

Biosimilars in oncology: everybody agrees but nobody uses?

BISHAL GYAWALI¹

¹Nagoya University Hospital, Nagoya, Japan.

Received by invitation March 22, 2017.

Summary. Reducing the cost of biologics is an important avenue for addressing financial toxicity in oncology, one of the biggest challenges for health systems. The use of biosimilars, the cheaper alternatives to biologics, is an important strategy to that end. But the enthusiasm of developing biosimilars is meaningless if they get to the market, but they're not prescribed by the physicians, concerned by unexpected side effects or inferior efficacy. A recent study found no differences between biosimilars and erythropoietin stimulating agents originators in the composite outcome including all-cause mortality, blood transfusion and major cardiovascular events. Such studies are important to allay the concerns of physicians and patients regarding the use of biosimilars. Physician and patient education, backed by clinical guidelines and patient advocacy groups, are the keys to improving the uptake of biosimilars in clinical practice.

Biosimilari in oncologia: tutti sono d'accordo, ma nessuno li usa?

Riassunto. Ridurre il costo dei biologici è un'importante opportunità per affrontare il problema della tossicità finanziaria in oncologia, una delle questioni più rilevanti per i sistemi sanitari. Fare ricorso ai biosimilari, le alternative meno costose ai biologici, è una strategia importante per raggiungere lo scopo. Ma l'entusiasmo provato nel riuscire a sviluppare questi prodotti resta privo di significato se non si traduce in una maggiore prescrizione da parte dei medici, preoccupati dalla possibile insorgenza di reazioni avverse o di minore efficacia. Uno studio recente ha dimostrato l'assenza di differenze tra gli Erythropoietin Stimulating Agents biosimilari e gli originatori, rispetto agli esiti di mortalità per tutte le cause, ricorso a trasfusioni ed eventi cardiovascolari maggiori. Simili studi sono importanti per rispondere alle preoccupazioni di medici e pazienti per quanto riguarda l'uso dei biosimilari. L'educazione del medico e quella del paziente, sostenute da linee-guida cliniche e da gruppi di patrocinio dei diritti dei pazienti, sono la chiave per migliorare la diffusione dei biosimilari nella pratica clinica.

Financial toxicity is emerging as one of the biggest challenges of modern cancer care due to the high cost of new cancer drugs. This skyrocketing cost of modern cancer drugs has pushed cancer care beyond the realms of affordability for the majority of cancer patients¹. The majority of these newer expensive agents are biologics. Indeed, biologics account for the highest oncology-related drug expenditures in outpatient clinics despite being relatively fewer in number². Thus, reducing the cost of biologics remains an important avenue for addressing financial toxicity in oncology and the use of biosimilars, the cheaper alternatives to biologics, represents an important strategy to that end³.

The European Medicines Agency (EMA) defines a biosimilar medicine as a medicinal product, which is similar to a biological medicine that has already been authorized (the "biological reference medicine")³. Europe has been leading the movement to use biosimilars with regulatory approval process in place as early as 2005. Indeed, while EU approved its first biosimilar (epoetin alfa and filgrastim) in 2007, the US did so (filgrastim) only in 2015⁴. It is noteworthy that the first few biosimilars were of drugs used in supportive care of cancer, an area frequently overlooked in the discussion of financial toxicity^{5,6}. Indeed, biosimilar erythropoietin stimulating agents (ESAs) costs 25-30% less than the branded epoetin alfa and

thus improve both the accessibility and affordability of this drug used in the management of chemotherapy induced anemia⁷.

However, the tale of biosimilars in oncology is twisted. The development and approval of biosimilars is challenging; the adoption of approved biosimilars is a bigger challenge. The whole enthusiasm of developing biosimilars is meaningless if a biosimilar gets to market but isn't prescribed by the physicians. A certain amount of caution is understandable and necessary because unlike generics, a biosimilar has modifications of original compound. That's also why a biosimilar, unlike a generic, has to undergo trials and validations to demonstrate bioequivalence to the original product before it gets approved⁴. However, there are challenges even with the trials of biosimilars because physicians don't want to enroll their patients just in case the biosimilar proves inferior. Another concern is the emergence of sometimes unexpected side effects with biosimilars. For example, the association of pure red cell aplasia with an erythropoietin biosimilar led to fears about incorporating biosimilars into practice easily⁸. Hence, in order to appease the concerns regarding efficacy as well as safety of biosimilars, real world evidence (RWE) becomes crucial. Encouraging data from RWE helps build confidence among physicians in prescribing biosimilars.

