Measuring Anti-drug Antibodies: A Step Towards Optimization of Biologic Therapy

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Biologic agents have changed the face of rheumatology practice and redefined the clinical remission in various human diseases. Among various biologic drugs currently being used in practice, the drugs which have brought most significant improvement in the long term outcome in inflammatory rheumatic disease are the TNF inhibitors. Since the first description of infliximab use in rheumatoid arthritis, anti-TNF agents have expanded their horizon to spondyloarthropathies, juvenile idiopathic arthritis, psoriatic arthritis and arthritis associated with inflammatory bowel diseases. Subsequently, a number of biologic agents have been developed as anti-TNF agents which are either monoclonal antibodies like adalimumab or receptor fusion proteins like etanercept. However, primary and secondary failure to these agents are common and frequently lead to either change in the dose of the agent or change the agent itself or use another biologic agent with a different mechanism of action. Anti-drug antibodies (ADAs) to the biological agents are well known cause for the reduction in their efficacy over time causing secondary failure. Detection of these ADAs depends upon a number of factors including the background illness, the methodology of the assay and concomitant drugs used etc.

Unlike the western world, scenario is very different in India where the morbidity caused by the disease is compounded by the socio-economic issues. Biologic agents are costly drugs and an Indian patient has to bear the cost of treatment from out of pocket expenses. Therefore, using the available resources of the patient in the most efficient way is important for individualized care. Primary failure to a biologic agent can not be predicted and changing the biologic agent is the only way out. However, secondary failure to a biologic agent is mainly due to development of ADAs decreasing their efficacy. Inadvertent use of biologic agents in these patients not only leads to incomplete response but can also precipitate hypersensitivity reactions. Therefore, recognizing these ADAs beforehand is important to prevent wastage of resources of the patient and any untoward drug reaction.

There are many commercially available assays that can measure ADAs. This issue of the journal includes a study done by Ghia et al to measure ADAs against infliximab and etanercept. Authors have used an ELISA based assay provided by Pfizer (Promonitor® - ELISA) to measure ADAs. It’s a double ELISA which can measure ADAs to infliximab and etanercept. In a small sample of 16 patients who received infliximab and etanercept in 1:1 ratio, authors show that only 1 patient was found to have ADA against infliximab with negligible drug levels. No patient developed ADAs against etanercept. This study gives the proof of the concept of ADAs in Indian patients. All the patients were concomitantly taking methotrexate weekly. However, this study has a very small sample size and it is difficult to draw any definite conclusions. Since biologic use is not very high in Indian patients, a small sample size is expected. Moreover, there were 3 more patients who had very low drug levels but did not have any ADAs. There is no explanation for low drug levels in them. Also, their results need to be interpreted in the light of sensitivity and specificity of the assay which varies from assay to assay. Since their study shows a prevalence of 12.5% for ADAs, authors recommend testing for ADAs in patients on anti-TNF biologic agents to anticipate biologic failure beforehand.

Large studies and meta-analysis have shown that development and detection of ADAs is affected by a multiple factors. A large systematic analysis of 57 studies which included 34 studies on infliximab and 5 studies on etanercept showed ADA prevalence of 19-47% in rheumatoid arthritis and 26-50% in spondyloarthopathies emphasizing the effect of background illness. Similarly, using different assay procedures also affect the detected ADA levels. A number of assays have been developed to measure ADAs but there is considerable heterogeneity in the assay procedure and their sensitivity and specificity which leads to different prevalence of ADAs reported in different studies.

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With advancing technology, conventional ELISA systems have been replaced by fluid phase radio immune assay (RIA) which have distinct advantages over conventional ELISA. These are highly sensitive and specific and can also detect IgG4 subtype which is formed after prolonged exposure to the drug and is also neutralizing. The important limitations with RIA is need for equipped laboratory and involvement of radioactivity. The latest addition to these assay systems is the cell based reported gene assay which can even quantify the activity of the neutralizing antibody. Another important factor affecting the detection the development of ADAs is the time point at which they are tested. They can develop as early as after the first dose of the biologic and may take a few cycles to affect the drug levels. Development of ADAs is significantly affected by concomitant use of immunomodulator drugs. Studies have shown almost 40% decrease in the production of ADAs when immunomodulator drugs are used with biologic agents.

In the post genomic era, when we talk about individualization of therapy, it becomes extremely important to assess not just the need but the efficacy of a drug in every patient. Biologic agents are undoubtedly useful in regaining the functional status in the most refractory patients with rheumatic diseases but this comes at an equally high cost. Therefore, it becomes important to not just prescribe biologic agents when there is a need but also to withdraw if there is suboptimal response. ADAs are one of the important causes of secondary failure and can fortunately be measured by various assays. In a resource poor country like India, preventing the use of a biologic agent where it is not going to be beneficial due to ADAs is more important than to prescribe them blindly. Assays to detect ADAs help in rational use of costly biologic agents would go a long way in optimization and individualization of biologic therapy. However, a number of factors are involved in the development of ADAs and their detection by the available assays and the results can be highly variable. Therefore, first we need to study the development and effects of ADAs in more homogenous groups so that their results can be individualized.

References