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ORIGINAL RESEARCH

Comparison of utilization and total medicare fee-for-service expenditures for subcutaneous versus intravenous versions of a select group of therapies

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ABSTRACT

Introduction: Comparisons of subcutaneous (SC) and intravenous (IV) delivery of biotherapeutics in Europe have revealed differences in cost, convenience, and preference. In the US, claims-based studies comparing SC and IV delivery have been limited. This study compared resource utilization and expenditures between cohorts of patients receiving the same drug by the SC or IV route of administration (ROA) across several indications.

Methods: Medicare Fee-For-Service claims were compared between cohorts of patients who received SC- or IV-delivered abatacept, belimumab, daratumumab, infliximab, tocilizumab, trastuzumab/pertuzumab, or vedolizumab. For each drug, utilization rates and healthcare expenditures per service site were compared between ROAs. Observed differences in baseline characteristics were accounted for using Inverse Probability Treatment Weighting models that balanced pre-index differences between ROAs per drug. Each ROA comparison per drug and service site was weighted and conducted independently.

Results: Across seven drugs, a total sample size of 158,632 (72,820 IV; 85,812 SC) was analyzed. For most comparisons, high-spend sites were utilized at a higher rate for IV administration. In particular, all comparisons revealed more frequent hospital outpatient department utilization for the IV ROA. For five of the seven drugs, SC treatment was associated with lower mean total Medicare expenditures, with savings of up to $56,000 per patient annually. Although three SC treatments had higher medication index spend, the total spend for these drugs across sites was significantly lower for SC delivery.

Limitations: Limitations of this study include differences in billing between the SC and IV ROAs, potential treatment selection bias, and the assumption of equivalent efficacy.

Conclusions: To our knowledge, this study was the first and largest US Medicare claims analysis, comparing patients receiving SC or IV versions of the same therapeutic across multiple drugs and indications. Findings demonstrated that SC delivery may facilitate reduced resource utilization and expenditures across drugs and disease indications.

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Introduction

Biologics for the treatment of cancer and autoimmune disease have historically been given by the intravenous (IV) route of administration (ROA); however, subcutaneous (SC) alternatives for many of these treatments are increasingly available[1]. Each ROA has advantages and disadvantages that may influence the selection of an appropriate ROA for a given drug and indication, including differences in

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convenience, comfort, total cost, and overall patient preference, with evidence favoring SC delivery relative to IV for each of these factors[2–4]. However, comparisons of cost and resource utilization between SC and IV delivery options in the US are limited.

Published studies across disease indications have consistently demonstrated reductions in healthcare resource utilization and healthcare expenditures for SC delivery compared to IV, with most real-world evidence derived from European countries[5,6]. These studies were primarily time and motion micro-costing analyses comparing a variety of factors between SC and IV delivery, namely the physical space for administration, healthcare provider (HCP) time spent on delivery, and patient time spent traveling to and from an appointment, at an appointment, or away from work[5–8]. These studies found that switching to SC delivery of biologics could reduce the costs related to surgery for central venous access, healthcare resource utilization, fees for drug preparation, and the cost of consumables[5–8]. For example, switching patients from IV to SC daratumumab was found to save €29,460 annually in France and provided a 56.6% reduction in total expenses in Italy[9,10]. By contrast, in the US, differences in coding and billing processes between ROAs have complicated the real-world comparisons of SC and IV delivery. SC delivery can be managed and delivered through the pharmacy with the National Drug Code (NDC) as the identifier, while IV delivery is typically managed using a more complex billing claim system under the health plan management system[4].

Current US-based real-world comparisons of SC- and IV-delivered treatment expenditures primarily focused on one disease indication or one drug and had relatively small sample sizes[11–13]. To gain a more comprehensive understanding of the differences in real-world expenditures between the SC and IV ROA, we examined US Medicare Fee-For-Service (FFS) claims from patients with cancer and/or autoimmune conditions, as Medicare data include a large number of beneficiaries with a generally high utilization of healthcare services[14]. Results of these analyses were then used to compare cohorts of patients receiving the same drug by either SC or IV ROA across all included sites of healthcare service. The objective of this study was to analyze and compare healthcare resource utilization and total Medicare spend across Parts A, B, and D (including patient-out-of-pocket expenditures) of patients receiving either SC- or IV-delivered treatment across multiple indications in the US.

Methods

Data sources

The claims data assessed were from the 100% Medicare Research Identifiable Files (RIFs), 100% Part D Event (PDE), and 100% Master Beneficiary Summary File (MBSF) from 2019 through 2023. Drugs were identified using the US Food and Drug Administration (FDA) NDC Directory (https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory).

