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Pharmacokinetic characterization, benefits and barriers of subcutaneous administration of monoclonal antibodies in oncology

Ana Homšek[1], Jelena Spasić[2], Neda Nikolić[2], Tatjana Stanojković[3], Marija Jovanović[1], Branislava Miljković[1] and Katarina M Vučićević[1]

Abstract

Objective: Therapeutic monoclonal antibodies in oncology are slowly becoming the dominant treatment option for many different cancer types. The main route of administration, infusion, requires extensive product preparations, patient hospitalization and close monitoring. Patient comfort improvement, staff workload reduction and cost savings dictated the development of subcutaneous formulations. The aim of this review is to present pharmacokinetic characteristics of subcutaneous products, discuss the differences between intravenous and subcutaneous routes and to point out the advantages as well as challenges of administration route shift from the formulation development and pharmacometric angle.

Data sources: Food and Drug administration's Purple book database and electronic medicines compendium were used to identify monoclonal antibodies in oncology approved as subcutaneous forms. Using keywords *subcutaneous, monoclonal antibodies, pharmacokinetics, model*, as well as specific drugs previously identified, both PubMed and ScienceDirect databases were researched.

Data summary: There are currently six approved subcutaneous onco-monoclonal antibodies on the market. For each of them, exposure to the drug was similar in relation to infusion, treatment effectiveness was the same, administration was well tolerated by the patients and costs of the medical service were reduced.

Conclusion: Development of subcutaneous forms for existing and emerging new monoclonal antibodies for cancer treatment as well as shifting from administration via infusion should be encouraged due to patient preference, lower costs and overall lack of substantial differences in efficacy and safety between the two routes.

Keywords

Monoclonal antibody, subcutaneous administration, pharmacometrics, cancer, variability

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Introduction

Treating an oncology patient can oftentimes be met with a lot of difficulties both at the therapy initiation as well as during the treatment. In order to overcome the most difficult challenges in cancer patient care, a lot of research is directed towards the development of treatment protocols that are at least equally or more effective and safer than the previous ones. With the emergence of monoclonal antibodies (mAbs) many areas of cancer treatment have gained improved treatment outcomes, namely a great increase in patients' quality of life has been achieved. Compared to cytotoxic chemotherapy, mAbs have demonstrated

[1]Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade – Faculty of Pharmacy, Belgrade, Republic of Serbia
[2]Clinic for Medical Oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Republic of Serbia
[3]Department of Experimental Oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Republic of Serbia

Corresponding author:
Ana Homšek, Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade – Faculty of Pharmacy, Vojvode Stepe 450, 11000, Belgrade, Republic of Serbia.
Email: ana.homsek@pharmacy.bg.ac.rs

promising therapeutic potential in cancer clinical management, but also, in many cases, fewer toxic adverse events due to highly specific mechanism of action which avoids damage of healthy cells.[1]

The majority of mAbs available for cancer treatment are administered intravenously (IV), most commonly by infusion. The need for the development of subcutaneous (SC) formulations has been recognized by both pharmaceutical companies as well as health care professionals[2] mainly due to the ease of administration, patient comfort and reduced treatment costs. Currently, a small number of mAbs used in oncology are available in SC forms. The aim of this review is to assess the characteristics of SC formulations from the pharmacokinetic (PK) perspective, to highlight the benefits of this route of administration and challenges that need to be overcome.

PK characteristics of mAbs

mAbs are immunoglobulins consisting of amino acid chains bound together forming a unique Y-shaped protein. As such, these molecules have much more complex PK profiles in reference to small molecule drugs. Drug behaviour of mAbs *in vivo* is determined by their physicochemical characteristics, modifications and transformations of the chemical structure and its origin, binding properties and stability after the administration.[3,4]

