Essay

Subcutaneous immunotherapy—a wolf in sheep's clothing?

Introduction

Over the past decade, subcutaneous formulations of anticancer drugs—originally administered intravenously—have been increasingly developed and subsequently approved by the US Food and Drug Administration (FDA). This new route of administration benefits patients with increased convenience. In this essay, we describe and discuss the growing adoption of subcutaneous formulations and also consider the potential future economic effects, particularly in relation to immunotherapy.

Background

In 2017, rituximab was the first biological anticancer agent to receive FDA approval for subcutaneous administration for several indications, predominantly haematological. For the treatment of myeloma, daratumumab can now be given either intravenously or subcutaneously. The subcutaneous version of daratumamab received FDA approval in 2020. Subcutaneous trastuzumab initially gained FDA approval in 2019, followed by approval for a subcutaneous combination of trastuzumab and pertuzumab (Phesgo). Bortezomib, originally given intravenously with substantial neurotoxicity, was developed for subcutaneous administration in an effort to mitigate this toxicity. Although the efficacy and safety of subcutaneous formulations is now becoming well established, the additional convenience should also be considered, which is evident in terms of preparation time, infusion time, and active nursing time. After the initial dose of rituximab and trastuzumab, intravenous administration of subsequent doses of rituximab and trastuzumab requires at least 90 min, whereas subcutaneous administration is instantaneous. The time saving is even more pronounced with daratumumab since the maintenance intravenous administration can take 3–4 h.[1] These reductions in administration time minimise productivity losses for both patients and their caregivers and reduce the demand for health-care facility resources such as number of beds or chairs and active care time.

Behind the scenes of the patent world

The process of drug development is long and expensive, with many drugs not ultimately making it to the marketplace. In order to incentivise industry to invest in drug development, patent protections are appropriately granted. These patents provide the companies with exclusivity for their product for a specific period of time. During this period, high drug prices provide return on investment. This mechanism is essential for patients to ensure that incentives remain for future drug development. However, manufacturers often seek to extend the duration of high-level revenue for their products beyond the specified period of patent protection. Three common strategies used to prolong market exclusivity are evergreening, pay for delay, and product hopping.

Evergreening is a process of obtaining multiple patents on various aspects of a drug to extend market exclusivity. These additional patents can cover various components, such as mechanisms of action, chemical intermediates, active ingredients, methods of manufacturing, and packaging.[2] Pay for delay, another strategy aimed to prevent the entry of generic or biosimilar medications into the market, has become increasing prevalent in recent years.[3] Before introducing most generic drugs to the market, the generic manufacturer must file a legal challenge against the brand-name manufacturer, either to invalidate the existing patents or to show that the generic version does not infringe on them. However, in the past few decades, settlements that preserve these patents while delaying the generic drug's entry into the market have become common. In such cases, the generic manufacturer benefits from receiving substantial monetary payments from the brand-name company. Efforts have been made by the US Federal Trade Commission to combat these anticompetitive agreements.[4]

A third strategy, product hopping, involves a brand-name manufacturer reformulating its product to prevent substitution by a generic alternative and to encourage prescribing of the new formulation over the original. The primary objective is to transition patients to the new version, before generic equivalents of the original drug become available, thereby maintaining market exclusivity.[5] Product hopping can take various forms. One example involves modifying the formulation to extend the drug's duration of action. For example, memantine, a drug used for Alzheimer's disease, was reformulated to a once-daily extended-release version shortly before patent expiration of the original twice-daily formulation. Another example is the release of a double-strength, three-times weekly injection of glatiramer acetate, an immunomodulator for multiple sclerosis; although the formula was registered in 2005, it was strategically launched to the market in 2015, just as the original patent with daily dosing expired and generic alternatives were expected to enter the market. The new version was priced similarly to the original formula, but remained more expensive than the upcoming generics, resulting in higher earnings for an additional 2·5 years.[6] Product hopping can also involve altering the route of administration; examples include changing buprenorphine from a sublingual tablet to a dissolvable film,[7] and changing sumatriptan from a subcutaneous injection to a nasal spray.[5]

Subcutaneous immuno-oncology

Immune checkpoint blockers have revolutionised cancer treatment, with dozens of regulatory approvals since 2011. Outcomes for many patients with cancer have been transformed using these agents, and the discovery of this approach was appropriately lauded with the Nobel Prize. In the past few years there has been a trend towards the development of subcutaneous immunotherapy. Although the original standard administration was intravenous, the patent protection for many of these agents is drawing to a close. Meanwhile, most manufacturers have begun to develop subcutaneous versions of these agents, with some already approved and others nearing approval.

