Biosimilars: clinical-pharmacological considerations.

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The branded drugs patent expirations allow to reproduce the same drug on the market. Small molecule drugs are considered chemically identical once their therapeutic equivalence is assessed by chemical criteria. If they are satisfied, originator and generic become interchangeable.This regulatory approach isn't suitable for biological drugs and their copies: biosimilars[1]. They are proteins with different levels of complexity due to their size, structure and their production is sensitive to environmental conditions, manufacturing process and immunogenicity. For this reason it's impossible from a biological point of view to identically reproduce originator: biosimilar can only shows similarity with a reference drug[2]. EMA trusts in comparability exercise to set biosimilarity[3]. It involves assessment of evidences for the close similarity of the two products. However, even when biosimilarity has been established, neither substitution nor interchangeability are necessarily assessed[3]. Those requires additional clinical data derived from a long term real life practice,we actually haven't for second generation biosimilars.

Although biosimilars will play an important role in lowering therapy's cost, it's useful paying attention to some possible issues, especially concerning manufacturing process, clinical setting and pharmacovigilance.

Due to the variability of biologic synthesis, occasionally, drug's quality attributes could shift outside of established acceptable ranges as the result of an unknown deviation (drift) or known manufacturing change (evolution)[4]. These may impact quality, safety and efficacy of biologics. Though some variability is normal, any changes must be rigorously investigated and signaled by robust quality systems. Over time these alterations could compromise the biosimilarity assessed by comparability exercise[4]. In fact two products that were initially deemed biosimilar each could undergo unique patterns of drift/evolution, ultimately resulting in two products that are no longer biosimilar (divergence)[4].

This could interest especially unstable molecules as insulin analogues[5]. Insulin glargine biosimilar has come since 2016. It's the first time diabetology faces this kind of drugs with all issues related to clinical management of diabetics which can increase some differences between originator and biosimilar. Basal insulin administering frequency considers a drug exposure, generally, superior to the current available first generation biosimilars. Also for this reason more pharmacovigilance data from real life are needed.

Moreover, insulin treatment involves not only molecule itself, but also the therapeutic adherence[6]. Several factors, comparability exercise doesn't thoroughly consider, may affect adherence and influence treatment outcome: comorbidities, polypharmacy, device's patient use and the hypoglycemic risk in switching from an insulin to its biosimilar and vice versa[7].

In the specific case of insulin, some issues of preclinical studies may interfere the comparability exercise (sensitivity, standardization, PD analysis) and the capability of pharmacovigilance control is probably unable to detect all adverse events related to a specific biosimilar, also considering the wide insulin use in extra-hospital setting[5].

We focused on diabetology which is the last therapeutic area facing biosimilar issues and their clinical and forensic consequences.

[1] Mellstedt H. *Ann Oncol*. 2008;19(3):411–419.

[2] Carson KL. *Nat Biotech* 23(9): 1054 (2005).

[3] Guidelines, EMA, 23 Oct. 2014.

[4] S. Ramanan, *BioDrugs* (2014) 28:363–372

[5] L. Heinemann, *Diabetes, Obesity and Metabolism* 17: 911–918, 2015

[6] Colombo GL, et al., Impact of substitution among generic drugs on persistence and adherence, *Atherosclerosis Supplements* (2016)

[7] G. Polimeni, *Acta Diabetol* (2015) 52:423–431