genetic risk mirrors outcome of anti-tnf therapy in multiple sclerosis. *Nature* 2012;**488**:508-11.
7. Tnf neutralization in ms: Results of a randomized, placebo-controlled multicenter study. The lenercept multiple sclerosis study group and the university of british columbia ms/mri analysis group. *Neurology* 1999;**53**:457-65.
8. Kunchok A, Aksamit AJ, Jr., Davis JM, 3rd*, et al.* Association between tumor necrosis factor inhibitor exposure and inflammatory central nervous system events. *JAMA Neurol* 2020.
9. Lin S. Clinical features and genetic risk of demyelination following anti-tnf treatment. *J Crohns Colitis* 2020.
10. Guan Y, Zhang H, Quang D*, et al.* Machine learning to predict anti-tumor necrosis factor drug responses of rheumatoid arthritis patients by integrating clinical and genetic markers. *Arthritis Rheumatol* 2019;**71**:1987-96.