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Extrapolation concept at work with biosimilar: a decade of experience in oncology

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Early in 2017, The European Society for Medical Oncology (ESMO) published a position paper on biosimilars for oncology prescribers.[1] Since then, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved biosimilar versions of monoclonal antibodies (mAbs) used for the treatment of several cancer types (eg, rituximab in Europe, bevacizumab and trastuzumab in the USA).[2 3] The ESMO position paper was rightly welcomed as a timely addition to the discussion around this important topic.[4] The position paper correctly highlighted the importance of accurate information about biosimilars if misconceptions and misunderstanding are to be avoided among oncologists and other stakeholders.[1] It is encouraging that ESMO has continued on this mission to provide information and education; special sessions on biosimilars were incorporated into the main programmes for both the ESMO and ESMO Asia congresses in 2017, and the organisation has been represented at several other important meetings (including the 15th Biosimilar Medicines Conference). They also launched a survey on awareness of biosimilars among oncologists in 2017, the results of which are eagerly awaited.

Extrapolation is arguably the part of the biosimilar concept that is most commonly misunderstood. It is defined as the authorisation of a biosimilar medicine for clinical indications of the reference medicine without the need to conduct clinical trials of the biosimilar medicine in those indications.[5 6] Knowledge and understanding of extrapolation among oncologists is increasingly important given the introduction of biosimilar mAbs for the treatment of various cancers.[6] Key to understanding the concept is an awareness that extrapolation is a well-established regulatory and scientific principle that has been in use for many years, even before the advent of biosimilar medicines.[6] For example, the principle of extrapolation is applied following major changes in the manufacturing process of a biologic medicine. In such cases, the manufacturer is required (by regulatory authorities such as the US FDA and EMA) to conduct a thorough comparability exercise to establish that the premanufacturing and postmanufacturing change biologic medicines are sufficiently similar to allow continued authorisation. Clinical data (which are required in rare instances when the analytical comparison reveals differences that could potentially lead to different clinical properties[7]) are usually generated in one indication and extrapolated to the other indications, taking account of all data generated from the comparability exercise.[6] The same considerations apply to the comparability exercise for demonstrating biosimilarity; from regulatory and scientific viewpoints, the active substance of a biosimilar is just another version of the active substance of the reference medicine.[6 8]

Potential misconceptions around extrapolation may also arise from the term itself. In mathematical terms, extrapolation refers to the projection of unknown values from trends in known data. However, when applied to biosimilar medicines, extrapolation is based on the knowledge (from the thorough analytical comparability exercise) that the biosimilar medicine matches the reference medicine in all critical quality attributes. Health Canada recently acknowledged this problem with terminology and consequently deleted the term ‘extrapolation’ in the last update of their biosimilar guideline in 2016. They instead describe what is meant exactly, namely the authorisation of indications for the biosimilar.[9]

The clinical development programme for any biosimilar medicine, including biosimilar mAbs, will typically include a phase III confirmatory clinical study. Regulatory guidelines dictate that this study should be conducted in a sensitive indication, that is, one in which clinically relevant differences in safety (including immunogenicity) and effectiveness would be detected if present.[10 11] Sensitive indications

typically have a large effect size for the chosen end point (to enable detection of even small differences in efficacy), and involve a patient population that is immunocompetent (so that detection of relevant differences in immunogenicity is possible). The subject of sensitive indications may be another contributory factor to misunderstanding around extrapolation. Taking proposed biosimilar mAbs for breast cancer as an example, there has been debate about whether the neoadjuvant or metastatic setting is more appropriate as a sensitive indication.[12 13] In reality, there may not be one indication that is categorically the most sensitive, and the decision will be based on discussions with regulatory authorities within scientific advice procedures. Indeed, phase III confirmatory studies for proposed biosimilar trastuzumabs currently in development are being conducted in different indications.[14 15] It is important to understand that extrapolation is from the reference to the biosimilar medicine (ie, molecule to molecule) and not from one indication in which the biosimilar medicine has been studied to other indications. Each extrapolated indication must be justified scientifically and is assessed separately by regulators, who will approve or reject the indication based on this assessment. Factors considered include clinical experience with the reference biologic, the mechanism of action and target receptors involved, any differences in safety or immunogenicity between indications (including patient-related and disease-related factors), and the extent to which functional parts of the molecule can be analytically compared and analysed.[6]

It is now a decade since biosimilar filgrastims were approved for use by EMA. In the example of Zarzio (Sandoz), the confirmatory study was conducted in patients with breast cancer who had chemotherapy-induced neutropenia (CIN), with other indications granted on the basis of extrapolation.[16] Since then, generated data and clinical experience have demonstrated the safety and effectiveness of Zarzio in patients with other tumour types who have CIN,[16–19] and also other extrapolated indications such as stem cell mobilisation.[20–23] This experience indicates extrapolation successfully at work. It may also reassure oncologists that the concept of extrapolation is based on sound scientific principles.

ESMO is to be applauded for participating in the important discussions on biosimilar medicines in oncology, and for the initiatives undertaken in 2017 to provide accurate information and education on the subject. We welcome their continued involvement, and look forward to further position papers and initiatives on extrapolation and other important aspects of the biosimilarity concept.

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