Editorial Commentary

Subcutaneous delivery of immune checkpoint inhibitors: new route replacing intravenous administration?

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The use of intravenously delivered immune checkpoint inhibitors (ICIs) as antibody therapies has become a central node in the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) as well as extensive-stage small cell lung cancer. For NSCLC, the indications for ICIs targeting programmed death-1 (PD-1) and its ligand (PD-L1) have expanded covering resectable disease as neoadjuvant (1), adjuvant (2), and perioperative (3) therapies. Meanwhile, the number of indications has increased substantially across various types of cancers, with marketing approval covering at least 90 uses for more than 11 different ICIs (4). Because ICIs offer durable responses in a subset of patients who may require long-term repeated administrations over years, they are associated with an accumulating treatment burden in cancer patients with numerous indications, particularly within hospital and outpatient treatment settings. Therefore, the development of strategies to improve convenience and efficiency in healthcare by shortening the times for dose preparation and administration and to reduce patient time and discomfort in the clinic has become an important field of investigation.

Supported by patient preferences and healthcare professional satisfaction over intravenous administration for a range of reasons, including ease of administration, less emotional distress, and shorter treatment duration (5-8), monoclonal antibodies (mAbs) with subcutaneous formulations have been approved in the United States and European Union for several disease areas, including rheumatoid arthritis [e.g., etanercept (anti-TNFα), tocilizumab (anti-IL-6), anakinra (anti-IL-1), abatacept (selective co-stimulating modulator)], multiple sclerosis [e.g., ofatumumab (anti-CD-20)], and high-dose mAbs in oncology [e.g., trastuzumab (anti-HER2), rituximab (anti-CD20), daratumumab (anti-CD38)], as discussed in a previous report (9). For successful subcutaneous delivery of mAbs, the unique characteristics of the subcutaneous space, consisting of extracellular matrix, adipose tissue, blood and lymph vessels, fibroblasts, and macrophages, as well as the physicochemical characteristics of mAbs, including large molecular size and low permeability that limit diffusion, require consideration (10). Meanwhile, the maximum volume that can be safely injected into the subcutaneous space is considered to be 1.5 mL, meaning that subcutaneous formulations containing high drug doses in a limited injection volume need to be developed (11). This volume limitation for subcutaneous drug delivery together with the limitations for drug dispersion and absorption are, at least in part, mediated by hyaluronan. Hyaluronan forms

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a gel-like substance with water and acts as the main filter for the extracellular matrix (12,13). Consequently, novel drug delivery technologies involving recombinant human hyaluronidases, such as recombinant human hyaluronidase PH20 (rHuPH20), have been developed to overcome the barriers for subcutaneous delivery of co-administered mAbs (12). rHuPH20 induces local depolymerization of hyaluronan and enables temporal subcutaneous administration of reformulated existing intravenous drugs in relatively large volumes (12,13). rHuPH20 has already been approved in the United States and/or global markets as a drug delivery technology for daratumumab, trastuzumab, pertuzumab, trastuzumab, rituximab, and immune globulin.

Burotto and colleagues reported the primary results of a randomized phase III, open-label, multicenter, noninferiority study (IMscin001 Part 2) investigating the pharmacokinetics, efficacy, and safety of subcutaneous atezolizumab, an anti-PD-L1 mAb, compared with approved intravenous administration (1,200 mg every 3 weeks) in patients with previously treated locally advanced or metastatic NSCLC (14). In the study, a total of 371 patients were randomized at 2:1 to receive subcutaneous atezolizumab (N=247) or intravenous atezolizumab (N=124). The total injection volume of the ready-to-use subcutaneous formulation of atezolizumab (1,875 mg) was 15 mL containing 30,000 U of rHuPH20 (2,000 U/mL), with a suggested delivery time of <10 minutes. The subcutaneous atezolizumab regimen of 1,875 mg every 3 weeks was set based on the findings in the prior phase 1b IMscin001 Part 1 study, which demonstrated that this regimen provided similar exposure to an intravenous dosing regimen of 1,200 mg every 3 weeks (15). Despite the inherent limitations of subcutaneous drug delivery, such as interpatient variability in bioavailability, the study by Burotto and colleagues met the co-primary pharmacokinetics endpoints, cycle 1 observed trough serum concentration and model-predicted area under the curve from days 0 to 21, showing comparable levels of atezolizumab in the blood. Although the study was not formally designed to examine the noninferiority of efficacy endpoints, the objective response rates (subcutaneous: 12% versus intravenous: 10%) and progression-free survival durations (median survival: 2.8 months for the subcutaneous group versus 2.9 months for the intravenous group) were similar between the subcutaneous and intravenous arms, consistent with the findings in the pivotal OAK study (16).