Drug selection

Supplemental Table 1 delineates the attrition of drug selection. Drugs for analysis were selected using the FDA NDC Directory if the non-proprietary name of the drug had a "route name" of both SC and IV. Drugs were removed if they were diluents, vitamins, opioid agonists, or insulin, as this analysis focused on protein biologics. The criteria were then expanded to capture drugs with differing generic names between ROA, biosimilars, and those dosed in combination rather than as a monotherapy. Biosimilars were pooled with their respective drug cohorts based on ROA. Patient and claim volume in the Medicare FFS databases (i.e. 100% RIFs for Medicare Part B and 100% PDE data) were assessed for the remaining SC and IV drugs, leading to seven drugs, representing six therapeutic areas, included as index medications for analysis: abatacept, belimumab, daratumumab, infliximab, tocilizumab, trastuzumab/pertuzumab, and vedolizumab (Supplemental Table 2). A full list of queried drugs and reasons for culling is presented in Appendix A.

Assignment of route of administration to selected drugs

A hierarchy of rules were implemented to assign an ROA to each claim, as some Healthcare Common Procedure Coding System (HCPCS) and NDC descriptors were found to be non-specific to the ROA. The

hierarchy rules were as follows: 1. HCPCS modifier "JA" (indicating IV infusion) or "JB" (indicating SC injection) on the drug's claim line; 2. NDC code present on the Part B claim that identified a definitive ROA; 3. drug administration HCPCS code present on the same claim and day that identified the ROA (Appendix B); 4. if none of the above identified a Part B drug, then ROA was defined as "Unable to Determine"; 5. All Part D drug claims were assigned as SC.

Patient inclusion and exclusion criteria

Using this curated list of seven drugs, patients with more than one claim of any of the index medications administered by an HCP and continuous enrollment in Medicare Parts A, B, and D for 6 months prior to and 12 months after the index were assessed for eligibility. Patients were included in the analysis if they were continuously eligible in the post-index period through death. The index date was defined as the date of the first claim during the observation period (2017–2023). A summary of patient attrition can be found in Supplemental Table 2. Patients were excluded from analysis if they received an index medication prior to the index date, had claims for both the SC and IV ROA of the same drug after the index date, were under 18 years of age at index, or identified as having end-stage renal disease at any point during the study period. Patients could be selected for multiple analyses if they received more than one therapy on the list, as each SC versus IV analysis was conducted independently (e.g. analysis of abatacept was independent of infliximab).

For patients who met eligibility criteria, all Medicare Part A, B, and D claims were extracted and used for balancing study cohorts and assessing post-index outcomes. Data were drawn from the 100% Medicare FFS files (2017–2023) which included the Medicare Research Identifiable Files, Part D Event Files, and Master Beneficiary Summary File.

Pre-index period adjustments

Differences in baseline characteristics between the SC and IV groups after independently assessing each drug (i.e. age, gender, region, urban/rural residence, Medicare eligibility status, Charlson Comorbidity Score, and pre-index healthcare spending) were examined using the standard mean difference between groups. Inverse probability treatment weighting (IPTW) was used to control for covariates by creating a weighted sample that balanced baseline differences between treatment groups (Appendix C)[15], with the goal of emulating the conditions of a randomized control trial where treatment groups are expected to be balanced across key baseline characteristics. Covariates (relevance described in Appendix D) were included in the IPTW model for each drug cohort based on theoretical or clinical relevance and empiric evidence of imbalance, namely a standard mean difference of more than 10% between SC and IV ROA at baseline (summarized per drug in Supplemental Table 3), and therefore specific to each drug cohort to minimize the introduction of bias. The propensity of receiving SC treatment versus IV treatment was estimated for each drug using multivariate logistic regression, applying the covariates noted in Supplemental Table 3 to calculate a stabilized weighting score for each beneficiary: the proportion of IV beneficiaries or IV marginal probability of treatment divided by beneficiary propensity score, and the inverse of 1 minus propensity score for SC beneficiaries (Appendix C).

Post-index utilization and spend analysis

Healthcare utilization was assessed across Medicare Parts A, B, and D, with a focus on the following service sites: physician office, inpatient hospital, hospital outpatient department, emergency room (ER), durable medical equipment (DME), home health, hospice, skilled nursing facility (SNF), and pharmacy (Part D).

Prior to weighting, total Medicare payments (inclusive of patient out-of-pocket) were compared between SC and IV delivery for each site of service, and additionally summed across all sites to calculate the total Medicare spend for the SC and IV ROA of each drug. Additionally, the rate of utilization for each site of service was compared between the two ROAs of each drug. IPTW weights, determined using pre-index covariates, were then applied to compare the SC and IV ROA independently at each site of

service, as well as for total spend for care (across all sites). IPTW-weighted Poisson regression was used for modeling count data (non-negative integer values), such as the number of visits occurring within a fixed period. IPTW-weighted gamma regression was used when the dependent variable represented positive continuous data that was not normally distributed, such as total Medicare expenditure by site of service (and across all sites). For example, the post-period spend outcome (per patient per month spending) was calculated by multiplying post-period spend by the weighting factor applied for that individual patient and divided by the total number of months in the post-period.

