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# A multidisciplinary perspective on the subcutaneous administration of trastuzumab in HER2-positive breast cancer

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## ABSTRACT

Trastuzumab is the standard treatment in Canada for patients with breast cancer positive for HER2 (human epidermal growth factor receptor 2), dramatically improving outcomes in that patient group. However, its current intravenous (IV) administration is associated with long infusion times that place a significant burden on health care resources and patient quality of life. In an effort to provide a faster and easier administration method, a subcutaneous (SC) formulation of trastuzumab has been developed. Data from comparative trials demonstrate that the two formulations are comparable with respect to pharmacokinetics and efficacy. They also have similar safety profiles, with the exception of mild local and administration reactions with the SC formulation. Furthermore, the SC formulation is preferred by patients and health care professionals, and greatly reduces administration and chair time. Additional advantages include easier preparation and dosing, reduced drug wastage, and reduced discomfort at the injection site. By using well-thought-out administration procedures, the SC formulation can be given safely and effectively, potentially reducing the burden on health care resources and improving quality of life for patients.

**Key Words** Trastuzumab, subcutaneous administration, breast cancer, HER2 positivity

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## INTRODUCTION

Breast cancer (BCA) is the 3rd most prevalent malignancy in Canada, accounting for 13% of all cancers[1]. In 2017, approximately 26,300 Canadian women were newly diagnosed with BCA. Within the next 15 years, the number of new BCA cases is expected to rise by 25% because of the country's growing and aging population. That increase is likely to place a huge burden on the health care system, underscoring the need to optimize medical resources while ensuring that patients continue to receive high-quality care. In approximately 15%–25% of these malignancies, overexpression of the HER2 (human epidermal growth factor receptor 2) protein or amplification of the *HER2* gene—or both—arises and is associated with an aggressive disease course and poor prognosis[2,3]. However, the development of treatments that target HER2 have revolutionized the outcome of patients with HER2-positive BCA.

Trastuzumab, a humanized monoclonal antibody that targets the extracellular domain of HER2, improves overall survival in patients with early BCA (EBC)[2,4] and, when combined with chemotherapy, in patients with metastatic BCA[5,6]. As a result, trastuzumab is now the standard therapy for patients with HER2-positive BCA[7–9].

### Subcutaneous Trastuzumab

Despite the importance of trastuzumab for the treatment of HER2-positive BCA, the current IV formulation involves dose calculations, aseptic preparation of infusion fluids, long infusion durations, and often, the placement of a central line for administration, with potentially negative consequences for patients and health care providers (HCPs)[6]. In addition, administration of current HER2-targeted therapies consumes valuable resources in chemotherapy treatment units (for example, chair time, nursing resources). In an effort to provide a faster and easier administration method, a subcutaneous (SC) formulation of trastuzumab was developed[6,10] (Table I).

The SC formulation contains trastuzumab at a fixed dose of 600 mg in 5 mL solution, combined with recombinant human hyaluronidase PH20, an enzyme that temporarily degrades the extracellular matrix, allowing for the

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absorption of large volumes of solution[10,11]. The degradation of the extracellular matrix is temporary and facilitates injection of the solution with minimal tissue distortion, edema, or tissue irritation[12]. In contrast to the IV formulation of trastuzumab, the SC formulation does not require a loading dose and weight-adjusted dosing, simplifying administration by removing the need for reconstitution or dose calculation on the basis of body weight. Compared with the IV formulation, which is administered during a 90-minute period for the first infusion and a 30-minute period for subsequent infusions, the SC formulation is given in 2–5 minutes[10] (Table I). The reduction in administration time is a major benefit of the SC formulation; however, it is important to carefully follow the injection technique to ensure adequate drug exposure and to minimize injection-site reactions (ISRs)[10] (Table II).