Given that antidrug antibody development can be associated with lower serum drug levels and worse clinical outcomes in cancer patients treated with ICIs (17,18), one of the major concerns for subcutaneous administration of mAbs is the potential risk of increased immunogenicity, as observed for other subcutaneous mAbs in oncology. For example, a higher incidence of antidrug antibodies was reported for subcutaneous trastuzumab compared with its intravenous comparator (19). In the IMscin001 Part 2 study, however, there was no noticeable difference in the positivity rates of treatment-emergent anti-atezolizumab antibodies between the subcutaneous (19.5%) and intravenous (13.9%) groups (14). Unfortunately, information on whether these treatment-emergent anti-atezolizumab antibodies were neutralizing in action was not available. Because ICIs can enhance the nontumor-specific immune system, further immunogenicity analyses are required in patients receiving subcutaneous ICIs.

Regarding safety, no new signals were identified in the subcutaneous atezolizumab group in the Imscin001 Part 2 study (14). Reflecting the different administration routes, injection site reactions occurred specifically in the subcutaneous arm (4.5%), while infusion-related reactions occurred specifically in the intravenous arm (3.2%).

While Burotto and colleagues did not provide data on patient preferences (14), the CheckMate 8KX study investigating subcutaneous nivolumab, an anti-PD-1 antibody, with or without rHuPH20 in patients with advanced solid tumors found that most patients reported high satisfaction with subcutaneous administration and preferred it over intravenous administration, and that limited pain was associated with subcutaneous injection (20), consistent with the results for other subcutaneous mAbs in oncology (5-8). Taken together, these findings should facilitate a shift in ICI administration from the intravenous to subcutaneous route. Indeed, many studies have been investigating the pharmacokinetics, efficacy, and safety of different subcutaneous ICIs (*Table 1*). Among the ICIs listed in *Table 1*, sasanlimab, a humanized, hinge region-stabilized anti-PD-1 antibody, does not require any modification or combination to enable subcutaneous delivery (21). Furthermore, single-domain antibodies that lack the immunoglobulin light chain are more soluble and stable than complete mAbs, and can more rapidly penetrate tissues, thereby enabling subcutaneous administration (22). For example, envafolimab, a humanized single-domain anti-PD-L1 antibody fused to a human immunoglobulin Fc fragment, is the first subcutaneously injectable anti-PD-L1 antibody approved by the National Medical Products Administration in China. Despite the ongoing shift in focus for pharmaceutical companies toward the development of subcutaneous ICI formulations, there

Table 1 Overview of clinical trials on subcutaneous administration of immune checkpoint inhibitors

