Subcutaneous bologics: clinical pharmacology and drug development

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Biologics are a therapeutic class of drugs derived from living organisms that have been used in medicine for thousands of years. It was in the 20th century that the formal recognition and distinction of biologics emerged, marked by the introduction of the term itself and the mass production of biological products such as vaccines and sera.[1,2] This period spurred efforts to standardize their definition, production methods, and quality, leading to the enactment of the Biologics Control Act by the United States Congress in 1902.[3] The advent of genetic engineering in the late 1970s and early 1980s enabled scientists to modify genetic sequences, enhancing the stability, safety, and efficacy of existing agents while broadening their applications, notably seen in the enhanced targeting abilities of antibodies.[4] Subsequently, biologics research and production surged post-1980s, contributing to the development of innovative therapeutic strategies for various therapeutic areas, such as cancers, immune disorders, and rare genetic diseases.[5] This evolution of biologics transcended mere extraction of natural substances, evolving into the conception, engineering, and manufacturing of a diverse array of advanced molecular-, protein-, gene-, cell-, and tissue-based agents designed for highly precise targeting.

Biologics are typically administered via two primary pathways: intravenous (i.v.) and subcutaneous (s.c.) routes. The i.v. administration, which is typically developed first, entails direct injection into a vein, ensuring rapid systemic circulation and immediate impact. Conversely, s.c. delivery involves injection into the s.c. tissue, enabling slower absorption into the central circulation via blood capillaries or indirectly via the lymphatics. The transition from i.v. to s.c. delivery of biologics carries tremendous opportunities for the discipline of quantitative clinical pharmacology using model-informed drug development (MIDD) strategies as it positively influences the development of s.c. formulations and overcomes the s.c. drug development paradigm. Although i.v. administration ensures swift and potent bioavailability, s.c. administration has proven effective, safe, well-tolerated, and generally preferred by patients and healthcare providers resulting in reduced drug delivery-related healthcare costs and resource use. The selection of the administration route hinges on various factors, including the drug's properties, patient preferences, and the desired kinetics of therapeutic action.

The development of drug delivery strategies and delivery devices to support the s.c. administration of biologics is rapidly and continuously evolving. This has led to the development of fixed-dose s.c. formulations that are delivered independently of a patient's body weight using devices that allow self-administration outside of the hospital setting. These advancements have contributed to shifting care to the home setting, which is more convenient and patient-friendly than i.v. administered medicines. In

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Received January 5, 2024; accepted January 5, 2024. doi:10.1002/cpt.3179

evaluating the potential for developing an s.c. formulation for a biological compound, a multidisciplinary drug development team typically considers several key factors. These encompass essential aspects, such as basic pharmacology, immunogenicity, design of the delivery device, human interaction factors, bridging strategies, trial design, and tailored drug development strategy suited for pediatric or specific demographic groups. These considerations are prompted by pivotal questions that arise during the switch in the route of administration (ROA) from i.v. to s.c. development phase such as: (i) What dosing regimen (dose amount and frequency) for the s.c. formulation is required to ensure adequate systemic exposures and achieve comparable safety and efficacy with i.v.? (ii) What is the highest concentration of a biologic s.c. formulation that remains non-viscous while ensuring safety? (iii) What is the maximum comfortable injection volume for a single s.c. injection, and does it align with regulatory guidelines? (iv) Which patient population will utilize the s.c. device? (v) Is the s.c. device a pre-existing product or an innovative design? (vi) Is it necessary to conduct pharmacokinetic (PK) studies that involve varying the site of s.c. injection in the body (e.g., abdomen, tighs, and arms)? and (vii) What alterations occur in the immunogenicity profile when transitioning from i.v. to s.c. administration routes, and how do these changes affect the PK, efficacy, and safety profiles of the biologic?

This focused edition of *Clinical Pharmacology & Therapeutics* (*CPT*) dedicated to the clinical pharmacology development of s.c. biologics (**Figure 1**) offers an assortment of reviews, perspectives, and research articles dedicated to highlighting these key aspects, aiming to optimize the clinical advancement of s.c. biologics. The special issue commences with a comprehensive review by Davis *et al.*[6] outlining a myriad of challenges inherent in the development of s.c. monoclonal antibody (mAb) therapeutics either as a main ROA or following the development of an i.v. infusion presentation. The review starts with the pharmacology of s.c.-administered mAbs and orients readers to the specific considerations for the absorption of biological drugs via the s.c. route. Next, the authors describe the various factors that can affect s.c. administration including (but not limited to) injection volume, formulation, rate, and site of injection that can ultimately affect PKs and subsequently clinical responses (i.e., safety and efficacy). Additional topics covered in this review include a comparison of the immunogenicity between i.v. and s.c. routes, as well as essential components while designing s.c. formulation and different s.c. delivery devices. Additionally, this review presents four case studies illustrating the clinical development of