The potential benefits of SC administration include improved patient convenience, better adherence, reduced pharmacy preparation time, and optimization of medical resources[11]. To date, more than 2 million patients with BCa have been treated with trastuzumab; approximately 80,000 of them were treated with the SC formulation (Hoffmann–La Roche. Data on file)[7]. In addition, many patients now receive the SC formulation of trastuzumab in dual HER2 treatment in the neoadjuvant, metastatic, and adjuvant settings. The SC formulation is approved in Europe, but is not yet available in the United States or Canada[10].

In this review, we discuss SC trastuzumab as a potential alternative to the IV formulation in Canada, including an in-depth review of key published papers and abstracts about the treatment of HER2-positive BCa. A discussion of the use of SC trastuzumab for the treatment of other malignancies is beyond the scope of the review.

## METHODS

Relevant literature was acquired in a search of the PubMed database and online abstracts from meetings of the San Antonio Breast Cancer Symposium (SABCS), the American Society of Clinical Oncology, and the European Society for Medical Oncology. The search terms used were "trastuzumab," "subcutaneous," "intravenous," and "breast cancer." Only articles comparing the SC and IV formulations were included. The literature search included papers published up to August 2018. Where newer papers with longer follow-up were available, older papers reporting on a shorter follow-up period were not included. Papers were divided by primary outcome into those focusing on pharmacokinetics, safety, efficacy, preference or time savings, and home administration. Pharmacokinetics and preference or time savings studies were required to have a randomized design. Efficacy studies were required to have a randomized phase III design or to have been performed in a real-world setting. Safety studies were required to have a phase III design, but patients were not required to have been randomized. All studies examining the home administration of SC trastuzumab were included. Studies whose primary focus was the cost of the SC formulation compared with the IV formulation were not included if conducted outside of Canada, because such papers were deemed not relevant for the Canadian health care setting. Articles published in languages other than English were excluded.

**TABLE I** Administration of trastuzumab, by route and breast cancer (BCa) status[a]

| Dose | Intravenous | | | Subcutaneous | |
|---|---|---|---|---|---|
| | Early BCa | | Metastatic BCa 3-Weekly | Early BCa 3-Weekly | Metastatic BCa 3-Weekly |
| | Weekly | 3-Weekly | | | |
| Loading | 4 mg/kg over 90 min | 8 mg/kg over 90 min | 8 mg/kg over 90 min | None | None |
| Maintenance | | | | | |
| First | 2 mg/kg over 90 min | 6 mg/kg over 90 min | 6 mg/kg over 90 min | 600 mg over 2–5 min given in the thigh (alternating left and right) | |
| Subsequent | 2 mg/kg over 30 min | 6 mg/kg over 30 min | 6 mg/kg over 30 min | | |

[a] Adapted from European Medicines Agency, 2010[10].

**TABLE II** Administration technique for subcutaneous trastuzumab

| Factor | Approach |
|---|---|
| Patient education | ■ Educate patient on clothing selection to increase comfort and privacy. |
| Injection site | ■ Alternate between left and right thigh to maximize drug exposure (based on GAIN-2 trial).<br>■ Give at least 2.5 cm from the old site and never inject into areas where the skin is red, bruised, tender, or hard.<br>■ Ensure that other products for subcutaneous administration are injected into different sites during the course of treatment. |

[a] Adapted from European Medicines Agency, 2010[10].

## RESULTS

Of 49 papers identified in PubMed, 10 met the inclusion criteria (Tables III–VII). In addition, 7 abstracts from the SABCS, American Society of Clinical Oncology, and European Society for Medical Oncology meetings were included. A total of 70 patients from 18 Canadian centres participated in the relevant trials.

