Reumatología Clínica

Special article

How to Compare Biologic Drugs[☆]

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A R T I C L E   I N F O

A B S T R A C T

This consensus document reviews the evidence on the evaluation of biological drugs. The main conclusions of the group are: *a)* the current evidence on biological comparisons is based on indirect comparisons and is generally unreliable and with important methodological limitations. Therefore, *b)* it is considered necessary to amend the regulatory directives in the sense of strongly favoring randomized non-inferiority studies comparing face to face the new biological treatment with current standards, avoiding trials versus placebo, *c)* a key element in this process will be determined by consensus among regulatory agencies, scientific societies, the pharmaceutical industry and health authorities regarding the clinical differences that should be considered relevant in each of the conditions tested.

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¿Cómo comparar fármacos biológicos?

R E S U M E N

El presente documento de consenso revisa la evidencia sobre evaluación de fármacos biológicos. Las conclusiones principales del grupo son: *a)* la evidencia actual sobre comparación de biológicos se basa en comparaciones indirectas y es, en general, poco fiable y con importantes limitaciones metodológicas; por ello, *b)* se considera necesario modificar las directivas regulatorias en el sentido de favorecer decididamente los estudios aleatorizados de no inferioridad comparando cara a cara los nuevos biológicos con los actuales estándares de tratamiento, evitando los ensayos frente a placebo; *c)* un elemento clave en este proceso será la determinación por consenso entre las agencias reguladoras, las sociedades científicas, la industria farmacéutica y las autoridades sanitarias de las diferencias clínicas que deben considerarse relevantes en cada una de las patologías evaluadas.

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Introduction

Biological drugs have constituted a therapeutic revolution in rheumatic diseases as rheumatoid arthritis, (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA)–inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis, and in certain skin diseases[1,2]–moderate or severe psoriasis. Not only has this group of drugs demonstrated their effectiveness on symptoms, but can also in modifying the natural history of these diseases, preventing complications and the associated disability.[3–8]

Unlike traditional drugs obtained by chemical synthesis, biological molecules are protein based and generated by living cells. Their size and molecular weight are variable (from peptide chains to whole antibody molecules), and may be very high.[9] Although, by definition, there are no two biological molecules 100% identical, differences between family members-p, e.g., anti-TNF sharing a therapeutic target, may be important. The differences lie in their

amino acid chain or–in the case of biosimilar drugs, which generally have a sequence identical to the original in drug-p-amino acid modifications, e.g., glycosylations or fucosilations of amino acids side chains after synthesis and thereby conditioning three-dimensional folding, which can cause variations in substrate affinity or the degree of immunogenicity and cause differences in efficacy or safety.[10] Indeed, as an example, there is a significantly higher incidence of severe aplastic anemia associated with certain formulations of recombinant erythropoietin but not others[9]; recently, differences have also been seen in the fucosilation pattern of FcRIIa affinity γ, and, in in vitro studies, the antibody-dependent cytotoxicity mediated by cells between infliximab and the biosimilar Inflectra® The Canadian Agency for Drugs justified, on the basis of this data, that the approval granted to Inflectra® for rheumatic disease does not spread to IBD.[11]

The market for biologics has increased rapidly in recent years. Moreover, after the expiration of the patent and the end of the period of data protection for innovative original drugs, biosimilar drugs have appeared on the market, a term understood as copies of biological drugs already approved where similar physicochemical, efficiency and safety features have been demonstrated after undertaking the necessary 12 comparisons. The definition emphasizes two aspects: a) the fact that they will never be equal to the original drug, hence the term "similar" as opposed to the concept of 'identical', which would apply to the comparison of a generic drug with respect to the original molecule and, b) in the case of biologics drugs, bioequivalence a concept that involves similar areas under the curve between the parent drug serum levels and the copy, used to demonstrate the therapeutic equivalence of generic drugs–which is not definite equivalence or criteria for classifying a biological copy and original as having the same efficacy and safety. A comprehensive assessment of each new drug is therefore required. Not only must we analyze the physico-chemical characteristics, but we also require careful clinical assessment of efficacy and safety to consider a given copy as biosimilar.[12]

The parameters to be determined in this evaluation are debated,[9,13–19] although the overall orientation of regulatory agencies, and in particular, the European Drug Agency, has been to require randomized clinical trials comparing equivalence or non-inferiority of the efficacy and safety of biosimilar in relation to its original.[10] This contrasts with the approval process for innovative biologics, where most require studies comparing the drug with a placebo control group. As a rule, studies of 'equivalence' or 'non-inferiority' seek to show that these terms apply for a new therapeutic drug against a known standard–the new drug is "equivalent" or "not less than the known drug"–and in most cases no placebo is used.