Ethics

This study was performed in compliance with ADVI Health's data use agreement with the Centers for Medicare and Medicaid Services (CMS) for retrospective analysis of Medicare claims.

Results

Patient characteristics for each drug by ROA

A total sample size of 158,632 was analyzed, including 72,820 with treatment by the IV ROA and 85,812 with treatment by the SC ROA, representing patients with rheumatoid arthritis, lupus, multiple myeloma, Crohn's disease, breast cancer, and ulcerative colitis. The distribution of patients who received the SC or IV ROA for each of the seven drugs is presented in Table 1.

Statistically significant differences (standard mean difference >10%) in demographic and pre-period variables were found between the SC and IV cohorts for each of the seven drugs (Supplemental Tables 4–10). Six of the seven drugs had a statistically significant difference in mean age between the SC and IV ROAs. Patients receiving SC treatments were significantly older for daratumumab, infliximab, trastuzumab/pertuzumab, vedolizumab while patients receiving IV treatments were significantly older for abatacept and belimumab. Other differences were commonly found in Medicare/Medicaid dual eligibility status, region, urban/rural status, and pre-period spending.

Healthcare resource utilization and spend

Across all weighted drug comparisons of SC versus IV, rates of hospital outpatient department visits in the post-index period were significantly higher for patients receiving treatment through the IV ROA (Table 2). Similarly, ER visits were more commonly associated with IV administration or had no significant difference between ROAs (Table 2, Supplemental Tables 11–12). Two drugs, belimumab and infliximab, had significantly higher rates of physician office visits when delivered by the SC ROA compared to the IV ROA (Table 2, Supplemental Table 12). When delivered by the SC ROA, infliximab also had significantly higher rates of inpatient utilization as well as greater utilization of lower spend sites of care (DME, home health, hospice, and SNF) (Table 2, Supplemental Table 12).

The post-index mean total Medicare spend for patients receiving either the SC or IV ROA for each drug was calculated per study patient per month and extrapolated to annual spend (inclusive of Medicare and patient out-of-pocket costs), and differences in spend between ROA for each drug were compared (Table 3, Supplemental Table 13). For 5 of the 7 drugs (abatacept, belimumab, daratumumab, tocilizumab, and vedolizumab), the IV ROA was associated with higher mean total Medicare expenditure in the post-index period compared to SC, ranging from approximately $12,000 to $56,000 more per patient per year, with the exceptions being infliximab and trastuzumab/pertuzumab, whose differences

Table 1. Drugs included for analysis[16–25].

Generic drug name	IV patients included in the study	SC patients included in the study	Indication(s)
Abatacept	13,724	31,002	Rheumatoid arthritis
Belimumab	1,413	3,421	Lupus
Daratumumab	15,631	9,629	Multiple myeloma
Infliximab	25,882	8,443	Crohn's disease
Tocilizumab	5,181	22,515	Rheumatoid arthritis
Trastuzumab/Pertuzumab	4,487	658	Breast cancer
Vedolizumab	6,502	10,144	Ulcerative colitis/Crohn's disease

Abbreviations: IV: intravenous; SC: subcutaneous.

Table 2. Comparison of the post-index number of claims of visits to specific sites of care.

Index medication	Physician office visit[a]	Inpatient visit[a]	ER visit[a,b]	Hospital outpatient department visit[a]	DME[c]	Home health[c]	Hospice[c]	SNF[c]
Abatacept	IV	IV	IV	IV	IV	IV		
Belimumab	SC		IV	IV	IV	IV		
Daratumumab	IV	IV	IV	IV			IV	IV
Infliximab	SC	SC	IV	IV	SC	SC	SC	SC
Tocilizumab	IV	IV	IV	IV	IV	IV	IV	IV
Trastuzumab/Pertuzumab	IV		IV	IV		IV		
Vedolizumab	IV	IV	IV	IV				

Abbreviations: DME: durable medical equipment; ER: emergency room; IPTW: Inverse Probability Treatment Weighting; IV: intravenous; SC: subcutaneous; SNF: skilled nursing facility.
Post-index number of claims for visits were determined using Poisson regression analysis with IPTW weighting (variables per drug provided in Supplemental Table 3). Visits are defined as individual claims within the payment system, except for physician office, which were unique dates of service by the same billing National Provider Identifier. "IV" or "SC" indicates a significantly higher rate ($p < 0.05$); no designation represents no statistical difference. Blue shading indicates higher use for SC delivery. Green shading indicates higher use for IV delivery. Grey shading indicates no significant difference between routes.
[a]Indicates a major cost site.
[b]Emergency room visit is defined as either an inpatient or hospital outpatient department claim with charges associated with ER revenue centers. These claims were made mutually exclusive from either inpatient or hospital outpatient department visits.
[c]Indicates a lower cost site.