### Pharmacokinetics

A number of pharmacokinetics studies have examined the SC formulation of trastuzumab to determine the optimal dose and administration method (Table III). The 600 mg fixed SC dose was identified based on the results of a phase I/IB dose-finding study showing that an 8 mg/kg SC dose of trastuzumab resulted in an exposure comparable to that with an IV dose of 6 mg/kg[29]. Data generated from pharmacokinetics modelling and simulation suggested that a fixed SC dose of 600 mg given every 3 weeks would provide a serum trough concentration ($C_{trough}$) and an exposure equivalent to or greater than that for the standard IV formulation. The 600 mg SC dose every 3 weeks was retrospectively validated using data from the randomized phase III HannaH trial, which compared the SC and IV formulations administered neoadjuvantly with chemotherapy in 596 patients with operable HER2-positive BCA[11]. After a median follow-up of 12.2–12.4 months, the analysis showed that the pharmacokinetics profile of the 600 mg SC dose was noninferior to that of the standard IV dose [geometric mean ratio for $C_{trough}$: 1.33; 90% confidence interval (CI): 1.24 to 1.44; noninferiority margin: 0.80], with no loading dose required. Moreover, a multiple logistic regression analysis showed no correlation between serum trastuzumab exposure and body weight with respect to the rates of pathologic complete response (PCR) or serious adverse events. The foregoing results suggest that a fixed SC dose of 600 mg has a pharmacokinetics profile noninferior to that for the standard IV dose, with no effect of body weight on efficacy or safety.

The GAIN-2 study compared two intense dose-dense anthracycline/taxane–containing regimens in patients with HER2-positive EBC. After completion of the anthracycline and IV trastuzumab given concurrently with the taxane, 30 patients were randomized to continue adjuvant SC trastuzumab (600 mg) injected every 3 weeks into either the thigh or the abdominal wall to determine the optimal administration method for the SC formulation[13]. Results of the study presented at the 2017 SABCS meeting showed that the bioavailability of the SC formulation, as reflected by peak ($C_{max}$) and total exposure [area under the curve (AUC)] in cycle 7, was approximately 30% higher if administered into the thigh rather than into the abdominal wall (geometric mean ratio for $C_{max}$: 1.29; 90% CI: 1.05 to 1.58; geometric mean ratio for $AUC_{0–last}$: 1.29; 90% CI: 1.02 to 1.63), with no increase in toxicity. The results of the GAIN-2 study therefore suggest that the SC formulation should be injected into the thigh rather than the abdomen[10].

### Safety

A number of phase III studies have examined the safety profile of the SC formulation of trastuzumab as a primary

**TABLE III** Randomized studies examining the pharmacokinetics of subcutaneous (SC) compared with intravenous (IV) trastuzumab

| Reference (trial name) | Patients | | Treatment | Median follow-up | Pharmacokinetics | Safety |
|---|---|---|---|---|---|---|
| | (*n*) | Characteristics | | | | |
| Ismael *et al.*, 2012[11] [HannaH (NCT00950300)] | 596 | ■ HER2-positive early breast cancer<br>■ Operable<br>■ Locally advanced or inflammatory | ■ 8 cycles neoadjuvant chemotherapy<br>■ Concurrent trastuzumab: 3-weekly standard IV vs. SC (600 mg)<br>■ Adjuvant or neoadjuvant trastuzumab up to 1 year | 12.2–12.4 Months | ■ IV $C_{trough}$: 51.8 μg/mL (CV: 52.5%) before surgery<br>■ SC $C_{trough}$: 69.0 μg/mL (CV: 55.8%) before surgery<br>■ Geometric mean ratio: 1.33 (90% CI: 1.24 to 1.44)<br>■ $C_{trough}$ noninferior (margin: 0.80) | ■ Incidence of grades 3–5 AEs similar between the groups<br>■ More SAEs in SC group: 37 (12%) IV vs. 62 (21%) SC [mainly infections and infestations: 13 (4.4%) IV vs. 24 (8.1%) SC] |
| Mobus *et al.*, 2018[13] [GAIN-2 (NCT01690702)] | 30 | ■ High-risk early breast cancer | ■ Intense dose-dense anthracycline- or taxane-containing regimens with IV trastuzumab followed by adjuvant SC trastuzumab (600 mg) injected into thigh vs. abdomen | Not given | ■ Geometric least square means $C_{max}$ and AUC 0–21 days higher for administration in thigh than in abdomen<br>■ Geometric mean ratio for $C_{max}$: 1.29 [90% CI: 1.05 to 1.58]<br>■ Geometric mean ratio for $AUC_{0–last}$: 1.29 [90% CI: 1.03 to 1.63] | ■ Any grade AE: 96.7% overall<br>■ High-grade AE: 16.7% overall<br>■ No increase in toxicity for one group over the other |