Absorption

After the SC administration, the drug is delivered into the interstitial space of hypodermis, which consists of adipose tissue, fibroblasts, macrophages and unevenly distributed blood and lymph vessels.[5] Fibroblasts form the extracellular matrix (ECM) out of collagen, elastin and glycosaminoglycans, which represent the main barrier for drug absorption. By interacting with the ECM the drug is transported to a few blood capillaries and lymphatic vessels accessible in the hypodermis. Therefore, drug absorption can be accomplished by different routes: diffusion through the capillary walls or convection into the lymphatic system, or combination of both. Due to their large size (about 150 kDa) and low permeability, mAbs cannot diffuse through vascular endothelium, and they are mainly transported by lymph vessels.[2,5] This process, however, can last for hours or even days as, following the passage through the porous ends of lymphatic vessels, the drug travels into the larger vessels, enters collector sites to the first draining node, which is followed by efferent vessels, even larger vessels and finally thoracic or other ducts that drain lymph with the drug into the systemic circulation.[2] It is also important to note that a considerable amount of the mAb is susceptible to first-pass degradation via proteases at the injection site or in the draining lymphatic system.[6] To summarize, the absorption after SC injection is incomplete and slow with bioavailability of approximately 60–80% and time to maximum concentration values of 3–10 days.[6]

Distribution

As previously highlighted, physicochemical properties of mAbs limit their diffusion through the endothelial wall. Hence, the distribution of these drugs to tissues is restricted, and convective transport is most likely enabled only in those highly perfused with leaky vasculature.[7] As expected, the highest concentration of mAb is measured in plasma, where these drugs remain localized. Rather low concentrations have been quantified in cerebrospinal fluid, but the mechanism of distribution through blood–brain barrier is not completely elucidated suggesting that adsorptive endocytosis, receptor-mediated transcytosis or active transport are involved.[8] As particular cancer tissue represents the target site of mAbs, the distribution to that compartment is determined by drug's affinity to the tissue. Those with high affinity and capacity to tissue binding are expected to have greater volumes of distribution than anticipated. However, tissue concentrations do not increase linearly with affinity due to antibody binding to the cells on the edge of the tumour which then represents a barrier for further distribution into the tissue leading to delayed pharmacodynamic effect.[7]

Elimination

Certainly, the most specific PK process of these drugs is elimination. Since mAbs are too large to filtrate through kidney glomeruli, the main route of elimination is, in fact, proteolytic metabolism. In lysosomes, after active or passive internalization, mAbs degrade to smaller peptides or amino acids that can later be reused.[9] Additionally, alternative routes of elimination are related to the binding of the drug to particular targets in the body.[3] Specific metabolism is achieved when the drug interacts with the therapeutic target forming a complex which is internalized into the cell and catabolized. When the drug target is membrane-bound (cancer or immune cells), low doses are associated with non-linear PK until saturation is achieved, after which non-specific clearance leads to linear PK. Time-dependent PK is characteristic for drugs with a mechanism of action that can result in negative or upregulation of the target ligand.[9] Non-specific metabolism also includes proteolysis inside the cell, but the uptake does not require drug–target binding, and it is completed by pinocytosis. This route of elimination has a large capacity and is, therefore, not saturable. Binding to Fc-gamma receptors (FcγR) results in antibody-dependent cell-mediated cytotoxicity which subsequently can lead to drug elimination depending on the target level and contributes to total clearance. Immunogenicity of mAbs can also have an impact on drug clearance.

Anti-drug antibodies (ADAs), both neutralizing and non-neutralizing, can alter mAb serum concentrations and significantly increase total drug clearance. Despite many routes of elimination, these drugs have long half-lives for which the recycling neonatal Fc receptor (FcRn) is mainly responsible. In endosomes, a pH-dependent interaction between the Fc region of mAb and FcRn occurs and results in the efflux of the mAb back to the extracellular fluid.[9,10]

Sources of mAbs PK variability

Over the years, various sources of mAbs PK variability have been documented. Hence, the absorption phase variability is primarily related to the administration compartment and lymph system responsible for drug passage to systemic circulation. Absorption from the SC compartment is subject to the anatomical location of the administration, patients' race, age, gender, body weight, smoking habits and pigmentation.[11,12] Lymph flow rate exhibits diurnal variations and can be affected by patient age, physical activity or inflammatory disease conditions.[5,12] FcRn can contribute to SC absorption in two proposed ways – transcytosis through endothelial cells and protection from first-pass effect. Changes in drug affinity to FcRn or administered dose can lead to variations in drug absorption. Lastly, protease activity and concentrations can be altered especially in patients with comorbidities such as cancer, diabetes, osteoporosis and hypertension.[12] Some of the variability can be overcome by drug modifications and transformations (such as glycosylation and PEGilation) or co-formulation strategies, such as adding hyaluronidase.[4,12]