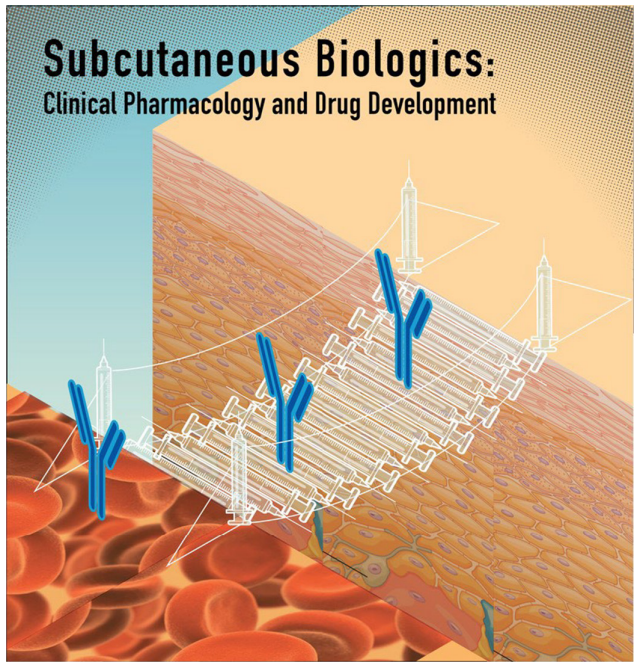

Figure 1 *Clinical Pharmacology & Therapeutics* March 2024 cover image – Subcutaneous Biologics: Clinical Pharmacology and Drug Development.

s.c. biologics: (i) by using i.v./s.c. bridging strategies to expedite PD-1/PD-L1 inhibitor developments, (ii) by simultaneous development with i.v. formulation for anti-severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) antibodies for quick deployment of both versions, (iii) as the primary route for bispecific T cell engagers (Bi-TCEs) to manage Bi-TCE-induced cytokine release syndrome, and (iv) in pediatric patients, as seen with dupilumab.

Additionally, in their review article, Ait-Oudhia *et al*.[7] delve into bridging strategies for biologics, involving the transition of a drug's ROA from i.v. infusion to s.c. injection while preserving its safety, efficacy, and PK profile. These strategies originate from various factors, particularly the enhancement of patient convenience and adherence. In the early stages of drug development, i.v. administration often prevails due to its simpler formulation and precise dosing. However, as drug candidates progress toward commercialization through clinical trials, the focus shifts toward patient-centric delivery methods. The s.c. injections present notable advantages, such as reduced healthcare visits and enabling self-administration, thereby bolstering treatment adherence. Nonetheless, executing a successful switch from i.v./s.c. necessitates thorough planning and rigorous testing. It requires robust bioavailability and comparability studies, complemented by MIDD analyses to demonstrate consistent efficacy and safety across both ROAs for finding an appropriate s.c. dosage and ensuring therapeutic blood concentrations. The authors' review results from a collaborative effort led by distinguished experts in the field of pharmacometrics and clinical pharmacology on challenges and opportunities for i.v.-to-s.c. bridging strategies during the pharmaceutical development of biologics and encompasses several key areas: (i) a comprehensive overview covering translational and clinical considerations for biologics' PK and pharmacodynamic (PD) modeling and simulation, (ii) emphasis on PK models crucial to biologics' s.c. absorption and the beneficial role of MIDD in i.v.-to-s.c. bridging strategies. (iii) illustrations of successful cases utilizing MIDD in bridging i.v./s.c. dosing, (iv) delving into global regulatory perspectives and scientific considerations from health authorities concerning the development of s.c. formulations, and (v) presentation of an interactive case study showcasing the design of an i.v./s.c. bridging study using MIDD. Notwithstanding that successful regulatory approval of i.v./s.c. bridging for biologics not only expedites regulatory endorsement but also broadens market accessibility, granting patients improved access to these highly effective therapies.

