Anti-drug antibodies and clinical implications

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Summary

Over the last few years, the use of biological agents has rapidly increased. One of the main reasons limiting their use is related to their immunogenicity, i.e. the immune system may react against these molecules by producing anti-drug antibodies (ADAs). Clearly the immunogenicity of these molecules is one of the main reasons for the loss of efficacy of the drug and the occurrence of adverse events. There are several reasons why a subject may develop ADAs, most important being the structural characteristics of the biological agent. Chimeric monoclonal antibodies, including infliximab and rituximab, are thought to have a higher immunogenicity vs. human or fully human monoclonal antibodies, including adalimumab and golimumab. Fusion molecules, eg. etanercept, have certainly demonstrated a lower immunogenic potential and this is shown by the fact that a low proportion of treated patients develop antibodies against this molecule. The study of the immunogenicity of biological drugs is not only one of the mainstay for the monitoring of the biological drug treatment, it can also be useful in the initial choice of the drug to be used in a specific subject as well as in the switch from one molecule to another.

KEY WORDS: biological agents; anti-drug antibodies; efficacy; adverse reactions.

During the last few years there has been a growing interest towards immune response to biological agents, an event that requires special attention in the management of therapies that are based on biological drugs. It is known that these agents are very different from classical chemical compounds and are characterized by an immunogenic potential, i.e. they can per se induce an immune response at both antibody and cellular level. In general terms, this is explained by the fact that they are large proteins, with a level of glycosylation that distinguishes them from native proteins. As it has been demonstrated, some of these drugs contain xenogenic, for example mouse xenogeneic; there are also neocarotenoids on junction sites, as in fusion proteins, or repetitive idiotypes that explain their high potential to induce an immune response. To put it very simply, a biological agent carries several epitopes that, clearly, can be recognized by the cells that present the antigen to T cells, which in turn will act in cooperation with B cells to produce antibodies (1).

In fact, we know by now that during the immune response to a biological agent, the first response is often provided by innate immunity: for example, monoclonal antibody aggregates may directly stimulate B cells and thus make them much more active in subsequent antigen presentation. We also know that in a subject who can produce higher quantities of interleukin (IL)-4 and IL-13, these will induce the production of anti-drug antibodies of IgE isotype, that play a crucial role in infusion-related reactions. An important event, however, is IgM production in the initial phase of administration of a biological agent (1).

Several methods can be used to detect the presence of anti-drug antibodies (ADAs). An important notion should be first stressed: the presence of these antibodies can be detected only if their production exceeds the levels of active drug in the serum (2).

The literature has shown a remarkable interest for the study of biological agent immunogenicity; this interest is shared by several disciplines, not only by dermatologists, rheumatologists and immunologists, but also by gastroenterologists and neurologists because immunogenicity has implications at all levels. If we take antibodies or TNF-α-blockers as a model for example, we can immediately understand how this issue can be relevant: for both infliximab and adalimumab, we can observe a high incidence of ADAs in several diseases; therefore, it is essential to understand what is the impact (if any) of this phenomenon on the management of therapies (3).

As it has been observed, on the one hand these antibodies may be responsible for a loss of efficacy of the drug, to be meant as a secondary loss of efficacy as
opposed to the primary loss of efficacy that is caused by lack of response independent of drug immunogenicity. Therefore, we will have neutralizing antibodies or clearing antibodies against the biological agent. Another event is infusion-related adverse reactions, that include not only hypersensitivity reactions – which may be acute or delayed and are characterized by several underlying mechanisms – but also aplasia or thrombocytopenia manifestations induced by specific mechanisms of the infusion-related reaction type (Figure 1).

From a practical point of view, loss of drug efficacy is a very interesting phenomenon. We observe that approximately 37% of non-responders have anti-infliximab antibodies; a similar proportion was reported with adalimumab. Responders usually fall within the group of those who do not develop ADA’s and the same applies for adalimumab.

The available literature has shown that reduced serum levels of infliximab, adalimumab and other biological agents are associated with loss of efficacy of the drug; this observation is based on the assumption that ADA’s may influence drug levels in the serum and therefore a different production of ADA’s may have an impact of such levels. It has been observed that anti-adalimumab antibodies correlates with low serum levels of the drug (this was clearly demonstrated in patients with Crohn’s disease but also in subjects with rheumatologic diseases), and we also know that low drug levels are associated with a loss of clinical efficacy (4). The available data on infliximab are substantially comparable: drug levels are definitely lower in subjects who are positive to anti-drug antibodies, and obviously this finding is observed in non-responders (5). Serum levels of anti-drug antibodies are lower in patients who are reported to be responders to the therapy. If we consider dermatological diseases, in subjects with plaque psoriasis, high levels of anti-adalimumab antibodies are associated with low drug levels in the serum and with a reduced clinical response (6). However, it should be noted that not all subjects who are positive for ADAs show a loss of drug efficacy or hypersensitivity reactions. As we shall see later, those who develop ADAs of the IgE isotype show some kind of reactions. According to the preliminary results by our group and still to be published, 7% of subjects who are positive to anti-infliximab antibodies maintain a good response to therapy; we still cannot say whether a monitoring of these subjects will reveal a loss of clinical efficacy over time, but this could be expected if the production of antibodies is not reduced. When ADAs serum levels exceed drug serum levels, a loss of clinical efficacy may also occur. In the case of etanercept, too, responders usually maintain higher drug levels in the serum, even if a reduction of drug levels – in this case – is not associated with immunogenicity but rather with other factors including an increased glomerular filtration or a higher BMI (Body Mass Index) (7). In support of this, we should note that to maintain the efficacy of a biological agent in the clinical practice, a frequent approach is to increase drug dosage. In a study published in 2012, this strategy was required in 35% of subjects treated with infliximab, in about 10% of those treated with adalimumab, and in a much lower proportion of subjects receiving etanercept, because this phenomenon is less relevant with etanercept (8).