“ *The whole enthusiasm of developing biosimilars is meaningless if a biosimilar gets to market but isn't prescribed by the physicians.* ”

In this context, a recent study published by Italian colleagues comparing the effectiveness and safety of biosimilars versus originators of ESAs is very topical and important⁹. In a population based cohort from Lazio, Italy the authors analyzed 13470 incident ESA users in the setting of chronic kidney disease (n=8161) or oncology (n=5309) between 2012-2014 using a registry. Thankfully and unsurprisingly, the study found no differences between biosimilars and originators in the composite outcome including all-cause mortality, blood transfusion and major cardiovascular events. In the oncology setting, the originators in fact suggested a possible detriment versus biosimilars with regards to all-cause mortality (HR for biosimilars versus originators 0.82, 0.70-0.97) although the composite outcome didn't show such differences. The authors appropriately conducted a sensitivity analysis in a subgroup of oncology patients and found that the cause of death was cancer in 41.9% patients on originator versus 35.9% patients on biosimilars. The authors also conducted genetic matched analysis (a method of multivariate matching) and found similar results including possible detriment with originators in cancer patients. Although possible detriment in all-cause mortality with ESAs have been demonstrated in previous trials of originators, the main take-home here rather is that the biosimilars were safe and effective. If anything, the biosimilars are more protective than the originators but this is a hypothesis to be explored in future studies.

While all the caveats of RWE do apply, this is a well-conducted study and the authors have done their best to control as many confounders as possible. Although some important confounders such as iron supplementation, body-mass index etc. haven't been controlled and 6 months of follow-up mightn't be enough to pick-up late signals, this study goes a long way to encourage and promote the use of ESA biosimilars in routine practice.

The credibility of RWE especially lies in the consistencies of findings. In this context, it is important to review another RWE study in the same setting published last year, again from Italian colleagues. Among 1003 incident ESA users from CKD and cancer setting, they found that the dispensed doses of biosimilars and originators were comparable and at three months, all raised Hemoglobin (Hb) levels similarly by an average of 2gm/dl¹⁰.

Taken together, these studies clearly suggest that biosimilar ESAs provide similar efficacy and safety (or may even be more protective) to originator ESAs. However, despite being approved in 2007, the uptake of ESA biosimilars has been very limited. Indeed, it is worrying to see that only 154 of 8161 CKD patients and 453 of 5309 cancer patients on ESAs received biosimilars⁹. For the oldest biosimi-

lar, it is disheartening to see such poor uptake and some serious questions need to be asked on why the market penetration of cheaper alternative to an expensive drug has been so poor. Some concerns on efficacy and safety as discussed above are legitimate but doesn't explain completely such poor uptake. The public health care system such as that existing in Italy could be one more incentive for physicians/patients not to seek cheaper biosimilar alternatives. However, as was recently shown, financial toxicity remains a severe problem affecting mortality even in the public health system of Italy¹¹. Thus, it is very appropriate that this study, also from Italy, tries to appease the users on the concerns of safety and efficacy of biosimilars.

Indeed, all these efforts to develop and trial biosimilars are in vain if they're not adopted in routine clinical practice. Thus, our efforts should be focused on improving the uptake of biosimilars. To that end, such RWE informing the efficacy, safety and practice patterns are very crucial. Another key point of intervention is education among physicians and patients. Indeed, as all decisions of treatment are made between the physician and the patient, all measures are rendered futile if not implemented by the physician or not accepted by the patient⁶. Thus, physician and patient education forms a key strategy and data from such RWE are useful to achieve the purpose.