Maintaining treatment adherence is pivotal when administering biologics via s.c. injection. Several factors, including the partial absorption of mAbs at a slower pace in the hypodermis, and injection specifics, such as volume, formulation, injection speed, site, and needle characteristics, can significantly influence both PKs and the likelihood and intensity of adverse effects, such as injection site reactions or discomfort. These factors carry substantial implications for adherence to treatment regimens. While PK bridging is a common method to bridge auto-injectors (AIs) with pre-filled syringes (PFSs) for s.c. injections of biologics, the Li *et al*.[8] publication delves into scenarios where PK comparisons are inconclusive. The authors outline instances where successful regulatory approvals for mAb and Fc-fusion protein products using AI devices were achieved despite non-comparable PK. Three specific approaches are highlighted: (i) modifying the AI product and conducting a new PK comparability study, (ii) leveraging clinical experiences from other AI devices, with or without modifications, and (iii) performing risk–benefit assessments based on available data. The authors highlight that whereas 71% of biologics licensing applications (BLAs) for mAbs and Fc-fusion proteins showed matching PK for AI with PFS, the remaining 29% BLAs required further analysis, such as clinical efficacy studies, PK evaluations, or risk–benefit assessments to understand safety and efficacy implications due to exposure differences, which ultimately escalates drug development costs and strains healthcare finances. As such, focused scientific endeavors are needed to fill knowledge gaps and reduce reliance on expensive clinical studies for AI development and approval.

Administration of a biological therapeutic can trigger an immune response, including the production of antidrug antibodies (ADAs). These ADAs can interact with the therapeutic agent and affect its PKs, efficacy, and safety. For instance, ADAs can alter the product's PKs, reduce its PDs, and compromise clinical efficacy. In some cases, ADAs can cause undesirable effects, such as hypersensitivity, infusion reactions, and severe adverse events when they cross-react with an endogenous non-redundant protein.[9] Examples include thrombocytopenia in patients treated with

thrombopoietin and pure red cell aplasia in patients with chronic renal disease treated with epoetin alfa.[10–12] Immunogenicity has been reported with various products, including fusion protein therapeutics, and continues to receive considerable attention from regulatory agencies, the pharmaceutical industry, and clinicians.[13] As a case study on the evaluation of ADAs on the PKs, efficacy, and safety of biologics, in their research article, Liao *et al*.[14] present the results of a phase III clinical trial (STELLAR) in participants with pulmonary arterial hypertension (PAH) treated with sotatercept, a first-in-class breakthrough biologic. Sotatercept is a novel soluble fusion protein that inhibits activin signaling and is being developed to treat PAH. During the STELLAR trial, participants were randomly assigned to receive s.c. doses of sotatercept or a placebo, administered every 3 weeks alongside existing therapies for up to 72 weeks. Among the 162 participants assessed, 42 (25.9%) tested positive for ADAs within the first 24 weeks, with 11 (6.8%) of them also positive for neutralizing antibodies (NAbs). The onset of ADAs occurred at a median of 3.29 weeks, with a median duration of 6 weeks. No substantial differences were observed in PKs, efficacy, or safety across subgroups classified as ADA-negative, ADA-positive without NAbs, and ADA-positive with NAbs. As such, sotatercept has been granted Fast Track designation by the US Food and Drug Administration (FDA) for the treatment of PAH.

Incorporating MIDD analyses throughout the drug development process is crucial, particularly when developing an s.c. ROA for biologics. This effort is vital to ensure accurate dose selection and maintain the efficacy and safety profiles of the i.v. formulation counterpart. Wang *et al*.[15] reviewed FDA regulatory experiences with biologics approved for a second ROA. Among the 11 biologics initially approved for i.v. ROA, subsequent approvals were granted for an s.c. ROA. These programs leveraged prior i.v. data, investigating PKs under the new s.c. ROA and evaluating s.c. regimens in clinical trials. The programs relied on MIDD to ensure comparable exposures or responses to the reference ROA (i.e., i.v.). Approvals for the s.c. ROA demonstrated noninferiority in PKs, PDs, and/or clinical end points or efficacy/safety against a placebo. Clinical trials consistently displayed noninferior systemic exposures, supporting the use of PK- and PD-based bridging for dosage selection and efficacy substantiation in securing approvals for s.c. ROA.