HER2 = human epidermal growth factor receptor 2; $C_{trough}$ = serum trough concentration; CV = coefficient of variation; CI = confidence interval; AEs = adverse events; SAEs = serious adverse events; $C_{max}$ = peak drug concentration; AUC = area under the curve.

endpoint (Table IV). The SafeHer study assessed the safety of adjuvant SC trastuzumab (600 mg every 3 weeks) delivered by handheld syringe or single-use injection, with or without chemotherapy in 2573 patients with HER2-positive EBC[15]. Overall, 2282 of those patients (88.7%) experienced an adverse event (AE), with 128 (5.0%) discontinuing the drug. In addition, 596 patients (23.2%) experienced a grade 3 or greater AE, with 24 (0.9%) reporting a cardiac disorder. Grade 3 or greater AEs of interest included blood and lymph system disorders (7.3%), followed by infections and infestations (3.0%), and gastrointestinal disorders (2.9%). Approximately 20% of patients experienced ISRs, most of which were grade 1 or 2, with the exception of 1 grade 3 event (injection site discomfort). The PrefHer study also examined SC trastuzumab in 488 patients with HER2-positive EBC who had completed neoadjuvant chemotherapy[7,16,22,23]. Patients were randomized to receive 4 cycles of SC trastuzumab (600 mg every 3 weeks) administered by single-use injection device or handheld syringe, followed by 4 cycles of standard-dose IV trastuzumab, or vice versa. A safety analysis of PrefHer showed fewer AEs during treatment with the IV formulation, regardless of the sequence of treatment[16]. However, the difference in the frequency of AEs was attributed mostly to local ISRs and administration-related reactions (ARRs) reported with the SC formulation. After those AEs were excluded, no clear differences in AEs, serious AEs, or drug discontinuation were evident between the treatment arms.

A number of ongoing phase III studies are examining the safety of SC trastuzumab when combined with chemotherapy (Table IV). The multinational UmbHER1 study is assessing the safety and tolerability of the SC formulation given sequentially by handheld syringe and by single-use injection device in 240 patients with HER2-positive EBC[17]. All patients received adjuvant or neoadjuvant treatment with anthracycline-containing regimens, followed by SC trastuzumab in combination with taxanes and then as monotherapy for a total of 18 cycles. Interim results were presented at the 2017 SABCS meeting. Overall, grade 3 or greater AEs were experienced by 26.8% of the patients, with 7.5% reporting a serious AE. In addition, 8.8% of patients reported a decrease in left ventricular ejection fraction, mostly related to the study drug (18 of 20 patients); however, no cases of chronic heart failure were reported. Notably, 21.9% and 68.0% of the patients experienced all-grade ISRs and ARRs respectively. In addition, the MetaPHER study is examining the safety of SC trastuzumab 600 mg combined with IV pertuzumab (840 mg loading dose, followed by 420 mg subsequently) and IV docetaxel (75 mg/m$^2$ up to 100 mg/m$^2$) every 3 weeks in 150 patients with HER2-positive metastatic or locally recurrent BCa[14]. Interim results presented at the 2016 SABCS meeting showed no new safety signals with the SC formulation, with all-grade ARRs and ISRs related to SC trastuzumab reported in 3.3% of the patients (all being grade 1 or 2).