Molecule	Target	Trial name or clinical trial No.	Phase	Setting	Tumor type	Experimental treatment arm	Coformulation with hyaluronidase
Nivolumab	PD-1	CheckMate 8KX	1/2	Advanced	NSCLC, melanoma, RCC, CRC	Monotherapy	Yes/no
		CheckMate 67T	3	Advanced or metastatic	ccRCC	Monotherapy	Yes
Pembrolizumab	PD-1	KEYNOTE-555	1	Advanced	Melanoma	Monotherapy	No
		NCT06041802	2	Recurrent or metastatic	cSCC	Monotherapy	Yes
		NCT05722015	3	Metastatic	NSCLC	Pembrolizumab plus chemotherapy	Yes
		NCT04956692	3	Metastatic	NSCLC	Pembrolizumab plus chemotherapy	No
Sasanlimab	PD-1	NCT02573259	1b/2	Locally advanced or metastatic	NSCLC, UC	Monotherapy	No
		CREST	3	Non-muscle invasive	Bladder cancer	Sasanlimab in combination with BCG	No
Atezolizumab	PD-L1	IMscin001 Part 1	1b	Advanced or metastatic	NSCLC	Monotherapy	Yes
		IMscin001 Part 2	3	Locally advanced or metastatic	NSCLC	Monotherapy	Yes
Durvalumab	PD-L1	NCT04870112	1/2a	Locally advanced or metastatic	NSCLC, SCLC	Monotherapy	Unclear
Envafolimab	PD-L1	NCT02827968	1	Advanced	Malignant solid tumors	Monotherapy	No
		NCT05024214	1b/2	Advanced	Solid tumors	Envafolimab plus lenvatinib	No
		NCT03667170	2	Locally advanced or metastatic	dMMR/MSI-H malignant solid tumors	Monotherapy	No
Ipilimumab	CTLA-4	CheckMate 76U	1/2	Advanced	Melanoma, UC, HCC, NSCLC, RCC	Monotherapy or in combination with subcutaneous nivolumab	Yes

PD-1, programmed death-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; CRC, colorectal cancer; ccRCC, clear cell renal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; UC, urothelial carcinoma; SCLC, small cell lung cancer; dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high; HCC, hepatocellular cancer; BCG, Bacillus Calmette-Guerin.

remain some issues to be addressed. First, the amounts of subcutaneous ICI mAbs that can lead to reductions in the patient burden and clinic time as well as the overall cost need to be explored in the current chemo-immunotherapy era. Some patients may prefer not to undergo the additional subcutaneous puncture associated with ICIs in addition to the intravenous administration of other anticancer agents in chemo-immunotherapy regimens. In terms of costs, subcutaneous atezolizumab delivery required a 56% dose increase compared with intravenous delivery (1,875 versus 1,200 mg) to achieve similar drug exposure because of the lower bioavailability (14). In addition to the use of the drug delivery technology with rHuPH20, subcutaneous atezolizumab would incur an additional manufacturing

burden (23). Furthermore, pharmacoeconomic studies of subcutaneous ICIs will need to be updated following the upcoming arrival of intravenous ICI biosimilars that should reduce the prices of intravenous ICIs. Second, there is no clear relationship between drug exposure and efficacy for ICIs (24). Impressively, for example, the addition of ultra-low-dose nivolumab (20 mg Q3W), representing only approximately 6% of the United States Food and Drug Administration-approved flat dose of 240 mg once every 2 weeks, to triple metronomic chemotherapy for head and neck cancer showed a clinical benefit comparable to that observed with single-agent PD-1/PD-L1 inhibitors at approved doses (25). Therefore, when aiming at cost reduction, it may not be the best strategy to optimize the dose of subcutaneous ICIs based on their noninferiority to pharmacokinetic parameters of corresponding intravenous products. Exploration of alternative approaches to reduce the cost while maintaining treatment benefits is also encouraged, such as administering intravenous ICIs at the approved doses less frequently (23).

In summary, the introduction of subcutaneous mAbs in cancer immunotherapy is one of the notable areas of investigation for improving patient care and healthcare resource utilization. The IMscin001 Part 2 study (14) demonstrated that subcutaneous administration of atezolizumab (1,875 mg Q3W) was noninferior to intravenous administration of atezolizumab (1,200 mg Q3W) in terms of drug exposure, with similar efficacy, safety, and immunogenicity between the two arms. The study has led to the approval of subcutaneous atezolizumab by the Medicines and Healthcare products Regulatory Agency in the UK and the European Commission for use with all of the indications previously approved for the intravenous formulation. The fact that the innovative subcutaneous atezolizumab formulation can cut treatment time by up to 80% with simplified administration should be appreciated and will likely lead to further approvals by other agencies in the future.

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