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Review

Challenges and Opportunities for the Subcutaneous Delivery of Therapeutic Proteins

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ABSTRACT

Biotherapeutics is a rapidly growing drug class, and over 200 biotherapeutics have already obtained approval, with about 50 of these being approved in 2015 and 2016 alone. Several hundred protein therapeutic products are still in the pipeline, including interesting new approaches to treatment. Owing to patients' convenience of at home administration and reduced number of hospital visits as well as the reduction in treatment costs, subcutaneous (SC) administration of biologics is of increasing interest. Although several avenues for treatment using biotherapeutics are being explored, there is still a sufficient gap in knowledge regarding the interplay of formulation conditions, immunogenicity, and pharmacokinetics (PK) of the absorption of these compounds when they are given SC. This review seeks to highlight the major concerns and important factors governing this route of administration and suggest a holistic approach for effective SC delivery.

Introduction

Recently, a shift toward safe and effective subcutaneous (SC) delivered proteins has garnered the attention of major pharmaceutical companies and health care providers alike, with over 200 approved biotherapeutics and growing.[1] The biggest advantage to this route of administration is a cheaper, more convenient method of dosing that accommodates both patient and physician. Patient convenience likely improves due to ease of at home self-administration, as many of these therapeutics require multiple doses for long-term therapy.[2] Even for therapeutics that must be administered by a physician, SC injection take mere minutes compared with the one to several hours necessary for intravenous (IV) infusion.[3,4] In addition to these general advantages, unique advantages associated with individual therapeutics have been observed on a case by case basis. Erythropoietin is an often cited example of a therapeutic protein with better efficacy dosed SC rather than IV because of a prolongation of systemic exposure when given this route that allows for a reduction in dosing.[5,6] This phenomenon can be described by the concept of flip-flop kinetics, where the absorption rate is the limiting step for drug clearance.[7] Flip-flop kinetics have also been reported for low-dose interferon beta-1a in monkeys, with an absorption rate constant of 0.104 h^{-1} compared with an elimination rate of 0.2 h^{-1}, which has beneficial clinical implications for SC dosing.[8] Another benefit has been documented for alemtuzumab, where evidence of improved tolerance by reducing or eliminating flu-like symptoms caused by IV infusion-related reactions.[9] A reduction in adverse injection-related event severity has also been reported for rituximab in a clinical trial comparing the 2 routes of administration.[10] Although this route of administration offers significant practical benefit, it is not without complication. Many of the obstacles associated with SC delivery can be categorized based on 3 general concerns: formulation issues, immunogenicity, and PK (Fig. 1, top). Table 1 highlights several examples of approved proteins and their given formulations, as well as a summary on their bioavailability, immunogenicity, and concentration. One such means to improve protein therapeutic success is to treat each of these characteristics as interdependent on one another throughout development, using a mix of biophysical studies and preclinical trials to guide a holistic approach.

Subcutaneous (SC) dosing is generally dosed as a small volume comparative to IV infusions, which allow for large volumes and proper dispersal of protein. Higher volumes of injection generally lead to patient discomfort and sometimes pain at the site of administration.[38] Considering the EC50 of monoclonal antibodies (mAbs) is quite high, the dosing range is between 150 mg and 1.2 g per dose. The resulting concentrations generally lead to protein