## Efficacy

The HannaH trial examined the efficacy of SC trastuzumab in the neoadjuvant setting and included PCR and $C_{trough}$ as co-primary endpoints[11] (Table V). After a median follow-up of 12.2–12.4 months, the SC formulation was shown to be noninferior to the IV formulation, with PCR being 45.4% and 40.7% respectively (difference of 4.7%; 95% CI: 4.0% to 13.4%; noninferiority margin: –12.5%). Moreover, a 6-year follow-up analysis of the HannaH study showed noninferiority for the 6-year event-free survival and OS rates, which were 65% and 84% for the two formulations respectively (event-free hazard ratio: 0.98; 95% CI: 0.74 to 1.29; OS hazard ratio: 0.94; 95% CI: 0.61 to 1.45)[20]. In addition, all efficacy outcomes were consistent in the bodyweight subgroups[11,19]. The efficacy of SC trastuzumab is also being examined in the German HerSCin trial, a real-world study in 130 patients with HER2-positive EBC[18]. Interim results presented at the 2016 American Society of Clinical Oncology meeting showed that 33% of patients receiving neoadjuvant therapy ($n$ = 18) have achieved a PCR after a median treatment duration of 8.5 months. No new safety signals were reported, with treatment-related AEs and serious AEs occurring in 17% and 2% of patients respectively[18].

## Preference and Time Savings

A number of randomized studies have examined patient or HCP preference or time savings for the SC formulation compared with the IV formulation of trastuzumab (Table VI). In the MetaspHer trial, 113 patients with HER2-positive metastatic BCa who completed first-line chemotherapy and trastuzumab and achieved a long-term response (>3 years) were randomized to receive 3 cycles of adjuvant SC trastuzumab (600 mg) followed by 3 cycles of standard IV trastuzumab, or the reverse order[27]. The SC formulation was preferred by 85.9% of the patients (95% CI: 78.8% to 93.0%; $p < 0.001$), with only 14.1% of the patients (95% CI: 7.0% to 21.3%) preferring the IV formulation. Moreover, 63.6% of HCPs (95% CI: 53.6% to 73.7%) were most satisfied with the SC formulation. In the PrefHer study, the primary endpoint was the proportion of patients indicating an overall preference for SC or IV trastuzumab, assessed by patient interview[22,23]. In the initial analysis, published in 2013 ($n$ = 248), the SC formulation administered by single-use injection device was preferred by 216 patients (91.5%; 95% CI: 87.2% to 94.7%; $p < 0.0001$); only 16 patients (6.8%; 95% CI: 3.9% to 10.8%) preferred the IV formulation[22]. A subsequent analysis published in 2014 ($n$ = 488) confirmed those findings, demonstrating that the SC formulation was preferred by 415 of 467 patients (88.9%; 95% CI: 85.7% to 91.6%; $p < 0.0001$), with only 45 patients (9.6%; 95% CI: 7% to 13%) preferring the IV formulation[23]. The later analysis also showed that 64.9% of the patients (95% CI: 60.4% to 69.2%) expressed a "very strong" preference for the SC formulation. Reasons given by patients for preferring the SC formulation included "less pain" (61% of patients) and less bruising (41% of patients). In the PrefHer study, the SC formulation was also reported to be preferred by 77% of HCPs (95% CI: 71.1% to 82.2%).

A number of studies have used data from the PrefHer study to determine the time savings for the SC compared with the IV formulation of trastuzumab (Table VI). A prospective observational time-and-motion study in 8 countries ($n$ = 488) involved in the PrefHer trial quantified patient time in the infusion chair and active HCP time[25]. Results showed that a mean of 55–57 minutes of patient chair time was saved with the SC formulation ($p < 0.0001$).