Table 3. Comparison of mean total spend[a] post-index.

Index drug	IV patients PPPM total spend	SC patients PPPM total spend	IV difference to SC PPPM	Annualized difference (IV to SC)	*P*-value	Difference ratio
Abatacept	$10,395	$9,183	$1,212	$14,539	<0.0001	1.13
Belimumab	$12,341	$9,707	$2,634	$31,612	<0.0001	1.27
Daratumumab	$68,816	$66,387	$2,429	$29,147	<0.0001	1.04
Infliximab	$8,381	$8,428	−$47	−$566	0.6507	0.99
Tocilizumab	$13,243	$8,573	$4,669	$56,031	<0.0001	1.54
Trastuzumab/ Pertuzumab	$32,425	$32,485	−$2	$19	0.9987	1.00
Vedolizumab	$12,895	$11,684	$1,211	$12,536	<0.0001	1.10

Abbreviations: IPTW: Inverse Probability Treatment Weighting; IV: intravenous; PPPM: per study patient per month; SC: subcutaneous.
Results are presented as PPPM due to the varying length of observations for some patients in the post-index period. Total spend includes mean PPPM and were calculated using a gamma regression model with IPTW weighting (variables per drug provided in Supplemental Table 3). The difference ratio was calculated as IV PPPM divided by SC PPPM. Green shading indicates higher spend for IV delivery. Grey shading indicates no significant difference between routes.
[a]Total spend is the sum of all payers: Medicare, patient out-of-pocket, and any third-party payers (less than 1% of claims on average).

did not reach statistical significance. Three drugs (abatacept, daratumumab, and vedolizumab) were associated with significantly higher expenditures for index drug medication for the SC ROA compared to IV; however, the total spend for these three drugs across all sites of care was significantly lower for the SC ROA (Supplemental Table 13).

Spend for treatment in a physician's office was higher for the SC cohort for all drugs included in the study (Supplemental Table 13). Pharmacy (Medicare Part D) spending for non-index drugs (e.g. Part D spending for all other Part D drugs other than the index drug) was significantly higher for patients receiving the IV ROA across all drug cohorts except for trastuzumab/pertuzumab.

Discussion

To our knowledge, this study represents the most comprehensive US-based comparison of healthcare resource utilization and spend between patients receiving either SC or IV delivery of the same drug across 7 drugs and 6 indications. Data presented here revealed that for most studied therapeutics, SC delivery was associated with a reduction in both healthcare utilization rates and expenditures based on the analysis of a total sample size of 158,632 (72,820 IV; 85,812 SC) representing patients with rheumatoid arthritis, lupus, multiple myeloma, Crohn's disease, breast cancer, and ulcerative colitis. Consistently, the IV ROA demonstrated higher utilization rates for most therapies across major sites of service. After adjusting for observable baseline differences between the SC and IV groups, the analyses revealed statistically significant reductions in total Medicare FFS expenditures (including patient out-of-pocket costs)

ranging from $12,000 to $56,000 per year with the use of the SC ROA for 5 of the 7 therapies studied compared to their IV counterparts.

The key finding that the SC ROA was often associated with a lower overall cost of care compared with the IV ROA for the same drug is consistent with prior studies that demonstrated lower time allocation, resource use, and expenditures associated with the SC ROA in multiple disease indications across several countries[5,8,26–37]. However, the limited number of prior US studies comparing expenditures between SC and IV delivery are more variable and of smaller scale[11–13]. A claims analysis of the Medco Health Solutions PBM database included 1,090 US patients with rheumatoid arthritis and demonstrated that annual spend was approximately $16,000 less per effectively treated patient with SC-administered biologics compared to IV[11]. A meta-analysis drawing from 916 patients administered epoetin found that the SC ROA used lower doses of drug compared to the IV ROA, which translated to annual savings of approximately $1,761 ± $1,080 per patient[12]. In contrast, a claims analysis using the PharMetrics Plus database found that of 1,639 patients newly diagnosed with primary immunodeficiency, median primary immunodeficiency-related total costs for IV immunoglobulin treatment were lower than for SC treatment, partially due to higher SC drug costs relative to IV[13]. Differences in previous US studies may be due to each analysis examining individual drug classes and indications as well as whether SC dosing was self-administered or HCP-administered, emphasizing the need for further studies to examine a wider variety of classes and disease areas. The IV formulations of the therapies in our study are HCP-administered and the SC versions of vedolizumab, infliximab, belimumab, abatacept, and tocilizumab have an option for self-administration.

