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Anti-tumor necrosis factor drug therapy: The usefulness of monitoring drug levels and anti-drug antibodies in clinical practice☆

Tratamiento con fármacos anti-TNF: utilidad de la monitorización de niveles de fármaco y anticuerpos antifármaco en la práctica clínica

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Introduction

Biological treatment targeting cells or relevant molecules in the immune response has revolutionized the treatment of various autoimmune and inflammatory diseases such as chronic rheumatoid arthritis, spondyloarthropathies, psoriasis, psoriatic arthropathy or inflammatory bowel disease. Biological treatments encompass a group of drug products made using recombinant DNA technology from cells or living organisms (human cell lines, bacteria or yeast). They are protein macromolecules, mostly cytokines, monoclonal antibodies and fusion proteins. In general, they are targeting molecules on the surface of T lymphocytes, B cells, or different cytokines or their receptors. Due to their protean and exogenous nature, they can induce an immune response that can compromise their clinical efficacy and/or safety.

Biological treatment targeting TNF is the most used in clinical practice. The experience accumulated over nearly 2 decades has resulted in substantial improvements in its use. Currently, the availability–even though still not widespread in routine care–to measure serum levels of drug and anti-drug antibodies (ADA) allows an individualized therapeutic monitoring, it adds an objective parameter to clinical response criteria, adapting amount of drug to patient response, leading to a more cost-effective efficacy.

The purpose of this article is to describe the advances in therapeutic monitoring of anti-TNF drugs, review its utility in different clinical scenarios and propose a practical guide, based on the experience gained during more than 5 years in various diseases in 5 different centres across the country.

Bioavailability of tumor necrosis antifactor drugs

The anti-TNF drugs may be administered subcutaneously – etanercept (ETN), adalimumab (ADL), golimumab and certolizumab pegol (CTZ) with different regimens – or intravenously (Infliximab [IFX] and biosimilars of the same product). The different properties of each one (structure, chimeric or humanized nature, degree of aggregation, receptor binding), administered dose, body mass index and degree of disease activity influence the pharmacokinetics and pharmacodynamics, in the formation of immune complexes between the drug and its target and in the formation of ADA and, therefore, they are related to the clinical efficacy and the occurrence of possible adverse effects.[1]

Except CTZ, they are all IgG1, having a constant Fcγ1 fragment in their molecule. The major catabolic processes responsible for the bioavailability of immunoglobulins (which is what they are), unlike most synthetic drugs, do not take place in the liver or kidney but in tissues where reticuloendothelial system cells play an essential role through their Fc receptors for IgG and neonatal Fc receptors for IgG

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regulating the transport of IgG across epithelium and IgG *turn-over*. The existence of polymorphisms in these receptors determines differences in IgG catabolism between individuals.[2]

Other patient-dependent factors such as age, sex, body mass index, albumin concentrations, also relate to the pharmacokinetics of the anti-TNF, hence the great interindividual variability. Available data indicate that the maximum therapeutic efficacy depends on the bioavailability of the drug and that this is proportional to its plasma concentration. Drug and ADA monitoring – for these form immune complexes with the drug, increase their clearance and therefore directly affect their bioavailability – has been proposed as a useful tool for optimizing treatment with anti-TNF.

Immunogenicity of tumor necrosis antifactor drugs

The anti-TNF agents in the market are, according to their origin, chimeric, humanized or "fully human". Being complex proteinaceous molecular structures, they are all inherently immunogenic. Assessing their immunogenicity, whose expression is the presence of AAF, is a requirement of the European Medicines Agency prior to marketing authorization.

The ADA can be neutralizing or non-neutralizing, depending on whether they are targeting the binding site of the drug with TNF or not. While the pharmacodynamic characteristics may be altered by the presence of neutralizing antibodies that interfere directly with TNF binding, and therefore, its therapeutic action, both neutralizing and non-neutralizing antibodies alter the drug's pharmacokinetics. In both cases, they form immune complexes that increase their clearance, resulting in insufficient drug concentrations and ultimately treatment failure.[3] The formation of small size immune complexes has also been described, which can stay longer in circulation and have been associated with anaphylactic reactions.

