Editorial Commentary

Pros and cons of subcutaneous (SC) versus intravenous (IV) administration of immune checkpoint inhibitors in non-small cell lung cancer

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The advent of immunotherapy as the fourth pillar in the armamentarium against cancer over the last two decades has resulted in significant increases in the utilization of these agents. Immune checkpoint inhibitors (ICIs) now form an integral component of systemic therapy in more than 20 different cancer indications (1), including non-small cell lung cancer (NSCLC). These agents have led to improved outcomes, yet durable responses are observed in less than 20% of all patients. Nevertheless, in many indications such as in NSCLC, ICIs are used as monotherapy or in combination with other drugs for prolonged periods, months to years. Currently, these ICIs are administered intravenously and require frequent patient visits and significant resource utilization of infusion centers. This has led to reconsideration of the way ICIs are administered, specifically, whether a subcutaneous method of administration could decompress infusion center resources and importantly, translate into a better patient experience and quality of life.

A trial published in 2023 suggests pharmacokinetic (PK) equivalence of intravenous (IV) versus subcutaneous (SC) administration of atezolizumab, an ICI that targets programmed death ligand 1 (PD-L1) (2). Studies asking a similar question, using other ICIs, have either been completed (nivolumab) or are ongoing (pembrolizumab). This commentary will analyze this clinically relevant question in the context of the published study IMscin001, a randomized phase III, open label, multicenter study examining the PKs, efficacy, immunogenicity, and safety of atezolizumab SC versus IV administration, randomized in a 2:1 manner, in previously treated locally advanced or metastatic NSCLC (2). The SC preparation consists of a

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coformulation of atezolizumab and recombinant human hyaluronidase PH20 (rHuPH20). Given no appreciable difference in pharmacokinetics or pharmacodynamics between SC and IV administration, the study provides evidence for the use of SC atezolizumab as an alternative to IV. In the ensuing sections, we will examine pharmacology, healthcare resource utilization, impact of cost/care delivery models and patient preferences. Finally, we will outline the current landscape of trials in this space and offer guidelines regarding how to, or whether to, choose SC versus IV formulations.

Pharmacology

Atezolizumab is an IgG1 kappa monoclonal antibody (mAb), that binds to PD-L1 and blocks the interaction with PD-1, thereby enhancing T-cell activity against tumor cells. The PKs of mAbs depend on the route of administration. Monoclonal antibodies are large molecules (150,000 Daltons) that require parenteral administration, traditionally achieved via IV route, the most direct method to gain access to the systemic circulation. SC administration requires absorption, their bioavailability is inherently lower and can vary from 50–100% of the IV route (3). Reasons for this variability are not completely understood. Currently marketed mAbs bioavailability is estimated to be approximately 60–80% (3). Therefore, larger doses and potentially larger volumes are required for SC administration to achieve PKs similar to IV. Adding hyaluronidase to the formulation, an enzyme that hydrolyzes hyaluronic acid in SC connective tissue, permits accommodation of volumes larger than is traditionally considered acceptable in the SC space. Hyaluronidase also facilitates drug absorption into the general circulation. Intravenous administration of mAbs can result in rapid, higher peak serum concentrations and lower troughs, compared to SC, which result in lower peaks and higher troughs. In other words, SC route achieves steadier serum concentration levels. However, the authors of IMscin001 did not find a difference in trough levels or area under the curve (AUC) estimates between IV and SC atezolizumab after cycle 1. Notably, the every 3 week dose of SC atezolizumab was 1,875 mg versus the IV dose was 1,200 mg. There was no difference in response rate or progression free survival but due to a short, 5-month follow up time, overall survival endpoints were not reported. The systemic side effect profile may be greater with IV compared with SC formulations of mABs, whereas local site effects may be greater with SC. Immunogenicity is thought to occur with higher frequency in SC versus IV. These aspects have been reviewed by Ness *et al.* (4). Specifically, with respect to ICIs, the data on side effects of SC versus IV are sparse. Generally, IV administration may be associated with a higher incidence of infusion related reactions, similar to most IV infusions; these include fever, chills, and rarely, allergic reactions during the infusion or shortly thereafter. Other studies that compared SC versus IV ICI include a phase 1 dose-escalation trial that assessed the safety, efficacy, and pharmacokinetics of PF-06801591; grade 3 or higher treatment-related adverse events occurred in 16% of patients with IV compared with 6.7% SC. Immune-related adverse events occurred in 40% of patients treated intravenously and 20% treated subcutaneously (5). This suggests that SC administration may be associated with a lower incidence of certain adverse events compared to IV administration. Additionally, a study using SC envafolimab, a single-domain anti-PD-L1 antibody, reported that 16% of patients experienced at least one grade 3 or 4 treatment-emergent adverse event, with no grade 5 events related to the treatment. Injection site reactions were all grade 1–2, and there were no infusion reactions (6). Furthermore, when comparing overall side effects, including immune-related adverse events (irAEs) like colitis, pneumonitis, and thyroid dysfunction, there is no clear consensus that IV administration leads to more severe or frequent side effects compared to SC administration. In keeping with this, the authors of IMscin001 did not find statistically significant differences in adverse events between the SC and IV formulations, except for higher proportion of hyperglycemia and higher serum creatinine in the IV arm. Expectedly, injection site reactions were higher in the SC arm (4.5%) *vs.* none in the IV arm. There were equal numbers of patients who experienced toxicity-related treatment discontinuation in each arm. In the SC group, 19.5% of patients were positive for treatment-emergent anti-atezolizumab antibodies compared with 13.9% in the IV group. Summarizing, the phase III study comparing IV (n=247) versus SC (n=144) formulation of atezolizumab demonstrated equivalent PKs, efficacy, and adverse event profile, with the caveat that follow-up was short, and the dose used for SC was 30% greater than the approved IV dose (*Table 1*).