Disposition variability is reflected in vascular and tissue characteristics, target properties, binding affinity, gene polymorphism and expression of FcRn and FcγR,[4] target and ADA development. Distinctive features of cancer tissue (uncontrolled proliferation, neoangiogenesis of abnormal blood vessels, lack of lymphatics) may influence the volume of distribution of mAbs. Target properties refer to internalization rate and turnover, accessibility, expression, antigen shedding, heterogenicity and polymorphism.[12] ADA development is highly variable both between patients (comorbidities and disease nature, genetic factors, immune status) and within one patient (drug concentration; nature of ADA distribution – isotype, affinity; time on treatment).[12,13] Albumin is the most common covariate for mAb clearance since both mAbs and albumin bind to FcRn, but to a different site.[14] In some cancer types (multiple myeloma and chronic lymphocytic leukaemia), kidney glomerular pores can expand which is accompanied by increased tubular proteolysis and leads to increased clearance of mAbs. Patients with diagnosed proteinuria or protein-losing enteropathy also experience decreased exposure to mAbs.[12] Finally, concomitant use of other drugs that can influence any of the aforementioned processes can affect the PK of mAbs.

Comparison of IV and SC administration routes

Formulation considerations

Generally, the safest, cheapest and the least invasive route of drug administration would be oral. However, mAbs are not only unable to pass through gastrointestinal membranes, but they also disintegrate in the intestinal lumen.[15] Therefore, the majority of mAbs used in cancer treatment have been formulated for IV administration, as an infusion. Before the administration, it is necessary to prepare the medicine by diluting the formulation with solvents. In this step, it is crucial to establish strictly controlled conditions, adequate solvent pH, ionic strength, temperature to preserve stability of the active substance. Also, product compatibility with infusion bags and sets should be ensured due to the possible transit of plastic substances and additives into prepared drug formulation.[16] During product dilution, besides lowering mAb concentration, concentration of excipients, such as surfactants, also decreases. This can lead to antibody aggregation or adsorption to surfaces, which potentially causes patient under-dosing.[16] Even though many of the listed issues have been successfully overcome, it still remains necessary to prepare mAbs' solutions in aseptic conditions by medical professionals. Challenges of SC drug formulations in many ways differ from infusions. First of all, unique characteristics of SC space and patient comfort limit the volume of administered drug solution to a maximum of 1.5 mL.[17,18] Hence, the developed formulations contain high drug doses in limited injection volume, which increases the viscosity of these preparations. Challenges of SC preparation formulation are related to the final product manufacturing, stability assurance as well as injectability of the medicine.[17] SC formulations are manufactured as liquid preparations in self-administration devices, so lower stability is expected and hence a shorter shelf-life. Also, a small number of buffers and excipients are approved for these types of formulations.[18] Aforementioned antibody aggregation and adsorption also represent an issue for SC formulation, especially in pre-filled syringes which are the most commonly used devices.[15] To increase stability of preparations, freeze- or spray drying have been suggested, but after a detailed investigation of appropriate conditions to ensure product stability. Nevertheless, using appropriate excipients and coating the surfaces inside the delivery devices stability of these preparations can be ensured. In order to improve the absorption from the injection site PEGylation was proposed, since it can increase lymphatic uptake. This formulation was developed for trastuzumab and it successfully increased the bioavailability by almost 25%. However, no significant change in exposure and even increased drug clearance led to the abandonment of this approach.[19] Finally, an appropriate excipient was found in hyaluronidase, enzyme that

transiently degrades hyaluronan which is the main filler of the ECM.[20] It not only enabled the administration of greater injection volumes, but also provided a more gradual kinetic profile with continuous absorption.[21,22] Addition of hypertonic buffer has also been implemented to further facilitate absorption and increase drug exposure by increasing drainage into lymphatic vessels.[23]

