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Editorial

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A Look Beyond the Biosimilarity of the Molecules

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The advent of monoclonal antibody biosimilars [MABS] represents a serious challenge for the entire landscape of biologicals in medicine, with a series of interrogations for the healthcare community. The first serious interrogation was to establish if the industry was able to reproduce entire antibodies, multimeric glycosylated proteins, from the originator product on the market. The very exhaustive and comprehensive comparability exercise conducted to demonstrate CT-P13 biosimilarity to infliximab, meeting all the stringent requirements requested for European Agency for the Evaluation of Medicinal Products [EMEA] approval, clearly showed that nowadays the technology exists to reproduce glycosylated monoclonal antibodies with a high standard of biosimilarity.[1]

The second interrogation is the extrapolation of indications. The theoretical concern here is whether it is sufficient to test a MABS in one randomised trial at one dose in one indication to establish that this MABS will bring the same clinical benefits with the same safety in all the other indications of its originator. This question is valid only if there are theoretical reasons linked to the mode of action of the antibody, its dosing, or a feature of one indication yet untested, that make us believe that the MABS may show a previously unrecognised dissimilarity as compared with the originator. However, in the case of the first infliximab MABS CT-P13, which was tested without unusual signal in randomised trials in two indications covering the range of dosing of the originator, the likelihood of a disease-specific event to occur in a third indication decreases substantially. This debate is still ongoing.[2,3] Nevertheless, according to evidence-based medicine principles, each MABS should be studied in each further indication. Such later studies will participate in the demonstration of biosimilarity of the MABS and, perhaps more importantly, will contribute in pharmacovigilance regarding the new compound and its production chain. Another dimension of Phase IV studies is to show that the efficacy and safety results of the trials are reproduced in clinical practice. The study by Krisztina Gecse *et al.*, in the current issue of *ECCO-JCC*, contributes therefore original data to several aspects of the demonstration of biosimilarity of CT-P13.[4] As the originator elicited higher frequencies of immunogenicity problems in imflammatory bowel disease [IBD] than in rheumatological indications, the absence of such signal in this prospective Phase IV study adds to the demonstration of the safety of CT-P13, even if larger studies are still needed.

At this stage, the most challenging issue remains pharmacovigilance. Indeed, the arrival of the first MABS in the large field of immune-mediated inflammatory diseases [IMID] will probably affect the overall use of biologicals in these indications, far beyond its originator, to the other anti-tumour necrosis factor [TNF] agents and even to biologicals with other mechanisms of action. Indeed, in the absence of direct comparison trials among biologicals, there is no evidence to support the use of one biological over the others in most indications. If one compound, here infliximab, becomes much less expensive, it might be difficult for physicians, bound in all healthcare systems to provide cost-responsible care, to continue to make cost-independent choices, as is done currently with biologicals in the same price range. In some jurisdictions, switch to infliximab MABS is made practically mandatory by large tender systems.[5] In others, hospital or insurance tender systems will lead choices. The presence of one cheap biological will put price pressure also on the other anti-TNFs to remain competitive as they share most indications with infliximab.[6] In turn, the pressure will extend to the other biologicals with similar indications, leading to a global price pressure. If large price differences persist, then there is a risk that third party payers seek to influence drug choices beyond the originator and its MABS.

This price pressure will push the biological drug producers to seek for savings along the drug production chain and the product testing process. This pressure will translate itself into an increased number of manufacturing changes, a number which will grow with the number of players and with the market expansion that lower prices will certainly also induce. As each manufacturing change carries a risk of introducing an unwanted alteration in the molecule or in its surrounding dissolving solution, there will be a statistical growth of the likelihood of a problem to occur, with clinical impact on efficacy or in safety. There is a precedent of such a problem after the introduction of erythropoietin biosimilars.[7] All physicians, regardless of their prescription habits towards biologicals, should thus participate in the pharmacovigilance effort that the regulators demand. Clinical nurses and pharmacists should also be involved. Several large databases are already available and disease-specific banks at the national and international levels are under development for this purpose.

The naming of MABS is also a current interrogation, in particular to help patients to know what they receive and in the traceability of the various products. Traditionally drugs are prescribed by their International Nonproprietary Name [INN], set by World Health Organization [WHO] rules. This organisation actively consults the various stakeholders to define INN rules for biologicals,[8] whereas some national regulators have taken or are taking position. There is no clear answer here, as using the same INN for an originator and its MABS has advantages as much as drawbacks, and the use of several related INNs poses other problems. If naming is important, the real issue for biologicals pharmacovigilance might well be the traceability of manufacturing changes, which are not in the INN and not easily recovered by the user from lot numbers. To take the best advantage of the errors of the past and to follow the potential risks where they might occur, it may be just as important as a global naming policy to forward drug changes information to the end user. This strategy would help identify early a potential problem and thus lower the number of patients exposed, the ultimate goal of pharmacovigilance.

As drug development complexity will increase in the future, with advances not only in therapeutic antibody technology[9] but possibly also in complete chemical synthesis,[10] the maturation of the mechanisms to monitor the safe introduction of new complex compounds in clinical care is a priority.

Conflict of Interest

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