Healthcare resource utilization

Given the frequency and duration of administration of ICIs,

Table 1 IV versus SC administration of atezolizumab

Characteristics	Atezolizumab	
	IV	SC (thigh)
Formulation	Human IgG1	Human IgG1 with recombinant hyaluronidase
Target	PD-L1	PD-L1
Dose Q 3 weeks	1,200 mg	1,875 mg
Pharmacokinetics (2)		
C_{trough} µg · d/mL (at the end of cycle 1) [%CV]	85 [33]	89 [43]
$AUC_{0–21d, ss}$ µg · d/mL [%CV]	3,328 [20]	2,907 [32]
Total volume, mL	20	15
Pharmacodynamics (2)		
Response rate	12%	10%
PFS (months)	2.9	2.8
Treatment-emergent anti-atezolizumab antibodies	13.9%	19.5%
Logistics		
Pharmacy prep time (minutes)	30	0
IV line start (minutes)	15	0
IV infusion time-chair time (minutes)	30	30 (observation)
Patient preference	+	+++
Cost of drug	++	Unknown
Cost of administration	++	+

IV, intravenous; SC, subcutaneous; IgG1, immune globlulin-G1; PD-L1, program cell death ligand-1; Q, every; C_{trough}, trough concentration; %CV, (coefficient of variation) percent; AUC, area under the curve; ss, steady state; PFS, progression free survival; prep, preparation.

it has been proposed that SC use will decompress infusion center resources, including chair time for IV therapy, IV kits, pharmacy and nursing time, thereby reducing time and cost commitments for the healthcare system. Let us consider the resources required for IV versus SQ administration. First, considering pharmacy and nursing resources: IV formulation requires sterile compounding, withdrawing drug from a commercial vial form, measuring, and transferring the required amount of drug into the infusion bag. The bag will require tubing with or without a filter as per each individual manufacturer's approved labeling. The infusion will also require a pump that a nurse will program the infusion rate and time. Finally, an IV line will have to be placed into the patient in order to complete the infusion. Minimum materials for sterile compounding include an ISO 7 clean room, an ISO 5 biologic safety cabinet, diluent bag, primary or secondary line, in-line filter, syringes & needles for drug transfer, infusion pump, and a line into the patient, skilled labor to perform these tasks, their required garb and time to garb and clean. On the other hand, a SC formulation can be drawn up at chairside from the commercially supplied vial by the infusion nurse into a SC syringe and injected under the skin into the patient. Minimum materials include a syringe & 2 needles (1 for drug withdrawal and 1 for SC administration), alcohol swabs for the vial and injection site, as well as the knowledge and skill of the nurse who administers the injection. Second, chair time: It has been reported that chair occupancy time is significantly shorter for SC versus IV in other studies of monoclonal antibodies, such as rituximab. Patients receiving R-IV combination therapy had a mean chair time of 249.9 minutes, compared with 156.7 minutes for R-SC, representing a 37% reduction (P<0.01). The difference was even greater in those receiving rituximab monotherapy (214.7 minutes for IV versus 81.3 minutes for SC, representing a 62% relative reduction (P<0.001).

According to the authors, this translated into >500.65 and 620.67 hours per year of chair time savings for R-IV and R-SC respectively. Importantly, they demonstrated an increase in patient satisfaction with R-SC over R-IV (7).