**TABLE IV** Phase III studies examining the safety of subcutaneous (SC) compared with intravenous (IV) trastuzumab

| Reference (trial name) | Patient | | Treatment | Median follow-up | Safety |
|---|---|---|---|---|---|
| | *(n)* | Characteristics | | | |
| Kümmel *et al.*, 2016[14] [MetaPHER (NCT02402712)] | 150 | ■ HER2-positive metastatic or locally recurrent breast cancer | ■ SC trastuzumab (600 mg) every 3 weeks, plus IV docetaxel (75 mg/m$^2$ up to 100 mg/m$^2$), plus IV pertuzumab (840 mg loading dose, 420 mg subsequently) | 3 Weeks | ■ No new safety signals<br>■ All-grade AEs: 90.7%<br>■ Grade 3 or greater AEs: 39.3%<br>■ Grade 1 or 2 administration-related reactions: 3.3% |
| Gligorov *et al.*, 2017[15] [SafeHER (NCT01566721)] | 2573 | ■ HER2-positive stage I–III early breast cancer | ■ SC (600 mg) every 3 weeks for 18 cycles with or without adjuvant chemotherapy<br>■ Cohort A: vial and handheld syringe<br>■ Cohort B: Single-use injection device | 28 Days | ■ 89% experienced AEs<br>■ 5% of AEs led to discontinuation<br>■ Grade 3 or greater AEs: 23.2%<br>■ SAEs: 12.7%<br>■ Grade 1–2 injection site reactions: 20.2% in Cohort A (1 Grade 3) vs. 19.5% in Cohort B |
| Gligorov *et al.*, 2017[16] [PrefHer safety (NCT01401166)] | 488 | ■ HER2-positive early breast cancer, adjuvant | ■ Neoadjuvant chemotherapy followed by SC trastuzumab (600 mg) for 4 cycles followed by IV (standard dosing) for 4 cycles compared with the reverse<br>■ Cohort 1: SC trastuzumab by injection device<br>■ Cohort 2: SC trastuzumab by handheld syringe | During treatment | ■ Fewer AEs with IV formulation<br>■ Differences mostly attributable to variance in injection-site and administration-related reactions<br>■ After first period, when such reactions are excluded, AEs were similar in the SC and IV groups<br>■ SAEs similar between groups<br>■ No Grade 4 or 5 AEs |
| Zambetti *et al.*, 2017[17] [UmbHER1 (NCT0190497)] | 240 | ■ HER2-positive early or locally advanced breast cancer | ■ Adjuvant or neoadjuvant chemotherapy followed by SC trastuzumab and taxanes followed by trastuzumab monotherapy for 18 cycles<br>■ Cohort A: SC trastuzumab by handheld syringe<br>■ Cohort B: SC trastuzumab by injection device | Not given | ■ No new safety signals<br>■ Grade 3 or greater AEs: 26.8%<br>■ SAEs: 7.5%<br>■ Administration-related reactions: 68% (mild or moderate)<br>■ Injection-site reactions: 21.9% (mild or moderate) |

HER2 = human epidermal growth factor receptor 2; AEs = adverse events; SAEs = serious adverse events.

**TABLE V** Randomized and real-world studies examining the efficacy of subcutaneous (SC) compared with intravenous (IV) trastuzumab

