## Shakespeare, Biosimilars and Switching

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I had thought to call this piece “to switch or not to switch, that is the question” as a cheap variation on one of William Shakespeare’s most famous lines from Hamlet. However, I thought that you the reader and William Shakespeare deserved better than that. I will return to Shakespeare at the end, in case you opened this article to get more about him rather than about switching with regard to biosimilars.

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 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" 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, 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, 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. 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 how it can be assessed. As a move in this direction, Mielke at al. (2018) have proposed three approaches. They assessed them via a simulation exercise and, by way of illustration, applied them to data from a real study in psoriasis patients.

As, logically, the assessment of switchability should be based on an equivalence or non-inferiority type test, a correct definition of the null hypothesis is vital. A complication is that a test for equivalence can be based on several characteristics of the data (e.g., difference in mean value, difference in distribution) and so is not unique. We focus on tests of equivalence of the mean, but we also assess the properties of our methods in the situation where switching increases the variability of the efficacy measure. An important conclusion is that the preferred method depends on how switching is expected to affect the response (e.g., will patients experience an unstable treatment response or will there be a systematic change in the response after switching?).

To end with, I give you an unadulterated quote from Shakespeare's A Midsummer Night's Dream, which I think is appropriate to the topic of this article (it is spoken by Helena): "So we grow together, like to a double cherry, seemed parted, but yet an union in partition; to lovely berries moulded on one stem".

If you found this article interesting, you might also like my previous one on Bayes, Biosimilars and Sir Mick Jagger.

**Reference**

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*, Early View.

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