Within the same framework, Zhao *et al*. undertook a population PK (PopPK) modeling approach with the goal to comprehend the PK behavior of a novel s.c. version of nivolumab and strategize appropriate dosing plans for upcoming clinical trials. In the phase I/II clinical trial (CheckMate 8KX study), data on nivolumab PKs were gathered from various s.c. doses, both with and without recombinant human hyaluronidase PH20 enzyme (rHuPH20), which were combined with existing i.v. nivolumab data from 19 previous studies. A merged s.c./i.v. PopPK model was built to simultaneously describe nivolumab PKs when given through both s.c. and i.v. routes. The final model was derived from an established i.v. PopPK model, incorporated an additional compartment for absorption after s.c. administration, and estimated relevant absorption parameters. The analysis revealed that using rHuPH20 with nivolumab s.c. significantly hastened its absorption compared with using nivolumab s.c. alone. No other factors significantly impacted the absorption rate or bioavailability. Through MIDD approaches, exposure-response relationships for safety and efficacy measures across various cancers were established. Notably, a dose of 3 mg/kg i.v. every 2 weeks was effective and well-tolerated across multiple studies. This analysis aimed to predict s.c. nivolumab exposures comparable to or exceeding those of the 3 mg/kg i.v. dose while staying below the exposures from the 10 mg/kg i.v. dose, considering variability due to bioavailability and body weight. Based on simulations, the 1,200 mg s.c. flat dose with rHuPH20 was projected to achieve exposures equal to or higher than the 3 mg/kg i.v. dose across varying body weights, factoring in potential bioavailability uncertainty. This dose was selected for further assessment in the phase III trial (CheckMate 67T study). In essence, the combined s.c./i.v. PopPK model effectively characterized the PK of nivolumab following s.c. administration, guiding the selection of s.c. dosing for subsequent clinical trials in patients with solid tumors. The analysis contributed to evaluating the overall benefits and risks of different nivolumab s.c. dosing strategies in these patients.

Another instance demonstrating the utility of a MIDD-based strategy to improve treatment accessibility and patient adherence with an s.c. formulation is exemplified in Faraj *et al*.'s[17] publication. Currently, acute bleeding

events in patients with hemophilia demand i.v. therapy, but s.c. options promise faster post-bleeding intervention, potentially enhancing treatment effectiveness, and patient well-being, and reducing bleeding-related complications. In a phase III multicenter study, the authors evaluated Marzeptacog alfa (MarzAA) administered via s.c. for acute bleeding in patients with hemophilia. Results show comparable efficacy to the standard-of-care (SOC) with a notable reduction in time from bleed detection to initial dosage compared to i.v. administered SOC therapy. Using a model-based approach, the authors assessed MarzAA's efficacy against SOC and identified influential factors impacting the improvement in bleeding episodes, such as age, bleeding severity, location, and disease burden phenotype. This new analytical framework offers promise for enhancing hemophilia care through s.c. MarzAA, presenting a significant advancement in treatment accessibility and efficacy for acute bleeding events.

Despite the regulatory approved conventional administration routes for Bi-TCEs being i.v. injection or continuous i.v. infusion, as exemplified by tebentafusp, mosunetuzumab, and blinatumomab, efforts are being made by the pharmaceutical industry to focus on the s.c. dosing of Bi-TCEs due to the aforementioned advantages of s.c. over i.v. ROAs. Due to the intricate PKs and PDs inherent to Bi-TCEs, mechanistic-physiologically-based PK (PBPK) models provide a sophisticated framework to combine diverse datasets to forecast PKs within a physiological milieu. The research article by Zhang *et al*.[18] introduces a mechanistic PBPK model tailored for Bi-TCEs. Its primary aim was to create a robust framework guiding the development of optimal dosing schedules for clinical use. The model underwent thorough qualification across eight different Bi-TCEs, covering various tumor types and administration methods, ensuring accuracy for both i.v. and s.c. dosing. What made this model distinctive was its inclusion of physiological development stages, allowing accurate prediction of drug behavior in pediatric patients when administered i.v., specifically focusing on the initial Bi-TCEs generation (the antibody fragments with molecular weight of 45–55 kDa). Further enhancements enabled precise predictions for pediatric patients receiving s.c. doses, aligning well with existing literature on biologics. This foundational model highlights the unique ability of mechanistic PBPK models to factor in physiological changes, enhancing their predictive accuracy in drug behavior assessments and assisting the design of studies involving organ function. When combined with mechanistic PD models and exposure-response evaluations for safety and efficacy, the PBPK model platform by Zhang *et al*.[18] may become a useful tool in shaping dosing strategies during the clinical development of Bi-TCEs.

In conclusion, this special issue highlights the significance of investigating the administration of biologics through the s.c. ROA, which has the potential to revolutionize patient care by offering increased convenience, improved treatment adherence, improved treatment outcomes, and reduced healthcare burdens. The s.c. delivery is a minimally invasive and easily accessible approach for administering biologics, differing from the traditional i.v. ROA. The switch from i.v. to s.c. administration not only simplifies treatment processes but also holds promise for improving patient compliance and comfort, potentially leading to better treatment outcomes. Advancements in s.c. delivery could extend to various patient groups, including those needing prolonged therapies or specialized care for pediatrics. Overall, the focus on refining s.c. administration of biologics signifies a concerted effort to optimize treatments, aiming for superior patient experiences and heightened healthcare effectiveness.

ACKNOWLEDGMENTS

The authors express gratitude to Dr Danièle Ouellet for valuable scientific discussions and encouragement that inspired the creation of this special issue.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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