To ensure that subcutaneous administration has equivalent safety and efficacy to intravenous administration it must allow for the rapid, painless delivery of large drug volumes, which is achieved by co-administration of the anticancer drug with endoclycosidase, resulting in enhancement of tissue permeability and improved absorption of high-volume injections. As expected with subcutaneous formulations, the time to reach maximum plasma concentration is prolonged, and the peak concentration is lower than intravenous administration. For these reasons, the doses of subcutaneous formulations are usually higher. For example, subcutaneous nivolumab has received FDA approval to be dosed at 1200 mg every 4 weeks, compared with 480 mg intravenously, which has been supported by clinical and pharmacological data.[8]

In phase 3 clinical trials evaluating the safety and efficacy of various intravenous immune checkpoint blockers, immune-related adverse events were generally of low-grade severity, and included fatigue, decreased appetite, nausea, headache, and pruritus. Aggregated data shows that grade 3–5 immune-related adverse events occur in approximately 6% of patients and include pneumonitis, vitiligo, colitis, hypophysitis, hepatitis, and thyroiditis.[9] No significant difference in immune-related adverse events incidence has been observed between different dosing regimens.[10–12] In trials comparing subcutaneous versus intravenous administration of immune checkpoints blockers, no differences were found in the overall rate of immune-related adverse events, including of grade 3–4 events.[13–15] One could also hypothesise that the use of intravenous immunotherapy, which is usually in the hospital setting, could provide more opportunity to incidentally diagnose and treat immune-related adverse events.

Given that maximal receptor occupancy and equivalent clinical benefit has been shown for nivolumab at 0·3 mg/kg intravenously every 3 weeks[16] we have no concern of a loss of efficacy with the labelled subcutaneous dose. Similar support exists for the subcutaneous dosing of atezolizumab and pembrolizumab.[17] In the development of subcutaneous checkpoint blockers, the pharmacokinetics and pharmacodynamics have been closely evaluated. For example, one study found the first dose trough concentrations were equivalent for both intravenous and subcutaneous atezolizumab (85 µg/mL and 89 µg/mL, respectively).[13] Similar concentrations of treatment emergent anti-atezolizumab antibodies were also evident in both groups.[13] The study's cycle 3 trough with subcutaneous pembrolizumab (39 µg/mL) was higher than that with intravenous pembrolizumab (23 µg/mL).[14] These trough levels confirm that there should be no loss of efficacy, with the subcutaneous version, with no increase in immune-related adverse events, as there is no exposure–toxicity relationship. In another study, trough concentrations were also higher with subcutaneous nivolumab than with intravenous nivolumab, confirming the efficacy and safety of the subcutaneous version.[15]

All checkpoint blockers currently remain under patent protection, however many healthcare systems struggle with the financial burden related to these agents. Most low-income and middle-income countries are unable to provide wide-level funding for these therapies. The quality-adjusted life year (QALY) is an economic tool that combines the effect of medical interventions on both mortality and morbidity into a single metric.[18] By calculating the cost per QALY of different medical interventions, payers can compare the value of different interventions across various diseases and optimise health-care system efficiency by allocating resources to interventions that provide the highest value.[19] As cancer treatments are usually very expensive, the cost per QALY is often high. The expiration of patent protection together with arrival of intravenous biosimilars should help to combat these challenges and provide better value for payers. However, the arrival of subcutaneous immunotherapy might threaten the ability of healthcare systems to mitigate these financial challenges for many years to come—as the price of subcutaneous formulations will remain high, and patient preference might favour these over intravenous options, intravenous biosimilars could face barriers to wide-scale uptake.

Conclusion

Similar to the examples of rituximab, trastuzumab, and daratumumab, the product hopping of immunotherapy appears to show a benefit when considering convenience for patients and providers, especially in time savings. Subcutaneous immunotherapy can be administered more quickly than intravenous immunotherapy, although emerging research shows that intravenous administration duration can be substantially reduced.[20] Does this benefit offset the potential long delay in market entry of biosimilars? According to first-quarter sales and earnings by the manufacturer for 2025, pembrolizumab sales reached US$7·2 billion worldwide[21] and was approximately $29 billion in sales in 2024.[22] The rapid

entry and use of biosimilars could lead to vast savings of health-care resources. Most health-care systems suffer from substantial financial constraints, and such savings could be redistributed to provide other health-care services. Although the increased convenience from subcutaneous immunotherapy is real, we would argue that it is outweighed by the long-term cost of suboptimal biosimilar adoption. We propose that payers and providers around the globe reconsider the use of subcutaneous immunotherapy, taking into account the additional costs associated with these formulations compared with potential intravenous biosimilar versions.

Contributors

All authors were involved in the design, initial drafting, and subsequent editing of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

DAG declares research funding (paid to institution) from Merck, Bristol Myers Squibb, and Jannsen; consulting fees from VIVIO Health; and stock ownership in VIVIO Health. All other authors declare no competing interests.