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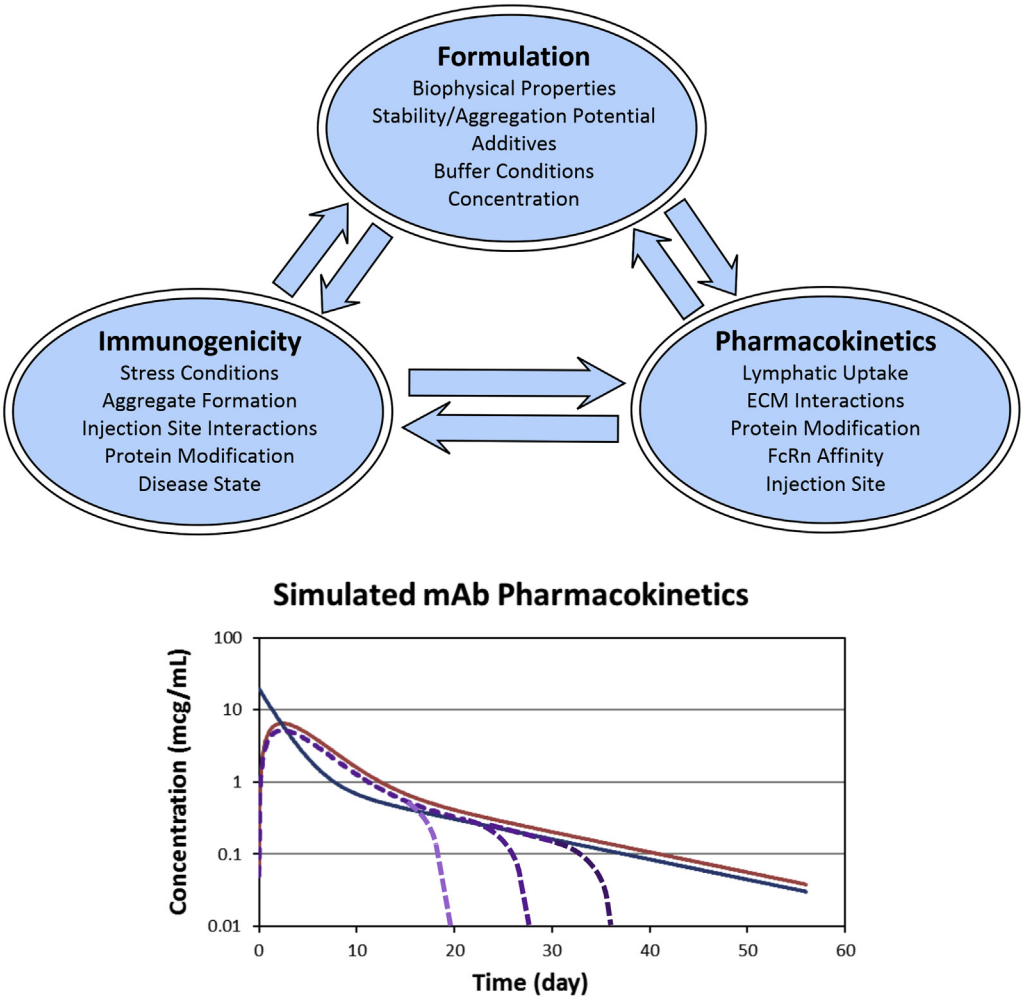

Figure 1. (Top) Considerations for protein development: a holistic approach. (Bottom) Simulated pharmacokinetic data based on a generic, model monoclonal antibody (mAb) with a two-compartment distribution. Blue line indicates IV dose, red line indicates SC dose with no immunogenicity, and purple line signifies SC dose with varying degrees of ADA response; after 14, 21, or 28 days postinjection.

crowding, which has been shown to increase the risk of aggregation due to protein-protein interaction.[39] Therefore, these formulations require added excipients and stabilizers that improve not only conformational stability but also colloidal stability of proteins within this crowded environment. Aggregation can interfere with protein absorption and allow increased interactions with immune cells within the SC space, as larger particles can remain trapped at the injection site for longer periods of time. There is still debate whether this environment is more or less immunogenic than traditional IV dosing, a phenomenon that garners a great deal of attention.[40] Finally, PK variability has been seen for a variety of SC dosed proteins, particularly mAbs that even share similar structure and molecular weight. From incomplete and variable bioavailability ranging from 50% to 100% to differences in absorption rate (0.1-0.4 inverse days) and Tmax (2-8 days), it is clear that several factors are involved in determining the PK fate of antibodies dosed via this route.[41] Problems associated with limited or incomplete bioavailability can be associated to unfavorable uptake, immunogenicity, poor absorption profiles, protein aggregation, and other factors.

Anatomy and Physiology of the Skin

The skin is the largest organ in the body, and in addition to its physiological roles of protection, hydration, and thermoregulation, it provides an excellent route for many pharmaceutical agents. The skin is composed of 3 important layers: the epidermis with sublayers stratum corneum, lucidum, granulosum, spinosum, and basale; the dermis; and the hypodermis, otherwise known as subcutaneous tissue.[42] The epidermis is primarily a protective layer containing keratinocytes and dendritic cells (Langerhans cells), which will later be discussed for their immunological role. This layer constantly rebuilds itself, constantly in motion allowing restructuring and building of the outermost exposed stratum corneum.[43] Between the epidermis and dermis lies a nonrestrictive, porous barrier that allows fluid and cell exchange while supporting both layers with connective fibrils and collagen.[44] Within this barrier and part of both of the aforementioned layers lie various sweat glands and hair follicles, which aid in temperature regulation and protection from the environment. The upper dermis layer contains loose connective tissue and many blood capillaries, as well as nerve endings and pain receptors highly responsive to external stimuli.[45] Deeper within the skin tissue nearing the border and transitioning into the subcutaneous space lie the remainder of the dermal layer and the extracellular matrix (ECM), which contains fibroblasts, macrophages, and adipocytes. At the junction between the dermis and hypodermis, larger blood vessels and lymphatic networks aid in fluid homeostasis and transportation of immune cells from the ECM and surrounding area to internal lymph nodes