Despite the increased availability of SC versions of drugs originally approved for the IV ROA in recent years[1] and the potential for reduced expenditures, the use of the SC ROA is strikingly lower in the US compared to Europe and Canada. For example, a study published in 2023 compared the use of the SC and IV ROA between two oncology centers of excellence, one in the US and one in Canada, revealing stark differences in ROA selection: 99.5% of patients at the US center exclusively received treatments by the IV ROA while 95.3% of patients at the Canadian center received treatments by the SC ROA at some point in their treatment journey[38]. A significant factor explaining this disparity may be the physician reimbursement policy of US health insurers. The buy-and-bill model of reimbursement financially incentivizes IV delivery of therapeutics by allowing the cost of IV drugs administered in an infusion center or other clinical setting to be billed to payers, potentially generating considerable revenue for oncology practices[4,39]. To this point, a previous analysis of Medicare data from 2006 to 2009 examined factors associated with prescribing initial treatments (IV-administered infliximab or SC-administered etanercept or adalimumab) for patients with rheumatoid arthritis, revealing that physician preferences for infused therapies were related to reimbursement and resulted in greater use of IV infliximab[40].

Beyond the generally higher cost to CMS for IV administration, this present study implies lower Medicare patient out-of-pocket spend for SC treatments compared to their IV counterparts across multiple indications. Out-of-pocket fees are determined as a percentage of the cost of the entire health encounter (e.g. 20% for Medicare Part B drugs) and therefore, patients can predict their expected out-of-pocket spending over a finite period of time given the expected dosing schedule. Some SC drugs require more frequent administration compared to their IV counterparts (e.g. abatacept, belimumab, infliximab, tocilizumab, and vedolizumab[16–20]) producing a potential concern that SC may cost more to patients due to an increased number of health encounters for administration. Therefore, for patients who may be more cost-sensitive, the direct out-of-pocket spend for a surmised increase in visit frequency may discourage SC use. However, the data presented here demonstrate that, in most cases, the SC ROA facilitated reduced downstream utilization of other Medicare services (e.g. hospitalizations, ER visits, SNF stays) that may subsequently provide downstream out-of-pocket savings for patients compared to the IV ROA. Previous studies have described several factors that can contribute to these observed savings for SC delivery, including lower drug preparation costs and time, drug wastage, use of consumables, administration time, and chair time[5–8,32,36].

There were several limitations to this study. One limitation is a potential ROA selection bias, which may have been influenced by unobservable factors (e.g. clinical presentation not captured by ICD-10, family or home situation of the patient) not captured by a claims analysis. Comparable efficacy and safety, as demonstrated in Phase 3 clinical trials comparing the SC and IV ROAs of a given drug, was assumed between

SC and IV formulations and therefore, real-world clinical outcomes were not tested in this study. To this point, variability in real-world treatment protocols and adherence can complicate the interpretation of clinical outcomes and make it harder to attribute any observations to ROA alone. While IPTW is a commonly used method to adjust for patient characteristics[41,42], it can be prone to extreme weights and subsequent bias[43]. However, this approach avoids model overfitting and instability by limiting each drug's IPTW model to the covariates that appeared most likely to contribute to imbalance or confound the results. It also minimizes influence on the data by avoiding unnecessary adjustment for variables with minimal observed imbalance, particularly when those variables are unlikely to be strong confounders for the treatment-outcome relationship in the specific drug cohort. The inclusion of every measured variable, particularly those that are already balanced or unlikely to confound the treatment-outcome relationship, could introduce instability in the weighting and increase the variance[44]. Upon evaluating the IPTW models, the effective sample size ratio remained high (approximately 92%) and comparable to the unweighted sample size, suggesting minimal influence on the overall model variance. Additionally, this research question does not appear to have been examined previously in Medicare FFS data; therefore, another limitation was that learning from and expanding on previous efforts in a similar dataset was not possible.

This study was also limited by differences in billing between the SC and IV ROAs as well as potential misclassifications of ROA. The specificity and visibility of the medical coding process can differ between SC- and IV-administered drugs, adding to uncertainty in our study. Real-world claims data also contain a degree of error in coding. A 2024 Medicare FFS Supplemental Report on Improper Payment Data found an improper payment rate of 10.3% (95% CI = 9.5%–11.2%) for all Part B services, with 18.5% of this rate attributable to incorrect coding[45]. Indexed patients who switched ROA at any point in the study were excluded. However, three therapies (vedolizumab, infliximab, and belimumab) require an IV induction period before changing to SC for some indications[17,18,20,21]. Therefore, patients on these therapies indexed between 2017 and 2022 who were in the SC maintenance phase when they entered the study (Supplemental Table 14) may have accrued expenses related to the IV ROA prior to indexing, which would have increased costs attributable to the SC ROA.