More importantly, clinical guidelines and patient advocacy groups form key pillars of this education channel. Sadly though, in the US it is known that many reputed guidelines¹² and patient advocacy groups¹³ have conflicted interests with pharmaceutical organizations thus mudding the water. Similar researches into the European (and global) guidelines or patient groups are also needed and could explain at least partly the problem of poor uptake of biosimilars. In any case, conflict-free clinical guidelines and patient organizations are keys to improving the uptake of biosimilars in clinical practice.

Having emphasized on the uptake of biosimilars, it is also important not to forget the importance of continued post marketing vigilance. Prospective observational registry-based studies of biosimilars with longer follow up should be encouraged. In case of ESA biosimilars in oncology, the possible protective effect of biosimilars versus originators is an important observation that deserves serious consideration in future studies. And last, but not the least, appropriate prescribing should always be practiced irrespective of biosimilars/originators. This is particularly important because cheaper price can sometimes encourage rampant prescription. For instance, when sunitinib was available for free to Nepalese cancer patients (<http://www.livemint.com/Companies/hJQ8FWj8hMN1Kol25PocN/Pfizer-to-launch-free-Sutent-access-programme-in-Nepal.html>), many

cancer patients in Nepal were being prescribed sunitinib off-label simply because it was available for free. Thus, at the other end of the biosimilar uptake spectrum, lies the overuse of biosimilars due to relatively cheaper price. It should be remembered here that ESAs (originators or biosimilars) are not frequently needed in cancer care. The objective in using ESAs in cancer patients is to avoid transfusion and related effects. ESAs themselves come with a price, increasing the risk of thrombosis and possibility of reducing survival and time to tumor progression. Knee-jerk use of transfusion or ESAs must be avoided based solely on an arbitrary hemoglobin cut-off. For a cancer patient, it mightn't matter much whether his Hb is 10 or 11 if it doesn't lead to any symptomatic changes. Indeed, we are never treating anemia, we are always treating a cancer patient who has anemia and for that individual, anemia may or may not be his/her concern or the cause of symptoms. Furthermore, major guidelines don't recommend the use of ESAs in cancer patients who are not on active therapy or receiving non-myeloablative therapy or receiving myeloablative therapy with curative intent. The whole patient and his/her disease status must, therefore, be considered before institution of ESA therapies. Indeed, in cancer medicine, it is as important to practice "avoiding wisely" as it is to "choosing wisely".

In cases where ESA therapy is judged to outweigh the risks, it becomes the responsibility of a physician to recommend a biosimilar given the reassuring evidence. A study has shown that 100% conversion to biosimilars in a hypothetical population of 100,000 patients would allow an additional 12,913 rituximab, 5171 bevacizumab or 4908 trastuzumab treatments under weight-based dosing¹⁴. It would be a double-standard by the oncology community to raise voice against financial toxicities of cancer treatment and yet not prescribe biosimilars when available and backed up by safety and efficacy data. Surely, voicing concerns and writing papers alone won't alleviate the problem of financial toxicity; it requires changes in practice patterns such as the adoption of biosimilars into routine clinics.

Conflicts of interest: the author has no conflicts of interest to declare.

The author

Bishal Gyawali, MD, is a medical oncologist with experience in cancer care in both low-income and high-income countries. After graduating medical school in Nepal with seven gold medals, he is now in the final year of his postgraduate training and PhD in medical oncology in Japan as a MEXT (Ministry of Education, Culture, Sports, Science, and Technology) scholar. His original and opinion articles have been published in top oncology journals. He also provides critical commentary on oncology updates of every month at his blogs on the

ecancer website (<http://ecancer.org/advanced-search.php?Keyword=bishal&btnSearch=1>). He is a reviewer for various oncology journals, an editorial adviser to the BMJ and a *Journal of Global Oncology* Editorial Fellow for 2017. His areas of clinical and research interests include evidence-based oncology practice, global oncology, cancer policy, cancer management in resource-limited settings, financial toxicities of cancer treatment, clinical trial methods, and supportive treatments of cancer.

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Corresponding author:

Dr. Bishal Gyawali
Nagoya University Hospital
65 Tsurumai-cho, Showa-ku
466-8560 Nagoya, Japan
Twitter: @oncology_bg
E-mail: bg.bishalgyawali@gmail.com