

Letters in Response to Previously Published Articles

Biologics or biosimilars: What is the difference?

Sir,

This is with reference to the study by Sharma *et al.* describing the efficacy of rituximab in the treatment of pemphigus.¹ We congratulate them on this work that is very relevant for current and future practice of clinical dermatology, yet as of now underrepresented in the Indian literature.

We noticed that the authors have refrained from mentioning the brand of rituximab (biologic/biosimilar) used. We, however, would like to emphasize the importance of such details, especially in studies where the molecule under evaluation is a biologic agent.

The various biologic agents available are classified as “original innovator” or “reference product” (the original patented molecule) and “biosimilars” or “subsequent entry biologics” (drugs developed later which claim similarity to the reference molecule in terms of gross structure and function). These drugs are high molecular weight proteins whose behaviors depend on their complex tertiary structure which may be affected by minor differences in sequences and posttranslational modifications such as glycosylation, hydroxylation and phosphorylation. Hence, the genetically engineered cell lines used for synthesis and other conditions for production and purification assume utmost importance in determining the molecular characteristics of the biological therapeutic agent.

In case of traditional smaller therapeutic molecules which are produced by well-defined chemical reactions, the process for synthesis and purification of a particular drug can be easily duplicated to produce a compound which is exactly similar to the patented/reference molecule. In contrast, biologic agents are produced by biotechnological methods using very

specific cell lines under highly controlled conditions, details of which are never fully disclosed by the manufacturers, making these production methods impossible to duplicate.² Thus, the resultant product is often not an exact copy of the patented or reference molecule, rendering the term “generics” invalid in this context.

The cell lines used and other methods of characterization and purification differ among the various manufacturers. The result is that different brands of the same biologic drug sometimes have variations in efficacy, safety and immunogenicity. Besides, we can also come across variations in effectiveness even between different batches of the same brand of the biological agent. Whether these biologic and biosimilar molecules can be considered interchangeable is still a matter of controversy and, though there are certain criteria set by regulating authorities, these are often not clearly defined.³

The current biologic and biosimilar brands of rituximab available in India differ in their molecular separation properties and adequate comparative studies to determine their relative biological effects do not exist.⁴

Another point which deserves mention is “interchangeability” of biologic agents. According to the United States Food and Drug Administration definition, the generic products should be comparable to the reference product in dosage form, strength, route of administration, quality, performance characteristics and intended use.⁵ In India, the “Guidelines on Similar Biologic” prepared by Central Drugs Standard Control Organization and the Department of Biotechnology have laid down the regulatory pathway for a “Similar Biologic” which claims to be similar to the reference biologic. According to the guidelines, “Similar Biologic product is that which is similar in terms of quality, safety and efficacy to an approved Reference Biological product based on comparability.”⁶

Thus, keeping the above things in mind, we feel that for a study of this kind to be clinically relevant and its

findings to be reproducible, it is important to mention the brand of biologic or biosimilar used.

Besides, we would like to point out that there appears to be a discordance between the authors' statement "15 patients had already received several cycles of monthly dexamethasone or dexamethasone-cyclophosphamide pulse therapy" and the data shown in Table 1 (in the study by Sharma *et al.*)^[1] where it appears that only nine patients (six for dexamethasone-cyclophosphamide and three for dexamethasone) had actually received pulsed therapy previously. The authors also mention that "10 out of 15 patients who had received intravenous pulsed therapy had complete remission with this initial treatment, but all of them relapsed after a mean duration of 9.5 months." However, it is not mentioned if long-term maintenance with any immunosuppressive drug had been instituted for these patients after pulsed therapy as was done after treatment with rituximab (oral prednisolone 0.5 mg/kg of bodyweight for 3–4 months and cyclophosphamide and azathioprine for 1 more year). We know that the retrospective nature of the study precludes any direct comparison between the two, but a clarification regarding this would help the readers get an idea of the potential benefit of rituximab, if any, over dexamethasone/dexamethasone-cyclophosphamide pulse therapy for induction of long-term remission in recalcitrant pemphigus.

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Conflicts of interest
There are no conflicts of interest.

Aparajita Ghosh, Anupam Das

Department of Dermatology, KPC Medical College and Hospital,
Kolkata, West Bengal, India

Address for correspondence: Dr. Anupam Das,
"Prerana," 19, Phoobagan, Kolkata - 700 086,
West Bengal, India.
E-mail: anupamdasdr@gmail.com

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