Future studies are warranted to further investigate health outcomes associated with each ROA. More specifically, rates of drug-specific adverse events, morbidity, mortality, drug adherence, and other variables may identify key differences in the utilization of each ROA. Additionally, an analysis of beneficiaries who switch ROA to determine reasons for switching may provide insight into patient and/or physician preferences. When taken in the context of the body of evidence of potential savings associated with SC delivery, these results provide the impetus for updates to current access and reimbursement policies by US payers and health policy makers to capture these potential downstream savings. As patients often report a preference for the SC ROA[46–48], updates should focus on addressing the misalignment of patient, physician, and payer interests concerning IV and SC ROA.

Conclusions

To our knowledge, this was the most comprehensive US Medicare FFS claims analysis to compare patients receiving SC- or IV-administered treatments across multiple disease indications in a real-world setting. This study demonstrated that, across most included biologics, SC delivery was associated with lower resource utilization and lower total Medicare spend compared to the IV counterpart. The results from this study highlight the potential financial advantages of pursuing SC delivery for patients which remain consistent across multiple disease indications.

Transparency

Declaration of funding

This study and analysis were sponsored by Halozyme, Inc.

Declaration of financial/other interests

PK is an employee of ADVI Health LLC.
CS is an employee of ADVI Health LLC.

JM is an employee of ADVI Health LLC.
PS is an employee and shareholder of Halozyme, Inc.

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Author contributions

PS was involved in conceptualization, funding acquisition, providing resources, and supervision of the study. PK and JM were involved in software implementation and validation of outputs. PK and CS were involved with project administration. PK, JM, and CS were involved in the investigation, formal analysis, and visualization of data for this study. All authors were involved in the study methodology as well as writing, reviewing, and editing this manuscript. All authors gave their final approval of this version of the manuscript to be published and agree to be accountable for all aspects of the work.

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Previous presentations

A portion of this work was previously presented as a poster at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2024, held 17–20 November 2024 in Barcelona, Spain.

Data sharing statement

The summary data that support the findings of this study are available on request from the corresponding author, PK. The raw data is not publicly available due to a data use agreement between ADVI Health and CMS.

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References

[1] Sánchez-Félix M, Burke M, Chen HH, et al. Predicting bioavailability of monoclonal antibodies after subcutaneous administration: open innovation challenge. Adv Drug Deliv Rev. 2020;167:66–77. doi: 10.1016/j.addr.2020.05.009.
[2] Stevenson J, Poker R, Schoss J, et al. Pharmaceutical and biotech industry perspectives on optimizing patient experience and treatment adherence through subcutaneous drug delivery design. Adv Drug Deliv Rev. 2024;209:115322. doi: 10.1016/j.addr.2024.115322.
[3] Collins DS, Sánchez-Félix M, Badkar AV, et al. Accelerating the development of novel technologies and tools for the subcutaneous delivery of biotherapeutics. J Control Release. 2020;321:475–482. doi: 10.1016/j.jconrel.2020.02.036.
[4] Epstein RS. Payer perspectives on intravenous versus subcutaneous administration of drugs. Clinicoecon Outcomes Res. 2021;13:801–807. doi: 10.2147/CEOR.S317687.
[5] Hedayati E, Fracheboud L, Srikant V, et al. Economic benefits of subcutaneous trastuzumab administration: a single institutional study from Karolinska University Hospital in Sweden. PLoS One. 2019;14(2):e0211783. doi: 10.1371/journal.pone.0211783.
[6] Landeiro LCG, Martins TC, Grigolon RB, et al. The burden of systemic therapy administration route in treating HER2-positive breast cancer (for patients, healthcare professionals, and healthcare system): a systematic literature review. Front Pharmacol. 2024;15:1338546. doi: 10.3389/fphar.2024.1338546.

