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LETTER

Letter to the Editor Regarding "The Challenges of Switching Therapies in an Evolving Multiple Biosimilars Landscape: A Narrative Review of Current Evidence"

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Key Summary Points

The recent review from Feagan and colleagues neglected to mention several key factors regarding biosimilar use and switching

Multiple switching scenarios apply mostly to chronic-use biologics and are less common with acute-use biologics

Any change in the production process of a reference biologic or biosimilar may affect the clinical activity, efficacy, safety, and/or immunogenicity of the product

Biosimilars can offer significant cost savings and expand access to critical therapeutic treatments

Dear Editor,

We read the article by Feagan and colleagues discussing potential challenges of biologic switching with considerable interest [1]. Although we agree with Feagan et al. that high-quality clinical and postmarketing studies should be conducted to improve our understanding of potential switching effects, we believe that several additional factors should be considered when discussing biosimilar use and switching.

The multiple switching scenarios discussed by Feagan et al. mostly apply to long-term biologic use, generally in the setting of chronic diseases. However, multiple switches are much less common when biologics are used for a shorter, finite time period. The question of acute-use versus chronic-use biosimilars is highly relevant; 13 of the 28 currently approved biosimilars in the USA are used primarily in acute disease settings, such as in oncology care with biosimilars of the originator biologics bevacizumab, filgrastim, pegfilgrastim, and trastuzumab [2]. The situation is similar in the European Union: 30 of 60 approved biosimilars are commonly used in acute disease settings (from the reference biologics bevacizumab, filgrastim, follitropin alfa, pegfilgrastim, somatropin, teriparatide, and trastuzumab) [3].

Studies of biologic or biosimilar switching for acute-use biologics have consistently demonstrated the safety of switching from a reference biologic to a biosimilar [4–8]. As an example, the biologic pegfilgrastim is commonly used as acute supportive care for patients receiving myelosuppressive chemotherapy. In a recent clinical study using a three-period, three-sequence crossover design, pegfilgrastim-cbqv was shown to be bioequivalent regardless of treatment sequence or period, and no unexpected safety signals were observed [4]. The

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safety of switching from originator biologics to biosimilars was also highlighted in a recent systematic literature review that examined 90 studies reporting data on single or multiple biologic switches [9]. This review concluded that most of these studies did not show differences in efficacy, safety, or immunogenicity between patients who remained on an originator biologic over time and those patients who switched from an originator to a biosimilar [9], including during multiple-switch scenarios [10–12].

As Feagan and colleagues correctly state, biosimilars by definition are similar but not identical to their originator biologic [13]. Although biosimilars undergo an extensive and robust regulatory process to ensure similarity to the originator product [14, 15], small differences in structural components may exist (e.g., posttranslational modifications) that are not clinically meaningful [13, 16, 17]. However, it is important to note that these differences may also be present between different batches of the reference biologic. The production and purification of biologics is a highly complex process, and batch effects or manufacturing changes (e.g., changes in raw materials, changes in equipment, changes due to upscaling production) can lead to variability in the efficacy, safety, and immunogenicity of reference biologics over time [18–20]. Although the regulatory requirements governing the evaluation of biosimilarity and those governing manufacturing changes differ, these processes share the same goal: to ensure consistent and predictable safety and efficacy of the biologic. As with the development of biosimilars, comparability exercises related to manufacturing changes commonly include physicochemical and biological characterization and may include animal or clinical studies, if necessary. However, the evaluation of a biosimilar is far more extensive, requiring full pharmacokinetic, functional, and immunogenic evaluation, and commonly requiring clinical studies as well [13, 14].

In their article, Feagan et al. also did not mention several significant benefits to patients and the healthcare system provided by biosimilars. Over the past decades, biologics have become cornerstones in the clinical management of numerous diseases. However, reference biologics are associated with significant costs and represent a disproportionally large fraction of net drug spending [21, 22]. Biosimilars are less expensive than the originator product, or at least stimulate price competition in the field of biologics, and offer significant cost savings to individual patients and the healthcare system [23–25]. In addition, biosimilars have the potential to increase accessibility for patients and expand access to critical therapeutic treatments at the national and global level [25–27].

In conclusion, it is critical to distinguish between chronic and acute disease settings when discussing potential risks of biologic/biosimilar switching scenarios. It is also important to recognize that minor changes in efficacy, safety, and immunogenicity of any biologic drug may occur over time, and these concerns are relevant for reference biologics as well as biosimilars. Finally, while further research is certainly valuable to improve our understanding of potential switching effects, we feel strongly that the benefits of biosimilars—increased competition, lower drug prices, and broader patient access—should not be overlooked.

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