Furthermore, when comparing biologics, the difficulty that appears is that, until recently, there are no published clinical trials directly comparing the efficacy and safety of two biological drugs. This lack of direct comparisons has led to attempts to compare them using other methods of evidence-based medicine, specifically through indirect comparisons analysis.[20–23] The simplest indirect methods are non-adjusted indirect comparisons. They consist in comparing the efficacy of two biologicals – which we will call A and B, using the efficiency of A in studies evaluating this drug, directly comparing the efficacy of drug B in their respecting studies of the same condition, without making any corrections. This method often gives incorrect results, therefore, its use is strongly discouraged.[24] A more correct alternative from the methodological point of view are adjusted indirect comparisons. In this case, we must have randomized trials comparing A and B vs the common comparator P (in the case of biological drugs, this is commonly a placebo). The effectiveness of A and B is compared through P in order to correct, at least partially, the differences between the populations of different studies. Indirect comparisons can be much more complicated, for
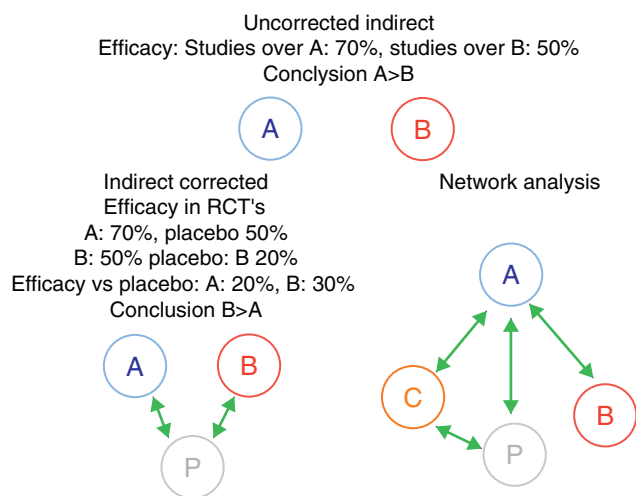

Fig. 1. Indirect comparisons, corrected, uncorrected or networked. An example is shown where the unadjusted indirect comparison between two drugs, A and B, is displayed, giving a totally different result, probably incorrect and the corrected result due to the different characteristics of the study population. Network analysis may include multiple comparisons between different agents (A–C) and/or with placebo. Uncorrected indirect efficacy: studies over A: 70%, studies over B: 50% conclusion A>B indirect corrected efficacy in RCT's A: 70%, placebo 50% B: igual efficacy vs placebo conclusion network analysis. RCT: randomized controlled trials.

example, if we evaluate multiple drugs (network analysis).[24–26] For these evaluations more sophisticated statistical techniques, such as Metaregression are employed (Fig. 1). However, if not used with extreme methodological rigor, these tools can generate inaccurate results. We will see that a good example is the evaluation of biological drugs.

Although the complexity of biological drugs creates serious difficulties when compared, showing that 2 drugs are clinically equivalent has important assistance and economic implications. This article aims to reflect on some important aspects needed to facilitate the evaluation of biologic agents: a) the utility and the ethical implications of certain design studies, and in particular the use of placebo, b) the use of non-inferiority studies, assessment variables to consider and the importance of differences (δ) in efficacy or safety that can be considered clinically significant, and c) the usefulness of the methods of evidence-based medicine and, especially, indirect comparisons. This has been accomplished through a multidisciplinary approach using a non-systematic review of the literature and further discussion and consensus which involved specialists in rheumatology, dermatology, gastroenterology, clinical pharmacologists and statisticians.

Method

The preparation of the document was performed from a systematic review and a consensus reached by two of the authors (XC and JVE). The rest of the forum participants received the document by e-mail, reviewed the document and made contributions that were collected in an initial document. In a single-face-to-face meeting, the discussion points were agreed upon, the structure and content of the final document were set, and responsibility was distributed to each of the participants. Thus, the respective specialists developed the basis for proposing a value of delta in each of the indications for biological drugs. Once established, coordinators (XC and JVE) integrated the various contributions to develop a second document, which was discussed through email. Finally, all forum participants gave their approval to the final content of the document.