ESR Researcher Project: Non-technical Summary

"Switchability assessment of biosimilars"

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Biosimilars are meant to be cheaper copies of biologic drugs. Biologics are large-molecule drugs that are developed from living organisms and have revolutionized the treatment and prevention of many disabling and life-threatening diseases like cancer, arthritis, psoriasis and growth disorders. Because of the complexities involved in their manufacture, biosimilars can only be considered as similar to their reference biologic rather than equivalent. This is in contrast to a generic drug, which receives marketing approval on the basis that it has been shown to be equivalent to its small-molecule reference (original) drug. In many countries, substitution of the originator product with the generic at the pharmacy level without the intervention of the prescribing doctor is acceptable.

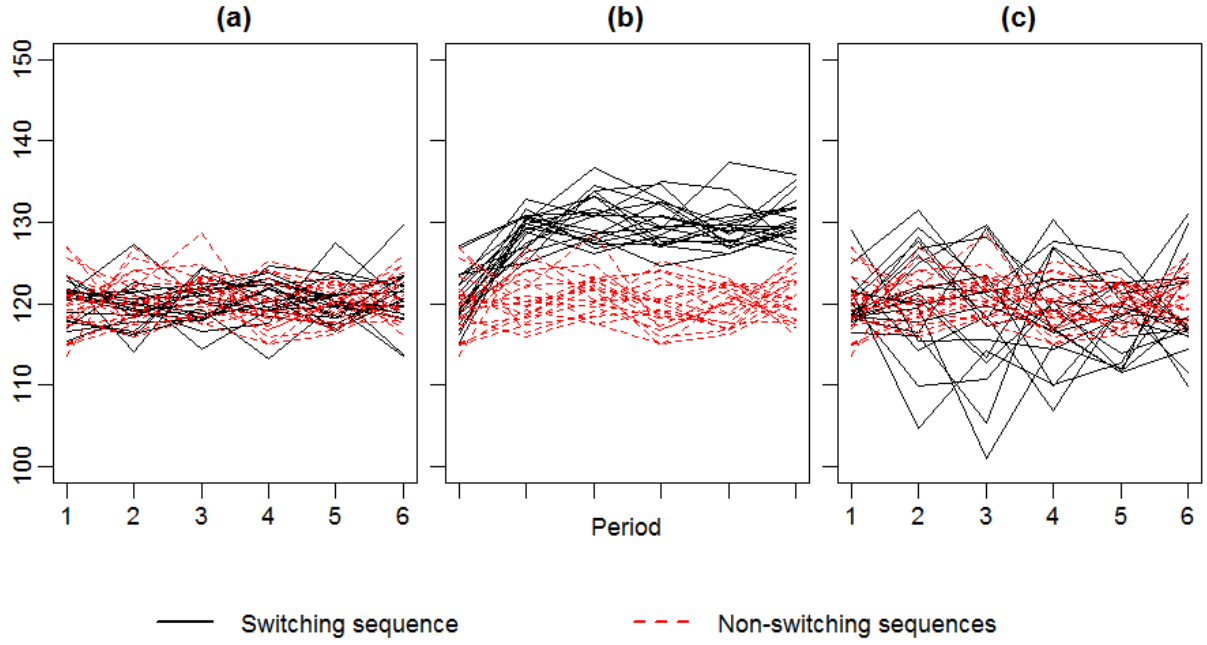
The situation for biosimilars is quite different. Despite patients, physicians and health care providers in Europe having more than ten years of experience with biosimilars, there are still debates if switching between a biosimilar and its reference product influences the efficacy of the treatment.

The European Medicines Agency states that "the Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine" [1] and recommends, "for questions related to switching from one biological medicine to another, patients should speak to their doctor or pharmacist". Within the member states of the European Union (EU), the viewpoints and handling of switching are diverse. The Finnish Medicines Agency [2], for example, published a position paper stating that "switches between biological products are common and usually not problematic", whereas the Health Products Regulatory Agency in Ireland [3], for example, explicitly "does not recommend that patients are switched back and forth between a biosimilar and the reference medicinal product".

In the USA, the Food and Drug Association (FDA) has the legal option to approve a biosimilar as an interchangeable biosimilar [4]. This status means that patients can be switched between the biosimilar and its reference product without the knowledge or approval of the prescribing doctor. So far, there are no approved interchangeable biosimilars in the US.

In order to determine if switching should be allowed, it is first necessary to agree on which pattern in the data can be expected if the biosimilar and its originator are switchable or not switchable. For that, we compare subjects who are switching (e.g., first biosimilar, then originator, then biosimilar …) to patients with continuous treatment with the biosimilar or the originator over the complete duration of the study. This is shown in the figure overleaf: each line represents the measurement of the treatment effect (also known as the treatment

response) of one subject which was observed over six periods (i.e., six assessments of the treatment effects). Situation (a) is a situation in which we do not see any difference in the treatment response between subjects who are switching (black) and subjects are not switching (red). In Situation (b), it seems as if subjects who are switching have a higher treatment response value compared to the non-switching patients. For example, this might mean that the target value for systolic blood pressure is not met, but patients still experience, unexpectedly, a too high systolic blood pressure even after being treated with the medicine which is clearly to be avoided. Therefore, we do not call this situation switchable. In Situation (c), patients in the switching sequences have still on average the same response as patients in the non-switching sequences. However, the variability is higher for patients who are switching compared to the non-switching patients. Coming back to the blood pressure example, this would mean that switching patients sometimes have a too high and sometimes a too low systolic blood pressure. Again, this is not desirable.



In our project we developed several statistical methodologies for distinguishing between Situation (a) and Situation (b) and (c) with a focus on testing Situation (a) vs. Situation (b). We evaluated the properties of the approaches, specifically the ability to distinguish between the different situations and applied the data sets to a real-world example. For more details, please see our publication [5].

References

[1] Questions and answers on biosimilar medicines (similar biological medicinal products). 2012. Available at http://www.medicinesforeurope.com/wp-content/uploads/2016/03/WC500020062.pdf (accessed 1 September 2018).

[2] Interchangeability of biosimilars - position of Finnish Medicines Agency Fimea. 2015 Available at

https://www.fimea.fi/documents/542809/838272/29197_Biosimilaarien_vaihtokelpoisuus_EN.pdf (accessed 24 March 2017).

[3] Considerations for physicians on switching decisions regarding biosimilars. 2017. Available at https://www.ifpma.org/wp-content/uploads/2017/03/Considerations-for-switching-decisions_IFPMA-vF.pdf (accessed 1 September 2018).

[4] Biologics Price Competition and Innovation Act. 2009 Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ucm216146.pdf (accessed 29 September 2016).

[5] Mielke, J., Woehling, H. and Jones, B. (2018). Longitudinal assessment of the impact of multiple switches between a biosimilar and its reference product on efficacy parameters. Pharmaceutical Statistics, 17 (3), 231-247.

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