Concentration-time profiles

Unlike the SC route, IV injection places the drug directly into the systemic circulation thus enabling the best accessibility and fastest drug passage to the treatment target. When PK profiles of both administration routes are compared (Figure 1.) it is clear that higher serum concentrations are achieved faster after IV, whereas slow absorption from hypodermis interstitial fluid postpones maximum concentration (C_{max}) achievement followed by SC injection.[15] Lower concentrations and lower bioavailability are attributed to first-pass metabolism, while absorption is slower due to slow lymph drainage to circulation. For some mAbs in oncology, response to treatment does not correlate to drug exposure,[24] therefore lower C_{max} values do not affect drug efficacy. Slower achievement of C_{max} may be advantageous for the patient, as C_{max}-related adverse reactions will less likely be manifested.[24] In order to improve absorption characteristics, previously mentioned formulation adjustments have been suggested. Hyaluronidase as a dispersion enhancer, which can be co-administered or added as an excipient, has successfully increased bioavailability (by 20% for human imunoglobulins)[25] and shortened the time to C_{max}. Individualized drug dosing based on the patient's weight or body surface is, however, only possible with the IV route. Currently, SC administration requires fixed dosage regimens for all patients, but population and PK-pharmacodynamic modelling demonstrate that differences in mAb exposure in various body weight groups are not significant, so fixed dosing can be justified from efficacy and safety perspective.[24] Similar half-lives indicate no differences in drug elimination.[15] Due to transport through lymph system, it has been assumed that more ADAs will appear after SC injection, but evidence has not been conclusive and varies from antibody to antibody.[24]

Patient and care giver perspective

Lastly, but certainly not less significant, patients' preferences should be reviewed. Although the current oncology practice requires patients' presence at the hospital wards or outpatient clinic regardless of the route of drug administration, most patients would still rather choose the SC over IV route provided that both are available. Identified benefits were shorter time of administration and effortless application.[15] Venepuncture for IV infusion can be challenging for some patients with needle phobia or if access to the vein is not visible or palpable. For SC administration, needles are smaller and access points are possible on different body parts (also on the back which could be helpful for

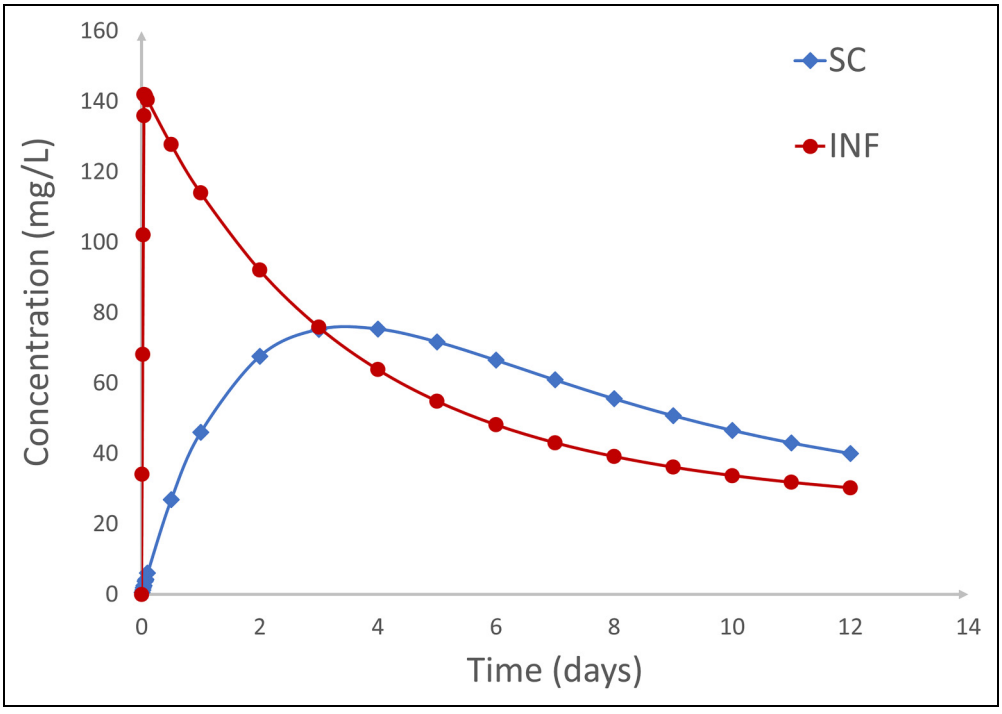

Figure 1. Concentration-time profiles after subcutaneous (SC) and intravenous (IV) drug administration.

patients with phobia).[18] The main reason for patients to prefer SC route was saving time, but they also experienced less discomfort and pain during administration, fewer side effects as well as less bruising or irritation on the injection site.[26,27] Beside patient preferences, health care professionals' experiences have also been investigated. Time of active dedication to any task regarding drug administration and preparation by a staff member has been reduced for SC treatment. During IV infusion administration, one health care professional is required to monitor the patient, but also hospital pharmacy staff spends a lot of time preparing the final product for the administration.[24] Pharmacoeconomic analyses suggest that overall care costs can be reduced by replacing IV with SC route where possible.[24]

