The case for measuring anti-drug antibodies in people with multiple sclerosis

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The advent of biopharmaceuticals (BPs) has led to significant improvements in the treatment of many chronic inflammatory diseases, and the number of BPs on the market and of diseases treated reflects their success. However, repetitive parenteral administration and intrinsic immunogenic properties of the drug can elicit an immune response, leading to production of anti-drug antibodies (ADA). This is a major limitation of the use of BPs and has to be taken into consideration in clinical practice and during drug development. With increasing knowledge about the immunogenicity of BPs and regular ADA testing in patients, we ensure optimized long-term treatment for the individual and thus optimal use of health care resources. This field has already been extensively investigated in the treatment of multiple sclerosis with IFN-β, but there is a clear need for consensus from academia, health care providers and the BP industry in managing ADA across all BPs and diseases.

IFN-β is one of an increasing number of biological protein therapeutics, or biopharmaceuticals (BPs), that have been developed to target a variety of previously untreatable diseases. Since BPs are designed to be similar or identical to the human homologous protein, they are expected to be well tolerated by the immune system. Despite these similarities, BPs can still be considered as foreign, potentially leading to breakdown of tolerance and development of anti-drug antibodies (ADA). This unwanted immunological response to BPs can influence the treatment response by altering the pharmacokinetic properties of a drug and by interfering with the biological activity and neutralization of its mechanism(s) of action, blocking the therapeutic and clinical effects of the drug [1–3].

In this editorial, we discuss the immunogenicity of IFN-β and how measurement of ADA has been implemented in clinical practice.

IFN-β has been widely used for nearly two decades in people with relapsing multiple sclerosis (MS). Development of ADA capable of neutralizing IFN-β bioactivity (the so-called neutralizing antibodies [nADA]) was detected during the first clinical trials, and since then, the immunogenicity of IFN-β and natalizumab and the significance of nADA have been extensively studied in MS. With more than 10 years experience in the routine analysis of nADA against IFN-β and over 5 years of experience with ADA against natalizumab, there are several conclusions that can be drawn. Firstly, immunogenicity clearly differs between products [4]. IFN-β-1b (Betaferon®), which is a bacterially produced non-glycosylated product with minor differences from the natural IFN-β, induces nADA in 38–47% [4], but not at very high titers [5]. This could be described as generating high seroprevalence but modest immunogenicity. IFN-β-1a (Avonex®, Rebif®) is a mammalian-produced product with glycosylation and the same amino acid sequence as the natural IFN-β, which induces nADA in fewer patients but provokes higher titers, that is, lower seroprevalence but higher immunogenicity [5]. Second, there is also a clear difference depending on how the drug is administered. If given subcutaneously three-times a week, nADA develops in

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5–24% of the patients, whereas if given intramuscularly once a week, nADA is induced in 1–6% of the patients [4]. Finally, the time it takes to develop antibodies and the persistency of these vary depending on the type of drug [6,7]. ADA against natalizumab develop earlier, but are less frequent compared with anti-IFN-β antibodies. Natalizumab induces persistent ADA in less than 10% of treated patients, the majority of whom become positive within the first 3 months of treatment. The transiently ADA-positive patients will revert to ADA negativity around 6 months after treatment initiation and have lower levels of ADA in their initial sample [8–11]. Thus, natalizumab, which is a humanized monoclonal IgG4 antibody, seems to be better tolerated by the immune system than IFN-β. Using therapies for MS as an example, this shows that the propensity to induce ADA depends on the type of drug and the production methods, as well as the mode and frequencies of administration. What is certain is that ADA can be measured and their biological effects quantified, and thus, can be taken into consideration for optimal treatment regimes. But is this done and is it always needed?