[7] Lopez-Vivanco G, Salvador J, Diez R, et al. Cost minimization analysis of treatment with intravenous or subcutaneous trastuzumab in patients with HER2-positive breast cancer in Spain. Clin Transl Oncol. 2017;19(12):1454–1461. doi: 10.1007/s12094-017-1684-4.
[8] O'Brien GL, O'Mahony C, Cooke K, et al. Cost minimization analysis of intravenous or subcutaneous trastuzumab treatment in patients with HER2-positive breast cancer in Ireland. Clin Breast Cancer. 2019;19(3):e440–e451. doi: 10.1016/j.clbc.2019.01.011.
[9] Pradelli L, Massaia M, Todisco E, et al. Improved efficiency of daratumumab treatment of multiple myeloma adopting the subcutaneous route: a micro-costing analysis in three Italian hematology centers. Cancer Med. 2023;12(23):21480–21489. doi: 10.1002/cam4.6699.
[10] Badibouidi F, Can-Köse L, Dupont L, et al. P098 Subcutaneous daratumumab versus intravenous daratumumab for the treatment of patients with multiple myeloma: a time, motion, and CST assessment study in a general hospital. Eur J Oncol Pharm. 2023;6:e40.
[11] Wu N, Bhurke S, Shah N, et al. Application of a validated algorithm to estimate the effectiveness and cost of biologics for rheumatoid arthritis in the US pharmacy benefit manager context. Clinicoecon Outcomes Res. 2015;7:257–266. doi: 10.2147/CEOR.S83932.
[12] Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. Am J Kidney Dis. 2002;40(3):439–446. doi: 10.1053/ajkd.2002.34881.
[13] Runken MC, Noone JM, Blanchette CM, et al. Differences in patient demographics and healthcare costs of patients with PIDD receiving intravenous or subcutaneous immunoglobulin therapies in the United States. Am Health Drug Benefits. 2019;12(6):294–304.
[14] Brown DS, Srinivasan M, Zott C, et al. Medicare data linkages for conducting patient-centered outcomes research on economic outcomes. Med Care. 2023;61(12 Suppl 2):S122–s130. doi: 10.1097/MLR.0000000000001896.
[15] Chesnaye NC, Stel VS, Tripepi G, et al. An introduction to inverse probability of treatment weighting in observational research. Clin Kidney J. 2022;15(1):14–20. doi: 10.1093/ckj/sfab158.
[16] ACTEMRA (tocilizumab). Prescribing information. South San Francisco, CA: Genentech, Inc; 2024. [cited 2024 Dec 23, 2024]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125472s058,125276s146lbl.pdf
[17] BENLYSTA (belimumab). Prescribing information. Durham, NC: GlaxoSmithKline LLC; 2024. [cited 2024 Dec 17, 2024]. Available from: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG-IFU.PDF
[18] ENTYVIO (vedolizumab). Prescribing information. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc; 2024. [cited 2024 Dec 23, 2024]. Available from: https://content.takeda.com/?contenttype=PI&product=ENTY&language=ENG&country=USA&documentnumber=1
[19] ORENCIA (abatacept). Prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2024. [cited 2024 Dec 17, 2024]. Available from: https://packageinserts.bms.com/pi/pi_orencia.pdf
[20] REMICADE (infliximab). Prescribing information. Horsham, PA: Janssen Biotech, Inc.; 2021. Available from: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf
[21] ZYMFENTRA (infliximab-dyyb). Prescribing information. Jersey City, NJ: CELLTRION USA, Inc.; 2023. [cited 17 Dec 2024]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761358s000lbl.pdf
[22] DARZALEX® (daratumumab). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2024. [cited 2024 Dec 6]. Available from: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf
[23] DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2024. [cited 2024 Dec 6]. Available from: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX±Faspro-pi.pdf
[24] PHESGO® (pertuzumab trastuzumab and hyaluronidase-zzxf). Prescribing information. South San Francisco, CA: Genentech, Inc; 2024. [cited 2024 Dec 6]. Available from: https://www.gene.com/download/pdf/phesgo_prescribing.pdf
[25] PERJETA® (pertuzumab). Prescribing information. South San Francisco, CA: Genentech, Inc; 2021. [cited 2024 Dec 6]. Available from: https://www.gene.com/download/pdf/perjeta_prescribing.pdf
[26] Burcombe R, Chan S, Simcock R, et al. Subcutaneous trastuzumab (Herceptin (R)): a UK time and motion study in comparison with intravenous formulation for the treatment of patients with HER2-positive early breast cancer. ABCR. 2013;02(04):133–140. doi: 10.4236/abcr.2013.24022.
[27] North RT, Harvey VJ, Cox LC, et al. Medical resource utilization for administration of trastuzumab in a New Zealand oncology outpatient setting: a time and motion study. Clinicoecon Outcomes Res. 2015;7:423–430.
[28] De Cock E, Pivot X, Hauser N, et al. A time and motion study of subcutaneous versus intravenous trastuzumab in patients with HER2-positive early breast cancer. Cancer Med. 2016;5(3):389–397. doi: 10.1002/cam4.573.
[29] Ponzetti C, Canciani M, Farina M, et al. Potential resource and cost saving analysis of subcutaneous versus intravenous administration for rituximab in non-Hodgkin's lymphoma and for trastuzumab in breast cancer in

17 Italian hospitals based on a systematic survey. Clinicoecon Outcomes Res. 2016;8:227–233. doi: 10.2147/CEOR.S97319.

[30] Farolfi A, Silimbani P, Gallegati D, et al. Resource utilization and cost saving analysis of subcutaneous versus intravenous trastuzumab in early breast cancer patients. Oncotarget. 2017;8(46):81343–81349. doi: 10.18632/oncotarget.18527.