SC administration of mAbs in oncology

Overview of currently registered SC mAbs

Based on experiences with SC administration of mAbs used for other indications, the same was attempted for mAbs indicated in oncology. The first mAbs administered SC in cancer treatment were trastuzumab and rituximab. Trastuzumab, indicated for the treatment of human epidermal growth factor receptor 2 positive breast cancer, was approved for SC administration after comparison studies showed no inferiority in efficacy and similar safety profile to the IV route.[28,29] Afterwards, the same was concluded in studies of rituximab, which is indicated for different types of lymphoma.[30–32] Both drugs are now approved as SC formulations to be administered in adequate fixed doses with the same dosing interval as with IV. Initiated by these studies, combination preparation of trastuzumab and pertuzumab for early stage and metastatic breast cancer was also investigated for SC administration, and fixed-dose recommendation was obtained also confirming no inferiority in exposure and similar adverse events compared to IV.[33] Additionally, SC formulations for all three previously discussed medicines are co-formulated with hyaluronidase.[20,34,35] Furthermore, there are many studies confirming patients' preferences, cost and time savings in favour of SC over the IV administration route.[26,36–39]

Previously mentioned antibodies led the way for other cancer treatment options in SC forms. One such was alemtuzumab, indicated for B-cell chronic lymphocytic leukaemia. SC drug preparation was found to be effective and safe for administration[40]; however, this drug was withdrawn due to commercial reasons.[41] Daratumumab is the newest approved antibody in the treatment of relapsed and refractory multiple myeloma with the option to be administered by either IV or SC route. Not only was the SC formulation as efficacious, but also safer for patients compared to IV.[42,43] Driven by previous experience, this formulation also contains hyaluronidase. A study was already conducted to prove that health care professionals spend less time with the patient.[44] Another example of a mAb is denosumab which is only available for SC administration. Although the primary indication for this drug is osteoporosis, it is also approved for giant cell bone tumour in the higher available dose of 120 mg (Table 1).[45] Atezolizumab, PD-L1 inhibitor, is also being investigated for SC administration and phase I studies have been successfully concluded.[46] Finally, a couple of new mAbs have also been developed in the SC form. Phase I study of sasanlimab demonstrated its antitumour activity across various tumour types and routes of administration.[47,48] If approved, sasanlimab would become the first anti-PD-1 antibody that can be administered both via IV or SC route. Phase II study for ecromeximab has been completed and suggests that the combination with high-dose interferon-α2b in metastatic melanoma patients was well tolerated.[49]

By reviewing products currently available on the market, higher doses of SC preparations are observed compared to the IV once calculated for patients with normal body weight (Table 1.). However, taking into account product bioavailability, it can be concluded that equivalent amounts of the drugs are being administered. The only exception is rituximab, where doses of SC product are larger even after calculating bioavailability and normal body surface area to compare the two routes. This medicine is quite specific since the administration of SC preparation is only allowed after IV loading dose, therefore, it only serves as a maintenance treatment option. Also, IV trastuzumab can be administered in two different dosing protocols, but the SC form is equivalent to the higher IV doses, so the recommended dosing regimen is the longer one.[50]

Pharmacometrics role in generating the evidence for SC mAbs registration

Pharmacometric data analysis is used to predict drug's PK parameter values, find a relationship between exposure and response, subsequently propose the appropriate dosage regimens and offer insight into sources of interindividual variability by developing models and performing simulation studies that explore drug behaviour. Regulatory bodies (EMA and FDA) strongly recommend the implementation of pharmacometric analysis in drug development.[51] Hence, the role of modelling and simulation trials in supporting fixed dosing of SC mAb formulation was essential. In addition, characterization of PK and exposure–response relationship including variability in mAb behaviour was in depth performed by utilizing non-linear-mixed effects modelling approach.

Table 2 gives an overview of PK parameters' estimates of onco-mAbs available as SC formulations. For each mAb a model was developed and compared to the ones

Table 1. Comparison of approved IV and SC preparations of onco-mAbs[50].