In Europe, there has been wide variation in the approach to nADA testing with extremes such as the UK, where no nADA testing was readily available until long after the first patients were treated, and Denmark, where nADA testing has been mandatory since the introduction of IFN-β. To assess the opinion of neurologists regarding nADA against IFN-β and how these views impact treatment of patients with MS, an online survey directed to neurologists in North America and several European countries was conducted in 2009–2010 (by RA Farrell and colleagues). A total of 368 neurologists from five countries (Austria: 77, Canada: 23, Sweden: 33, UK: 103, USA: 132) responded to the questionnaire. Danish neurologists were excluded as testing was mandatory. For all neurologists prescribing IFN-β, the concept of nADA was clear and the majority (95–100%) had the view that these antibodies do, or probably do, affect treatment efficacy. However, when it comes to implementing this knowledge in actual practice, less than a third of the neurologists tested all treated patients, except in Sweden where over 90% of the responders performed nADA testing. The alternative was to test only when patients had relapses, as an indication of lack of clinical effect, or not at all.

However, using the clinical effect of a drug that reduces annual relapse rates by 30% in a disease with an average of one relapse per year has a disadvantage and will require a period of at least 3 years before the effect of nADA becomes detected clinically. This is potentially a long period of non-beneficial administration of a drug, especially as there are alternative drugs available to switch to. For B- and T-cell depleting antibodies such as daclizumab and alemtuzumab, which are administered only once or twice per year and have an immediate and long-lasting effect, there are still limited data on the extent of nADA development and what effect on treatment efficacy this might have [12,13]. But since the biological response to these therapies can be detected early after treatment initiation, the measurement of ADA is less important to predict the clinical effect of these drugs. However, in cases when a drug is administered more frequently and the effect is more subtle, ADA testing remains important to enable early detection of patients at risk of becoming clinical non-responders to therapy before relapse or disease progression ensues. To understand the clinical significance, it is important to correlate the titer levels obtained by respective ADA assay with the *in vivo* bioactivity of the drug [13]. A titer level above which the bioactivity is significantly reduced or inhibited would indicate the threshold for a clinically significant ADA titer. Thus, if the biological effect of a drug is blocked, it is unlikely that patients will be clinical responders to the therapy. Importantly, alternative treatments should be considered in any patient who responds inadequately to therapy, regardless of ADA status [14].

If the effect of nADA is generally known among neurologists, why were Swedish neurologists more likely to include nADA in treatment decisions? Probably, the dissemination and implementation was helped by the sponsoring of the routine laboratory for nADA testing by the pharmaceutical companies, which made the nADA test initially available for free. During these years, a huge effort was also made to establish a Swedish national MS registry, giving all participating neurologists access and overview of test results, including nADA, of their patients. Positive feedback was given by the statistical evidences of improved care of the people with MS that could be readily analyzed in their own clinic and on a national level by using the registry. In addition, in the guidelines regarding nADA issued by the European, American and British neurological bodies (European Federation of Neurological Societies, American Academy of Neurology and Association of British Neurologists, respectively), only the European Federation of Neurological Societies recommended that patients treated with IFN-β should be routinely tested for the presence of nADA and that therapy with IFN-β should be discontinued in patients with persistent high titers of nADA. Since these bodies play an important role in influencing the day-to-day decisions of neurologists, one could expect these recommendations to have contributed to the differences in clinical practice regarding nADA between the countries.

Interestingly, in the case of IFN-β treatment in people with MS, the availability of routine testing could have changed clinical practice, and thus, reduced the occurrence of nADA in treated patients. Since 2003–2004, when routine nADA testing became available to Swedish neurologists, the nADA prevalence has significantly decreased from 32 to 19% in 2009–2010 [15]. This reduction in nADA positivity over the years could partly be explained by an increased awareness of nADA among treating physicians, leading to the use of less immunogenic IFN-β preparations, and partly by the development of less immunogenic drugs [15]. On a health economic level, it is plausible to expect that this has been of significant benefit for health providers and patients in terms of reducing number of relapses due to loss of treatment effect. It would be interesting to compare these parameters between countries with different ADA

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testing regimes to fully assess the advantages and disadvantages of including ADA as part of the decision-making process.

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