| Reference (trial name) | Patient | | Treatment | Median follow-up | Efficacy | Safety |
|---|---|---|---|---|---|---|
| | *(n)* | Characteristics | | | | |
| Ismael *et al.*, 2012[11] [HannaH (NCT00950300)] | 596 | ■ HER2-positive early breast cancer<br>■ Operable<br>■ Locally advanced or inflammatory | ■ 8 Cycles neoadjuvant chemotherapy<br>■ Concurrent trastuzumab: 3-weekly standard IV vs. SC (600 mg)<br>■ Adjuvant or neoadjuvant trastuzumab up to 1 year | 12.2–12.4 Months | ■ pCR: 40.7% IV vs. 45.4% SC<br>■ pCR difference: 4.7% (95% CI: 4.0 to 13.4)<br>■ pCR noninferior (margin: –12.5%)<br>■ Consistent across body-weight groups | ■ Incidence of grade 3 or greater AEs similar between groups<br>■ More SAEs in SC group: 37 (12%) IV vs. 62 (21%) SC [mainly attributable to infections and infestations: 13 (4.4%) IV vs. 24 (8.1%) SC] |
| Schmidt *et al.*, 2016[18] [HerSCin (NCT01959386)] | 130 | ■ Routine practice (Germany)<br>■ Adjuvant or neoadjuvant | ■ Use of SC trastuzumab | Median duration of treatment: 8.5 months | ■ pCR: 33% in neoadjuvant (*n*=18) | ■ Treatment-related AEs: 17%<br>■ Treatment-related SAEs: 2% |
| Jackisch *et al.*, 2016[19] (HannaH follow-up) | 596 | As for Ismael *et al.*, 2012 | As for Ismael *et al.*, 2012 | 40 Months | ■ 3-Year EFS: 73% IV vs. 76% SC (HR: 0.95; 95% CI: 0.69 to 1.30)<br>■ 3-Year OS: 90% IV vs. 92% SC (HR: 0.76; 95% CI: 0.44 to 1.32)<br>■ Supports noninferior efficacy of IV vs. SC | ■ AEs balanced between arms |
| Jackisch *et al.*, 2018[20] (HannaH follow-up) | 596 | As for Ismael *et al.*, 2012 | As for Ismael *et al.*, 2012 | 70.8–71.4 Months | ■ 6-Year EFS: 65% IV vs 65% SC (HR: 0.98; 95% CI: 0.74 to 1.29)<br>■ 6-Year OS: 84% IV vs. 84% SC (HR: 0.94; 95% CI: 0.61 to 1.45) | ■ All-grade AEs: 95% IV vs. 98% SC<br>■ Grade 3 or greater AEs: 54% IV vs. 53% SC |

HER2 = human epidermal growth factor receptor 2; pCR = pathologic complete response; CI = confidence interval; AEs = adverse events; SAEs = serious adverse events; EFS = event-free survival; HR = hazard ratio; OS = overall survival.

**TABLE VI** Randomized studies examining preference and time savings for subcutaneous (SC) compared with intravenous (IV) trastuzumab