	IV infusion			SC injection			
Drug	Dose	Duration	Dosing regimen	Dose	Dosing regimen	F	Injection volume and preferred site
Trastuzumab	D_L 8 mg/kg D_M 6 mg/kg	D_L 90 min D_M 60 min	Q3W	600 mg over 2–5 min	Q3W	77.1%	5 mL, thigh
	D_L 4 mg/kg D_M 2 mg/kg	D_L 90 min D_M 60 min	Q1W				
Rituximab	375 mg/m^2	3.5–4 h	Q1W, Q2M, Q3M	1400 mg over 5 min	Q2M, Q3M	71%	11.7 mL, abdominal wall
Pertuzumab (with trastuzumab)	D_L 840 mg D_M 420 mg	D_L 60 min D_M 30–60 min	Q3W	D_L 1200 mg over 8 min D_M 600 mg over 5 min	Q3W	71.2%	15 mL–D_L; 10 mL–D_M, thigh
Daratumumab	16 mg/kg	Week 1: 7h Week 2: 4h Subsequent weeks: 3h	Q1W, Q2W, Q4W (8 doses each)	1800 mg over 3–5 min	Q1W, Q2W, Q4W (8 doses each)	69%	15 mL, abdomen (7.5 mm to the right or left of the navel)
Denosumab	/	/	/	120 mg, additional doses on days 8 and 15 of the first month	Q4W	62%	1.7 mL, not specified

D_L: loading dose; D_M: maintenance dose; F: absolute subcutaneous bioavailability; IV: intravenous; mAbs: monoclonal antibodies; SC: subcutaneous; Q2M: every 2 months; Q3M: every 3 months; Q1W: weekly; Q2W: every 2 weeks; Q4W: every 4 weeks.

Table 2. Population pharmacokinetic (PK) parameters of monoclonal antibodies (mAbs) available as subcutaneous (SC) formulations[52–58].

Drug (Reference)	Absorption parameters (%RSE)	Distribution parameters (%RSE)	Elimination parameters (%RSE)	Covariables statistically significantly influencing PK
Trastuzumab (Quartino et al., 2016)	F: 0.771 (1.45) k_{res}: 0.404 day^{-1} (2.92)	V_c: 2.91 L (1.24) V_p: 3.06 L (3.23) Q: 0.445 L/day (10.5)	CL: 0.111 L/day (10.3) V_{max}: 11.9 mg/day (19.9) K_m: 33.9 mg/L (38.6)	BW on CL, V_p and V_c, ALT on CL
Trastuzumab (Hourcade-Potellere et al., 2014)	F: 0.873 (6.7) k_{res}: 0.28 day^{-1} (7.93)	V_c: 3.43 L (6.82) V_p: 1.71 L (17.7) Q: 0.24 L/h (12.7)	CL: 0.187 L/h (10.9) V_{max}: 3.49 mg/day (21.3) K_m: 6.12 mg/L (23.5)	BW on CL and V_c
Pertuzumab (Wang et al., 2021)	F: 0.712 (16.0) k_{res}: 0.348 day^{-1} (7.72)	V_c: 2.77 L (3.15) V_p: 2.49 L (7.69) Q: 0.616 L/day (5.23)	CL: 0.163 L/day (5.81)	race, ALB on CL; LBW on V_c, V_p and CL
Rituximab (Jamois et al., 2021)	F: 0.646 (0.992) k_{res}: 0.344 day^{-1} (7.17)	V_c: 4540 mL (2.20) V_p: 4270 mL (1.61) Q: 573 mL/day (3.59)	CL_T: 398 mL/day (11.1) CL_{INF}: 200 mL/day (1.78) k_{des}: 0.0745 day^{-1} (8.57) K_{Vmax}: 9.73 10^{-5} ng/mL/day (3.94) V_{max}:0.0187 1/day (4.5)	
Rituximab (Gibiansky et al., 2021)	F: 0.633 (2.52) k_{res}: 0.372 day^{-1} (3.86)	V_c: 4990 mL (1.82) V_p: 3700 mL (1.97) Q: 420 mL/day (3.23)	CL_T: 1550 mL/day (8.14) CL_{INF}: 207 mL/day (2.62) k_{des}: 0.0399 day^{-1} (5.19)	WBC and BSIZ on CL_T; BMI on k_{res} and F; and gender on V_c
Daratumumab (Luo et al., 2020)	F: 0.689 (2.7) k_{res}: 0.0117 h^{-1} (5.8)	V_c: 5.25 L (4.1) V_p: 3.78 L (7.0) Q: 0.00955 L/h (8.0)	CL: 0.00496 L/h (8.4) k_{des}: 0.0000783 h^{-1} (33.3) K_m: 2.56 µg/mL (16.0) V_{max}: 1.15 mg/h (9.7)	
Denosumab (Gibiansky et al., 2012)	F: 0.612 (0.193) k_{res}: 0.0107 h^{-1} (0.844)	V_c: 2620 mL/66kg (0.241) V_p: 1370 mL/66kg (0.501) Q: 45.5 mL/h/66kg (1.60)	CL_{lin}: 3.25 mL/h/66kg (1.54) K^{ss}: 208 ng/mL (2.15) k_{deg}: 0.00116 h^{-1} (0.769) k_{int}: 0.0112 h^{-1} (3.39)	BW on V_c and CL_{lin}, age on ka, race on V_c and CL_{lin}, tumour type on CL_{lin}