The immune response recognizes biological drugs as foreign agents, and therefore we should ask ourselves why some subjects do not produce ADAs. We know that antibodies can be either neutralizing or clearing. With respect to a chimeric drug, neutralizing antibodies are directed to the murine structures that represent the attack site of the drug at target. This also applies to a fully human drug such as adalimumab, which (as we will see later) shows a significant incidence of ADAs, or to fully-humanized drugs or other biological agents such as certolizumab. On the contrary, this
does not apply to fusion proteins because their structure does not differ from that of the proteins that are recognized by the immune system. However, all biological agents come into contact with clearing antibodies. In a recent study published in the *Annal of Rheumatic Disease*, Pauline van Schouwenburg demonstrated that adalimumab induced a response with anti-idiotpe antibodies that can inhibit 98% of the drug. This explains how the antibodies developed are mostly of the neutralizing type (9).

The available literature data on etanercept show that the proportions relating to the presence of ADAs vary greatly from one study to another, the higher proportions (approx 18%) being seen in a study on psoriasis, but in all cases there was no association with drug efficacy because ADAs were of the neutralizing type (10). However, ADAs do develop and therefore there is a formation of immunocomplexes that are cleared and subsequently captured by the reticulo-endothelial system and eliminated. In this case, too, the drug becomes ineffective and this occurs at the level of the liver and spleen.

Of course, also in this case there are substantial differences because the size of the drug-antidrug complexes thus formed greatly influence their susceptibility to be cleared. For infliximab, the immunocomplexes formed have a large size and a very high clearance at the spleen and liver level, with a high level of neutralization and the ability to directly activate B cells, which entails an immune response since the early stages. For etanercept, the immunocomplexes formed have a more limited size, with a very low clearance level and a poor neutralizing ability, which may explain the persistence of clinical response in the patients who receive this therapy (11).

Usually, if there is a loss of response to treatment and the presence of ADAs, a drug switch is highly recommended. An interesting option could be a preventive strategy because, especially in the initial stages of treatment, ADAs determination can be considered. In case of positivity, however, this does not necessarily implies a switch of therapy, although in the clinical practice the use of switching should be carefully pondered because biological agents are very different from chemical compounds. Tolerance is maintained if the antigen is presented to the immune system. It has been demonstrated that subjects who develop anti-infliximab or anti-adalimumab antibodies – who are, therefore, highly prone to develop anti-drug antibodies – show a similar clinical response to etanercept after switching as that observed in patients who receive etanercept as their first biological agent (12).

We can observe a classical IgE-dependent mechanism whereby subjects produce ADAs, but in vivo models have demonstrated that a drug-specific IgG-dependent mechanism may induce immediate hypersensitivity reactions, or that these antibodies may have the same effect as a result of complement activation (13).

This is highly different from what is observed, for example, with rituximab, a drug that is widely used also in rheumatology and is often associated with first-dose reactions. In this case, the mechanisms are not antibody-dependent but are related to cellular lysis, i.e. the target that is destroyed by the mechanisms resulting from drug action, with a massive release of cytokines (14).

In 2010, it was demonstrated for the first time that subjects who developed infusion-related reactions to infliximab were IgE-positive for this drug, and that in a non-negligible proportion of the subjects who developed reactions, these were reported when the drug was re-administered after a discontinuation period. This event seems to be related to the loss of tolerance that occurs when a drug is discontinued. These results have been recently confirmed in a wide range of cases (15, 16).

In this case, too, there was a close relationship with skin test results, which in the future may become a clinical strategy for the prevention of drug reactions. As we have seen, all biological agents have an immunogenic potential, but the production of neutralizing antibodies appears to be more frequent for monoclonal antibodies, for which an issue of anti-idiotpe antibody production is observed; the study of immunogenicity is clearly increasingly recommended also in the clinical practice, because this phenomenon seems to be one the main causes of loss of clinical efficacy during a therapy with biological agents.

References