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Addressing unmet clinical needs: the potential of biosimilars in the treatment of rheumatic diseases

Biosimilars in rheumatology

Biologic agents are an important therapeutic option in the treatment of patients with rheumatic diseases, including RA [1], AS [2] and PsA [3, 4]. Despite the positive attributes of these agents in the treatment of these conditions, patients are unlikely to receive biological agents as first-line therapy, and barriers to their use as second-line therapy (and beyond) may also occur [5]. This largely reflects the high cost of these agents, which is a challenge to funding bodies in many countries and which, in turn, has driven inequality of use [5].

Biosimilar agents are products that contain a similar version of the active substance of an already authorized original biological medicinal product [6]. These agents generally come with a lower cost than their reference biologics [5], which is expected to result in cost savings and greater access to effective anti-rheumatic drug therapy [7–9]. Despite this, there has been some concern among physicians about the use of biosimilars in clinical practice [10]. Confidence in the clinical profile of these agents should arise from an understanding of the extensive and rigorous process undertaken to establish comparability between the biosimilar and the reference medicinal product [6]. In this supplement, we explore this process and examine how the availability of these agents will be likely to impact clinical practice.

In a comprehensive overview of the regulatory aspects of the biosimilarity exercise, Declerck and Rezk [11] document the extent and detail of the scientific evidence required to establish biosimilarity under the European Medicines Agency approval system. Compared with novel biologic development, biosimilar development places greater emphasis on establishing preclinical quality characteristics, with appropriate *in vivo* pharmacology studies being conducted thereafter. Head-to-head comparisons are then conducted to determine pharmacokinetic and pharmacodynamic characteristics and efficacy and tolerability in phase I and III clinical studies, respectively. Post-approval risk-management requirements include the implementation of pharmacovigilance systems and risk management through, for example, the conduct of pharmacoepidemiological studies.

Vulto and Jaquez [12] build on the regulatory aspects of biosimilar development and describe how the manufacturing process is defined and refined through quality-by-design principles to achieve predefined critical quality attributes, thus guiding increasing confidence in achieving clinical comparability. The complex processes behind biosimilar development, production scale-up, manufacturing and quality control are discussed, underscoring the direct influence that these processes have on ensuring that the clinically relevant attributes of the molecule are maintained throughout the different steps of the manufacturing process and throughout the lifecycle of the product. Furthermore, the negative effects of supply interruption on healthcare provision are highlighted, together with reasons for product recalls and drug shortages and how these can be avoided.

As of March 2017, there are three anti-TNF biosimilar agents that have received approval and are available on the market for patients with rheumatic diseases in the European Union; the infliximab biosimilars CT-P13 and SB2 and the etanercept biosimilar SB4 [13–15], with more than 40 other biosimilar agents in development [16]. Schulze-Koops and Skapenko [17] examine the available scientific evidence for approved agents, summarizing results from key clinical trials, and discussing their introduction in the context of current rheumatology treatment guidelines and real-life clinical practice. These agents have shown close comparability to their reference medicinal products, and treatment guidelines have acknowledged the role of biosimilars in terms of their interchangeability with reference biological DMARDs (bDMARDs). Given that cost is a barrier to effective bDMARD use, the introduction of less costly biosimilars is likely to widen access, with *de novo* usage and switching to a biosimilar following lack of efficacy or tolerability with a dissimilar agent likely to be strategies that are most easily adopted.

In the final article of this supplement, Uhlig and Goll [18] underscore the importance of assessing immunogenicity and ensuring traceability as key elements in establishing the safety profile and in tracking and attributing any emerging adverse events related to biosimilar use. The authors also discuss how these agents can be integrated into clinical practice, addressing questions around switching, interchangeability and automatic substitution. Potential barriers to implementation from both healthcare professionals and patients are also highlighted. These authors document that switching studies

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have shown that biosimilars can be used in place of reference products. Additional ongoing studies and registries may help to optimize the process for switching, and different funding models are examining the optimal mechanisms to ensure effective uptake of these new treatments.

Overall, the articles in this supplement demonstrate the extensive process that needs to be followed to establish comparability of a biosimilar with the reference biological product, and the subsequent post-marketing surveillance that is implemented to monitor biosimilar safety. Given that biosimilar agents are generally less costly than their reference biologics, it stands to reason that there is opportunity for greater access to biological therapy and, indeed, there is growing evidence to support this supposition. The comprehensive development, assessment and monitoring processes that biosimilars need to follow in the European Union should provide rheumatologists with an extensive body of evidence to adopt these agents in clinical practice. Regulatory guidelines already acknowledge the use of biosimilar agents, and their place in therapy will probably be defined further with wider real-life clinical experience.

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Hendrik Schulze-Koops[1]

[1]*Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, Ludwig-Maximilians-University of Munich, Munich, Germany*
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Correspondence to: Hendrik Schulze-Koops, Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, Ludwig-Maximilians-University of Munich, Pettenkoferstrasse 8a, 80336 Munich, Germany.
E-mail: Hendrik.Schulze-Koops@med.uni-muenchen.de

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