Understanding drug resistance to biologic therapy

The importance of understanding the molecular mechanisms of resistance to biologics

Learning from other clinical disciplines

The introduction of biologic therapies for the treatment of inflammatory arthritis has transformed the clinical outcome in patients with otherwise refractory disease. Clinicians are now pushing for the early use of these compounds to halt the disease process and even consider the possibility of drug-free remission for some.

Whether the early use of biologics will have such an impact still needs to be assessed. If successful, this may shorten the duration of treatment—reducing long-term cost of treatment for some, but opening the door for treatment in many others. The choice of optimal outcome measure to determine when to stop a TNF inhibitor (TNFi) therapy in patients in remission remains unclear, but new guidelines have been issued [1], which reflect experience with biologics in the past that stopping therapy tended to be associated with rebound flare in some exceptions. Presently, 20–40% of RA patients treated with a TNFi fail to respond to therapy and the reason for this is unknown. Putting patients that fail one cycle of TNFi into treatment with another TNFi may improve responsiveness in some situations; however, the response tends to be poorer with the second TNFi [2].

Drug resistance, including multiple drug resistance, has been extensively studied for small molecule, non-biologic drugs in all areas of medicine, and molecular mechanisms of resistance are becoming better understood. The process of recombinant protein production uses organisms and mammalian cells that are not necessarily human and the purification process may not warrant perfect folding of all the therapeutic in a vial. Post-translational modifications and the use of non-human sequences can cause immunogenic properties in certain patients. Being able to predict these types of reactions that affect efficacy are a necessary step in preventing resistance.

In autoimmune diseases, for example, the use of AZA requires monitoring as the genetic component affects drug action. There is no reason to believe that resistance to a biologic therapy will not be similar, i.e. some of it will be natural (genetically determined) or acquired, i.e. develops with exposure to the drug. Attempts have been made to stratify patients according to certain genetic loci as predictors of TNFi response [3], but further corroboration of these findings is needed.

Acquired resistance to glucocorticosteroid treatment can take place by down-regulation of receptor expression due to DNA methylation of promoter sequences, which has also been shown to occur in sex hormones in prostate and breast cancer [4]. Resistance to MTX in leukaemia and subsequent relapse has been associated with gene amplification and overexpression of the enzyme dihydrofolate reductase. In RA, a pharmacogenomics model to predict responsiveness to MTX is being developed, which considers single nucleotide polymorphisms of multiple genes involved in folate metabolism [5]. Overexpression of efflux pumps capable of extruding DMARDs from cells have been shown in synovial tissue [6], which may affect their effectiveness. Similarly, gene amplification of the P-glycoprotein causes multiple drug resistance to anti-cancer drugs such as vinblastin, doxorubicin and adriamycin resulting in the overexpression of this molecule, which pumps out the drug from the tumour cells. Overexpression of P-glycoprotein has been reported in refractory RA patients [7].

Acquired resistance to infliximab in rheumatoid has been suggested but the mechanisms have not yet been elucidated. An antibody response to some TNFis has been shown, but whether these antibodies block binding of TNF needs further research. High levels of TNF expression in synovial membranes may be a predictor of response to anti-TNF therapy [8]. Genetic polymorphisms in the IL-10 gene may influence the immune response to anti-TNF [9].

In RA and asthma, lack of response to glucocorticosteroids has been linked to differential splicing of the glucocorticoid receptor to the β-isof orm that cannot perform transcriptional activation functions. Whether this is a natural resistance to CSs or an acquired resistance is not known, as studies before treatment have not been done. Resistance to biologic therapies could also be natural or acquired. A particular allele of the IL-28B receptor determines the success of IFN therapy during hepatitis C treatment [10]. Whether this allele also influences the response to IFN-β during multiple sclerosis treatment is unknown.

Acquired resistance to rituximab during leukaemia treatment has been reported and is linked to down-regulation of B-lymphocyte antigen CD20 in a clonal population of cancer cells. In an animal model of breast cancer, resistance to trastuzumab [anti-Human Epidermal growth factor Receptor 2 (HER2)] caused the overexpression of epidermal growth factor receptor [11], suggesting that the antibody could not block the heterodimerization of HER2.
Immunogenicity to biologics has been reported for small peptides, such as the growth hormone [12], cytokines and anti-TNF antibodies [13, 14]. No HLA typing studies have been performed to address which HLA haplotype will mount a stronger immune response to a particular biologic and which could, in principle, direct treatment to a specific subpopulation of patients who are less prone to neutralize a particular compound. Patient stratification or so-called personalized medicine needs further efforts. The importance of understanding the mechanisms of resistance at the molecular level is essential to develop new therapeutic avenues that are capable of preventing or blocking this effect. For example, in cancer, drugs are being investigated that block the multi-drug transporter to increase the efficacy of chemotherapy.

The purpose of this series of reviews on drug resistance to biologics is to broaden our knowledge about what is known not only in treating arthritic disease using glucocorticoids [15] and antibodies [16], but also in treating other clinical disciplines such as cancer [17] and multiple sclerosis [18], where there is a long-standing experience of using biologics. Our hope is that learning from other disciplines will aid the scientific community of rheumatologists to develop new therapies and methods of research to prevent resistance, as well as be able to better stratify patients to rationally target the mechanisms of resistance.

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References


