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How to address immunogenicity in the development of a rare disease biosimilar

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Rare diseases tremendously lack affordable treatment options. Orphan drugs have been neglected by the biosimilar industry for a long time. Patient's advocates that people with rare diseases have access to safe and effective biologic and biosimilar medicines. World-wide, 350M people are estimated to suffer from a rare disease, including 25-30M US and 30M EU residents. With >60% biologics account for the majority of the global orphan drug market. A major problem with protein-based therapeutics is their immunogenicity. Forms of immune response is activation of B cells, and T-cells, which help to activate B cells. The T-cells respond is a normalraection to an artificial protein therapeutic as if it were foreign, since it is different from the defective, natural protein. A T-cell response mismatch like this sometimes occurs in the case of the protein FVIII. Virtually all therapeutic proteins (biologics) elicit an immune response with the consequent production of anti-drug antibodies (ADA). The ADA to therapeutic monoclonal antibodies (mAbs) that are directed against the antigen-binding site of the therapeutic mAb are neutralizing. This nature of the ADA response explains why fully human antibodies can still be highly immunogenic. Biosimilars have to be tested for their immunogenicity as it is impossible predict if they will induce an immunogenicity similar to the one manifested by the corresponding innovator biologics. Infusion related reactions (IRRs) include hypersensitivity reactions and cytokine release syndromes. Hypersensitivity reactions have classically been divided into type I, II, III, and IV reactions; type I and III reactions are those most often observed following administration of biologics. Infusion related reaction is defined as a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances and as a disorder characterized by nausea, headache, tachycardia, hypotension, rash and shortness of breath and caused by the release of cytokines. Infusion-related reactions are common and timely related to drug administration and have been reported as anaphylaxis, anaphylactoid reactions and cytokine release syndrome, among other terms used. Animal toxicology studies are neither predictive of severe IRRs nor of anaphylaxis in human. Relative to intravenous (IV) administration, the SC route offers more convenience to patients, flexibility in dosing, and potential to reduce health care costs. There is a perception that SC administration can pose a higher immunogenicity risk than IV administration for a given protein. However, a recent comparative clinical study of sc vs iv administration of abatacept showed that the efficacy and immunogenicity are comparable between the two routes of administration.

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