[31] Lin HW, Lin CY, Yeh TP, et al. Quality of care in the course of subcutaneous versus intravenous trastuzumab administration in patients with breast cancer: an integrated time-motion study with mixed-methods research. BMJ Open. 2023;13(3):e059288. doi: 10.1136/bmjopen-2021-059288.

[32] McCloskey C, Ortega MT, Nair S, et al. A systematic review of time and resource use costs of subcutaneous versus intravenous administration of oncology biologics in a hospital setting. Pharmacoecon Open. 2023;7(1):3–36. doi: 10.1007/s41669-022-00361-3.

[33] Rule S, Collins GP, Samanta K. Subcutaneous vs intravenous rituximab in patients with non-Hodgkin lymphoma: a time and motion study in the United Kingdom. J Med Econ. 2014;17(7):459–468. doi: 10.3111/13696998.2014.914033.

[34] Mihajlović J, Bax P, van Breugel E, et al. Microcosting study of rituximab subcutaneous injection versus intravenous infusion. Clin Ther. 2017;39(6):1221–1232.e4. doi: 10.1016/j.clinthera.2017.05.342.

[35] Delgado Sánchez O, Gutiérrez A, do Pazo F, et al. Comparative cost analysis of intravenous and subcutaneous administration of rituximab in lymphoma patients. Clinicoecon Outcomes Res. 2019;11:695–701. doi: 10.2147/CEOR.S212257.

[36] Parra A, Hernández C, Prieto-Pinto L. Evaluation of the economic benefits, administration times, and patient preferences associated with the use of biotechnological drugs administered subcutaneously and intravenously in patients with cancer: a systematic review. Expert Rev Pharmacoecon Outcomes Res. 2023;23(9):1017–1026. doi: 10.1080/14737167.2023.2249232.

[37] Federici C, Rognoni C, Costa F, et al. Use of resource modeling to quantify the organizational impact of subcutaneous formulations for the treatment of oncologic patients: the case of daratumumab in multiple myeloma. Clin Ther. 2022;44(11):1480–1493. doi: 10.1016/j.clinthera.2022.09.006.

[38] Tang M, Abdelaal M, Lau J, et al. Subcutaneous vs intravenous administration of medications and fluids for patients with cancer in the US and Canada. JAMA Oncol. 2023;9(5):717–719. doi: 10.1001/jamaoncol.2023.0239.

[39] Pakizegee M, Stefanacci RG. Clinical pathways and policy to guard against misaligned incentives. J Clin Pathways. 2020;6(1):34–36. doi: 10.25270/jcp.2020.2.00113.

[40] Zhang J, Xie F, Delzell E, et al. Trends in the use of biologic agents among rheumatoid arthritis patients enrolled in the US medicare program. Arthritis Care Res (Hoboken). 2013;65(11):1743–1751. doi: 10.1002/acr.22055.

[41] Drzayich Antol D, Schwartz R, Caplan A, et al. Comparison of health care utilization by medicare advantage and traditional medicare beneficiaries with complex care needs. JAMA Health Forum. 2022;3(10):e223451–e223451. doi: 10.1001/jamahealthforum.2022.3451.

[42] Park S, Jung J, Burke RE, et al. Trends in use of low-value care in traditional fee-for-service Medicare and medicare advantage. JAMA Netw Open. 2021;4(3):e211762–e211762. doi: 10.1001/jamanetworkopen.2021.1762.

[43] Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. Stat Methods Med Res. 2017;26(4):1654–1670. doi: 10.1177/0962280215584401.

[44] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399–424. doi: 10.1080/00273171.2011.568786.

[45] U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES. Medicare fee-for service supplemental improper payment data 2024. 2024 [cited 2025 June 16]. Available from: https://www.cms.gov/files/document/2024-medicare-fee-service-supplemental-improper-payment-data.pdf.

[46] Anderson KC, Landgren O, Arend RC, et al. Humanistic and economic impact of subcutaneous versus intravenous administration of oncology biologics. Future Oncol. 2019;15(28):3267–3281. doi: 10.2217/fon-2019-0368.

[47] Bril V, Lampe J, Cooper N, et al. Patient-reported preferences for subcutaneous or intravenous administration of parenteral drug treatments in adults with immune disorders: a systematic review and meta-analysis. J Comp Eff Res. 2024;13(9):e230171. doi: 10.57264/cer-2023-0171.

[48] Pivot X, Gligorov J, Müller V, et al. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. Ann Oncol. 2014;25(10):1979–1987. doi: 10.1093/annonc/mdu364.