*Roni Levin, Amol Akhade, Manju Sengar, *Daniel A Goldstein*
danielg3@tauex.tau.ac.il

Department of Medicine 'B', Sheba Medical Center, Ramat Gan, Israel (RL); Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (RL, DAG); Bethany Hospital, Thane, India (AA); Tata Memorial Centre, Mumbai, India (MS); Center for Cancer Economics, Davidoff Cancer Center, Rabin Medical Center, Petach Tikvah 4941492, Israel (DAG)

1 Cook G, Ashcroft J, Fernandez M, et al. Benefits of switching from intravenous to subcutaneous daratumumab: perspectives from UK healthcare providers. *Front Oncol* 2023; **13:** 1063144.
2 Feldman R. May your drug price be evergreen. *J Law Biosci* 2018; **5:** 590–647.
3 Kesselheim AS, Murtagh L, Mello MM. "Pay for delay" settlements of disputes over pharmaceutical patents. *N Engl J Med* 2011; **365:** 1439–45.
4 Shah S, Silva MA, Malloy MJ. Are reverse payments and pay-for-delay settlements business as usual or an anticompetitive practice? *Nat Biotechnol* 2016; **34:** 716–19.
5 Gowda V, Beall RF, Kesselheim AS, Sarpatwari A. Identifying potential prescription drug product hopping. *Nat Biotechnol* 2021; **39:** 414–17.
6 Claytor JD, Redberg RF. Product hopping—an expensive and wasteful practice. *JAMA Intern Med* 2020; **180:** 1154–55.
7 Rome BN, Tessema FA, Kesselheim AS. US spending associated with transition from daily to 3-times-weekly glatiramer acetate. *JAMA Intern Med* 2020; **180:** 1165–72.
8 George S, Bourlon MT, Chacon MR, et al. Subcutaneous nivolumab (NIVO SC) vs intravenous nivolumab (NIVO IV) in patients with previously treated advanced or metastatic clear cell renal cell carcinoma (ccRCC): pharmacokinetics (PK), efficacy, and safety results from CheckMate 67T. *J Clin Oncol* 2024; **42** (suppl)**:** LBA360.
9 Brahmer JR, Long GV, Hamid O, et al. Safety profile of pembrolizumab monotherapy based on an aggregate safety evaluation of 8937 patients. *Eur J Cancer* 2024; **199:** 113530.
10 Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol* 2015; **33:** 1430–37.
11 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366:** 2443–54.
12 Garon EB, Rizvi NA, Hui R, et al, and the KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372:** 2018–28.
13 Burotto M, Zvirbule Z, Mochalova A, et al. IMscin001 Part 2: a randomised phase III, open-label, multicentre study examining the pharmacokinetics, efficacy, immunogenicity, and safety of atezolizumab subcutaneous versus intravenous administration in previously treated locally advanced or metastatic non-small-cell lung cancer and pharmacokinetics comparison with other approved indications. *Ann Oncol* 2023; **34:** 693–702.
14 Felip E, Rojas CI, Schenker M, et al. Subcutaneous versus intravenous pembrolizumab, in combination with chemotherapy, for treatment of metastatic non-small cell lung cancer: the phase 3 3475A-D77 trial. *Ann Oncol* 2025; **36:** 775–85.
15 Albiges L, Bourlon MT, Chacón M, et al. Subcutaneous versus intravenous nivolumab for renal cell carcinoma. *Ann Oncol* 2025; **36:** 99–107.
16 Ratain MJ, Goldstein DA. Time is money: optimizing the scheduling of nivolumab. *J Clin Oncol* 2018; **36:** JCO1800045.
17 Wesevich A, Goldstein DA, Paydary K, Peer CJ, Figg WD, Ratain MJ. Interventional pharmacoeconomics for immune checkpoint inhibitors through alternative dosing strategies. *Br J Cancer* 2023; **129:** 1389–96.
18 Kind P, Lafata JE, Matuszewski K, Raisch D. The use of QALYs in clinical and patient decision-making: issues and prospects. *Value Health* 2009; **12** (suppl 1)**:** S27–30.
19 Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull* 2010; **96:** 5–21.
20 van Rijssen L, Nagtegaal IEC, Ploos van Amstel FK, et al. Safety of accelerated infusion of nivolumab and pembrolizumab. *Eur J Cancer* 2025; **220:** 115373.
21 Merck. Merck announces first-quarter 2025 financial results. 2025. https://www.merck.com/news/merck-announces-first-quarter-2025-financial-results/ (accessed July 2 2025).
22 Merck. Merck announces fourth-quarter and full-year 2024 financial results. 2025. https://www.merck.com/news/merck-announces-fourth-quarter-and-full-year-2024-financial-results/?utm_source=chatgpt.com (accessed July 2 2025).

Essay

Abdominal shielding not recommended for diagnostic imaging with ionising radiation during pregnancy

In part due to its rare occurrence, cancer during pregnancy poses unique challenges that require careful consideration of both maternal and fetal health. For the best possible outcome for both mother and child, management during pregnancy should closely follow established guidelines.[1] Oncological staging is necessary to identify optimal personalised treatment plans for each patient, and should be performed in the same manner as for patients who are not pregnant. However, selecting appropriate imaging methods, especially among those that use ionising radiation, requires a careful balance between maternal benefits and fetal risks. This challenge complicates standardisation of diagnostic approaches and harbours the risk of underusing diagnostic imaging, potentially