We conducted a time-course survey at our hospital to compare chair time between IV and projected SC atezolizumab, imputing the SC times from the IMscin001 study. It is noted that 30 minutes observation time, following the SC administration is described in Supplementary Appendix (2). Over a 2-year period, 213 doses of atezolizumab were administered to 39 patients (n=10 hepatocellular carcinoma, n=29 with small cell lung cancer). Accounting for a 60-minute chair time for the first infusion of atezolizumab in each patient, followed by subsequent infusions over 30 minutes, the calculated chair time for 174 doses was 7,560 minutes (157 hours/year). If all of these doses were administered by SC route, the time to prepare and administer 15 mL, the volume of atezolizumab would take <10 minutes plus the observation time of 30 minutes; this translated into 8,520 minutes (177 hours/year). Therefore, there does not appear to be a chair-time benefit with SC, given the requirements according to the prescribing information for a 30-minute observation. Admittedly, chair time can vary depending on whether atezolizumab is administered as a single agent versus in combination with chemotherapy or other associated medications, such as intravenous fluids or IV bisphosphonates and logistics surrounding nursing and infusion center operations. While IMscin001 does not provide a direct comparison of chair time between SC versus IV atezolizumab, an implied shorter administration time of 7 minutes with SC compared with 30 minutes for IV administration has resulted in the National Health Service in Britain to roll out SC administration of atezolizumab in the maintenance setting (NHS, UK).

Costs

Costs associated with ICI are high. Many groups are studying various ways to reduce costs while maintaining efficacy, including exploring weight-based dosing (8). Others have found that extended interval dosing, while more convenient for patients, may in fact be more expensive (9) to the healthcare system. It has been proposed that a SC formulation may result in cost savings to the healthcare system. Subcutaneous formulations have the inherent advantage of reduced pharmacy workload and improved turnaround time—SC has no compounding required, allowing a bedside preparation. The IMscin-001 trial compared subcutaneous atezolizumab at 1,875 mg with IV atezolizumab 1,200 mg every 3 weeks. Since higher doses may potentially increase drug costs, it is unclear whether SC atezolizumab will ultimately be more affordable than the IV formulation. However, at the time of this writing, the cost of SC atezolizumab is unavailable and therefore a direct comparison is not feasible.

Patient preference

Subcutaneous injections of monoclonal antibodies involve volumes between 5–17 mL at one site, typically in the anterior abdomen or thigh. A clinical feasibility study demonstrated SC injections of 5 and 10 mL up to viscosity of 20 cP and an injection duration of 4.1 (5 mL) or 8.2 (10 mL) minutes were well-tolerated. Favorable subject acceptance and tolerance combined with rapid resolution of tissue effects suggest that the threshold of large volume SC injections may exceed the traditional 1.5–3.0 mL limits (10). A SC dose of atezolizumab is 1,800 mg at a concentration 125 mg/mL, the corresponding injection volume would be estimated to be 14.4 mL. In IMscin001, the injection volume was reportedly 15 mL. This is identical to the pertuzumab/trastuzumab/hyaluronidase co-formulated loading dose volume indicated for HER-2-positive early breast cancer. Importantly, injection site reaction incidence was 4.5%, of this, the most commonly reported as injection site pain at 2.4% and injection site reaction at 1.6%. The majority of these resolved without treatment, were reportedly grade 1 with a few grade 2, and did not result in treatment interruption, discontinuation or delays. Of 123 patients in a subsequent crossover study, IMscin002 trial of SC versus IV atezolizumab, 70.7% preferred SC atezolizumab to 21.1% preferred IV and 8.1% had no preference. Primary reasons given for SC formulation included: reduced clinic time (64.4%), administration comfort (46%), and reduced emotional distress related to treatments (29.9%) (11).

Taken together, there appears to be equipoise between IV versus SC atezolizumab with respect to pharmacological characteristics. As for costs, it is debatable. As described above, costs associated with IV formulation preparation and administration may not be offset by higher costs associated with higher dosages used in the SC formulation, required to achieve therapeutic levels. Similar to the atezolizumab dose, SC formulations of nivolumab and pembrolizumab are also higher than their IV counterpart. In the phase 1/2

CheckMate-8KX, subcutaneous nivolumab doses ranged from 720 to 960 mg compared with IV doses of 480 mg every 4 weeks (12). Similarly, the phase 3 clinical trial KEYNOTE-A86 used SC pembrolizumab at a dose of 285 mg every 3 weeks compared with 200 mg every 3 weeks with IV formulations (13).

In conclusion, the choice of SC versus IV atezolizumab and other ICIs will be based on several factors, including patient characteristics and preference, provider comfort for in clinic/hospital or offsite administration, including at home administration and need for concurrent therapies, including chemotherapy. The logistics of ICI administration is changing as cancer care is being decentralized with a profusion of free-standing infusion centers and mobile units that can deliver several "maintenance" type cancer therapies closer to the patient, including at home administration. Atezolizumab joins a list of other mAbs approved for cancer that have been or being developed as a SC formulation. At the current time, it appears that the patient who is receiving prolonged ICI therapy may have the final say in the choice of preparation, SC versus IV.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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