Challenges in the subcutaneous (SC) administration of monoclonal antibodies (mAbs)

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Many of the formulations developed for monoclonal antibodies (mAbs) have been for intravenous (IV) administration since drugs for indications such as cancer therapy could be easily administered in a hospital, often in an infusion center. This conventional route of administration usually was developed because of poor bioavailability by most other routes, greater control during administration, that is, if there are immediate adverse events the IV can be stopped, and faster pharmaceutical development. For clinical indications where treatment may be more convenient in a physician's office, clinic, or at home, the subcutaneous (SC) route of delivery is more appealing. In particular, the coupling of an SC formulation with a syringe and autoinjector increases the convenience and ease of use for the patient and ensures better compliance. IV administration of mAbs requires frequent dosing regimens and relatively high clinical doses, usually in the range of 5–700 mg per patient. The doses are often administered as a fixed dose (Campath 3–30 mg) or on the basis of body weight (Herceptin at 2–4 mg/kg) or body surface area (Erbitux 250–400 mg/m^2) of the patient. The frequency of IV administration is dictated by the requirement of maintaining a pharmacodynamically effective concentration and is linked to the circulatory half-life, typically 12–48 h for a murine mAb and 3–21 days for a chimeric, humanized, or human IgG1 mAb (Mould & Sweeney, 2007).

SC dosing is generally restricted to small volumes that do not exceed 1.5 mL, due to the tissue backpressure, resulting in loss of drug due to seepage, and injection pain (Jorgensen et al., 1996). Thus, the high doses required for effective mAb therapy necessitate the development of a high-concentration mAb formulation, often greater than 100 mg/mL. Prior to 2000, there was only one mAb formulation for SC delivery, and it was at 50 mg/mL (Enbrel). One mAb was developed for intramuscular (IM) injection and was formulated at 100 mg/mL (Syngis). Since then, 11 mAb formulations were approved for SC delivery, 5 greater than 100 mg/mL and one as high as 200 mg/mL (Table 4.1). The road to development of these high concentrations has not been easy, since aggregation and particulate formation are highly concentration dependent, and may become the dominant degradation pathway at high concentration.

The challenge of formulating at high concentration

Most of the chemical degradations of proteins are concentration independent, and thus designing stable formulations to minimize chemical degradations at high concentrations are very similar to those for more standard lower concentration formulations. On the other hand, protein aggregation is expected to be a predominant degradation pathway at high concentrations since bi- or multimolecular collisions can lead to aggregate formation.

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