Multiple factors contribute to the immunogenicity of anti-TNF drugs.[4] Some are inherent to the drug, such as the protein sequence (presence of non-human amino acids, similarity with endogenous proteins), the three-dimensional structure or the post-translational modifications (glycosylation, oxidation, binding to membrane lipids, etc.). Others depend on the manufacturing process, which can affect both aggregation and posttranslational modifications. The route of administration, individual patient characteristics and the use of concomitant medication are also related to the immunogenicity. In most of the published studies, concomitant use of immunosuppressive agents was accompanied by decreased ADA formation.

Depending on the sources consulted, the presence of antibodies against different anti-TNF is variable, as it depends on methodology and other variables. A recent meta-analysis indicates overall rates of 25.3% for IFX, 12.7% for ADL, 3.8% for golimumab, 6.9% for CTZ and 1.2% for ETN.[5] Antibodies rarely become transient or undetectable during treatment intensification, probably masked by an excess of the drug, although they continue occurring.[6]

Levels of drug and anti-drug antibodies: analytical aspects

The original approach to drug and ADA level determination was conducted by enzyme immunoassay (ELISA, solid phase assays) and radioimmunoassay (liquid phase assays).[7] Table 1 summarizes the different methodologies used.

Drug detection

The most commonly used methods nowadays are enzyme immunoassays, both antigen capture via a monoclonal antibody as well as directly. Most of the *kits* available use one of these 2 formats and although quantification varies from one brand to another, they generally correlate well.

Anti-drug antibody detection

The "bridge" ELISA is the method used by all *kits* because it is reproducible, simple and inexpensive. The assay takes advantage of the ability of antibody molecules (IgG) to form a "bridge" between the drug exposed on the plates and the same drug biotinylated or peroxidase-labelled. It presents 3 main problems: potential interference with rheumatoid factor, inability to detect IgG4 antibodies (of little importance because normally the production of IgG1 antibodies is associated to IgG4) and interference with the drug, that is, it only detects antibodies when they are in excess over the drug levels. Therefore, to maximize detection, it is necessary to make the determination during trough, when drug plasma levels are in their minimum concentration. Currently, several laboratories are attempting to develop assays where there is no drug interference. For this to happen, it is necessary to dissociate the immunocomplexes before performing the assays, blocking one of the components (antigen or antibody). These methods will allow early antibody production detection and provide information on the clinical impact of complexed antibodies and whether their formation may be transient in certain circumstances.

Current evidence on the usefulness of monitoring drug levels and anti-drug antibodies

Among the most relevant medical literature, there are numerous cases of patients with rheumatoid arthritis,[8] ankylosing spondylitis,[9] Crohn's disease,[10] psoriasis[11] and psoriatic arthropathy[12] where the presence of ADA is associated with low serum drug levels and decreased clinical efficacy of the anti-TNF agent. Recent publications on patients with Crohn's disease under maintenance therapy with IFX have reported that the presence of ADA is associated with a greater likelihood of active disease.[13] Despite this and their increasing use in clinical practice, scientific evidence on the practical utility of using algorithms that incorporate determining drug and antibody levels does not come from randomized trials but case series and meta-analysis. Among them, one of the most interesting is Garces et al. study of 1956 patients with rheumatoid arthritis, psoriasis and Crohn's disease treated with IFX and ADL.[14] They concluded that patients who developed antibodies had worse clinical response to anti-TNF and that concomitant immunosuppression decreased their formation. These authors, in a subsequent prospective study of 105 patients with rheumatoid arthritis previously untreated with anti-TNF or that had switched between different anti-TNF agents, demonstrated the clinical superiority of a treatment algorithm which included monitoring trough levels of drug and ADA.[15] They came to the same conclusions in a 3-year follow-up prospective study which included 407 patients with rheumatoid arthritis treated with ETN or ADL.[16]

In inflammatory bowel disease treated with IFX or ADL, different groups have also shown the utility of algorithms that include drug and antibody level determination in decision making. This is particularly relevant, since international guidelines on inflammatory bowel disease recommend empirical treatment intensification when primary or secondary treatment failure occur.[17] Recently, a prospective study of 82 patients treated with ADL (46 with Crohn's disease, 36 with ulcerative colitis) with a 3-year follow-up including clinical questionnaire, endoscopy and inflammatory biomarkers, described that patients in whom treatment decisions were based on using an algorithm that included ADL and antibody levels had a more favourable therapeutic response and clinical outcome than those in which treatment intensification was conducted