ALB: albumin level; ALT: alanine transaminase; BMI: body mass index; BSIZ: tumour size at baseline; BW: body weight; CL: clearance; CL_{INF}: non-specific time-independent clearance; CL_{lin}: linear clearance; CL_T: specific time-dependent clearance; F: absolute subcutaneous bioavailability; k_{des}: decay coefficient of time-dependent clearance; K_m: Michaelis–Menten constant; k_{res}: subcutaneous resorption rate constant; K_{Vmax}: rate of depletion of a hypothesized non-renewable target; LBW: lean body weight; Q: inter-compartmental clearance; %RSE: relative standard error; V_c: central volume; V_{max}: rate of target-mediated elimination; V_p: peripheral volume; WBCs: white blood cells.

already obtained for IV administration. Trough concentration (C_{trough}) was used for the comparison of the two administration routes since it best reflects the response to treatment. Similar C_{trough} levels suggest comparable efficacy and safety profile can be achieved with SC administration. As expected, two compartment models with first-order absorption and linear distribution to peripheral compartment best described the PK of these drugs. Due to target-mediated drug disposition, elimination phase of the majority of these mAbs was described with dual clearance, linear at higher concentrations when saturation of the target is achieved, and non-linear at lower concentrations. The exceptions were rituximab, which has a time-dependent component due to B-cell depletion,[52,53] and pertuzumab, whose model did not enclose the non-linear component.[54] In the denosumab model, a quasi-steady-state approximation was used to characterize non-linear clearance.[55] Body weight or body surface area was the main covariate influencing the PK of rituximab. Heavier patients had lower concentrations and skinnier patients consequently had higher ones; however, the administration of fixed doses calculated by the models resulted in no underdosing or overdosing of patients in different body weight groups. C_{trough} was found to best correlate with the response to treatment, except for trastuzumab where no exposure–response relationship was identified. Since C_{trough} was not significantly different among different body types as well as between SC and IV administration routes, it was confirmed that fixed dosing of SC formulations was justified for all drugs in Table 2. Statistically significant covariates identified in pharmacometric analysis were different among the presented drugs (Table 2). However, none of these covariates were clinically significant because the influence on PK was rather small and no dose modifications are required according to covariates. The exposure–safety analysis showed no correlation between drugs' exposure occurrence of severe adverse events following either administration route.

Conclusion

Manufacturers of biopharmaceutical medicines used in oncology are progressively more interested in the SC route of administration. Unique characteristics of mAbs influence their PK behaviour which can be a barrier to ensure effective, safe and comfortable patient treatment. Presented drug examples with successful transition from IV to SC administration route pave the way for the development of even more SC formulations for both drugs already on the market as well as those still undergoing trials. Slower absorption rate of SC medicines did not influence treatment effectiveness and have even improved tolerability of the mAbs. Pharmacometric analysis confirmed the use of fixed doses since no covariates had clinically significant influence on PK parameters. Although some formulation issues and unpredictability between different mAbs still present limitations, patient satisfaction, time and cost savings and non-inferiority to IV suggest SC mAb preparations could replace IV formulations in the near future.

Author's Contribution

AH and KV drafted and conceptualized the manuscript. AH, BM and KV acquired and interpreted data regarding pharmacokinetic characterization. JS, NN and TS analysed patient and caregiver perspectives and overview of the market. MJ and AH acquired pharmacometric role data. KV and BM revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. Each author participated sufficiently in the work.

Declaration of Conflicting Interests

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ORCID iD


Ana Homšek https://orcid.org/0000-0002-0127-5538

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