| Reference (trial name) | Patients | | Treatment | Patient satisfaction or time savings | Safety |
|---|---|---|---|---|---|
| | *(n)* | Characteristics | | | |
| Pivot *et al.*, 2012[21] [HannaH (NCT00950300)] | 596 | ■ HER2-positive early breast cancer<br>■ Operable<br>■ Locally advanced or inflammatory | ■ 8 Cycles neoadjuvant chemotherapy with concurrent trastuzumab<br>■ 3-Weekly standard IV compared with SC trastuzumab (600 mg)<br>■ Adjuvant or neoadjuvant trastuzumab up to 1 year | ■ Average duration: 60–90 minutes for IV vs. 3.3 minutes for SC | ■ Low incidence of injection-site reactions (1.9%)<br>■ Most injection-site reactions with injection time ≥6 minutes (20%) |
| Pivot *et al.*, 2013[22] and Pivot *et al.*, 2014[23] [PrefHER (NCT01401166)] | 248<br>488 | ■ HER2-positive early breast cancer, adjuvant | ■ Neoadjuvant chemotherapy followed by SC trastuzumab (600 mg) for 18 cycles followed by IV (standard dosing) compared with the reverse<br>■ Cohort 1: SC by injection device<br>■ Cohort 2: SC by handheld syringe | ■ SC preferred by 89% (95% CI: 85.7 to 91.6; $p<0.0001$)<br>■ Very strong patient preference in 65%<br>■ Time-saving as strong reason<br>■ Less pain (61%), less bruising (41%) with SC<br>■ 77% Health care provider preference for SC (95% CI: 71.1% to 82.2%) | ■ AEs in 51.3% IV vs. 61.0 SC ($p<0.05$)<br>■ Difference attributable to injection-site reactions<br>■ With injection-site reactions excluded, rates of AEs were similar |
| Burcombe *et al.*, 2013[24] [PrefHer U.K. Time and Motion (NCT01401166)] | 24 from PrefHer | ■ As for Pivot *et al.* 2013 and 2014<br>■ Conducted in the United Kingdom | ■ As for Pivot *et al.*, 2013 and 2014 | ■ Chair time: 75.0 minutes IV vs. 19.8 minutes SC (saved 55 minutes)<br>■ Mean administration time: 58.1±5.8 minutes IV vs. 24.6±13.2 minutes SC<br>■ IV also required an additional 34.5±13.6 minutes for preparation | Not applicable |
| De Cock *et al.*, 2016[25] [PrefHer Time and Motion (NCT01401166)] | 488 | ■ As for Pivot *et al.*, 2013 and 2014<br>■ Conducted in 8 countries | ■ As for Pivot *et al.*, 2013 and 2014 | ■ SC saved 55–57 minutes of chair time compared with IV ($p<0.0001$)<br>■ 13–17 Minutes health care provider time saved with SC compared with IV ($p<0.0001$) | Not applicable |
| Lopez-Vivanco *et al.*, 2017[26] [PrefHer Spain Time and Motion (NCT01401166)] | 307 from PrefHer | ■ As for Pivot *et al.* 2013 and 2014<br>■ Conducted in Spain | ■ As for Pivot *et al.*, 2013 and 2014 | ■ 50% reduction in health care provider time: 27.2 minutes IV (95% CI: 21.8 to 32.6) vs. 13.2 minutes SC (95% CI: 8.9 to 17.5)<br>■ Reduction in chair time to about one fifth former time (78%–85%)<br>■ Reduction in treatment room time to about one quarter former time (59%–81%) | Not applicable |
| Pivot *et al.*, 2017[27] [MetaspHer (NCT01810393)] | 113 | ■ HER2-positive metastatic breast cancer | ■ 3 Cycles adjuvant SC trastuzumab (600 mg) followed by standard IV trastuzumab compared with the reverse | ■ SC preferred by 85.9% of patients (95% CI: 78.8% to 93.0%; p<0.001)<br>■ IV preferred by 14.1% of patients (95% CI: 7.0% to 21.3%)<br>■ Health care providers most satisfied with SC (63.6%; 95% CI: 53.6% to 73.7%) | ■ AEs in 44.1% IV vs. 67.6% SC<br>■ AEs consistent with safety profiles of SC and IV formulations |

HER2 = human epidermal growth factor receptor 2; CI = confidence interval; AEs = adverse events.

In addition, active HCP time was reduced by a mean of 13–17 minutes per session with the SC formulation ($p < 0.0001$). A smaller prospective time-and-motion study involving 24 patients from PrefHer was also completed in multiple centres in the United Kingdom[24]. Results showed that the mean active HCP time for IV administration was 92.6 minutes; it was 24.6 minutes for SC administration. In addition, mean time spent in the care unit and infusion chair was 94.5 minutes and 75 minutes respectively for the IV formulation, and 30.3 minutes and 19.8 minutes for the SC formulation. The overall time savings for the SC formulation compared with the IV formulation was reported to be 68 minutes. A third substudy from PrefHer that was conducted in 3 Spanish centres ($n = 307$) showed a 50% reduction in active HCP time for the SC compared with the IV formulation [13.2 minutes (95% CI: 8.9 minutes to 17.5 minutes) vs. 27.2 minutes (95% CI: 21.8 minutes to 32.6 minutes) per cycle respectively][26]. Factors that reduced the time spent by HCPs included avoiding IV catheter installation and removal, line flushing, and drug reconstitution. In addition, chair and patient treatment room time showed reductions to approximately one fifth (78%–85% savings) and one fourth (59%–81% savings) respectively, resulting in a total of 24 hours saved throughout the treatment course.

Furthermore, a secondary analysis from the HannaH study, presented at the 2012 European Society for Medical Oncology meeting, also confirmed that considerably less administration time is required with the SC formulation than with the IV formulation (3.3 minutes vs. 60–90 minutes, Table VI)[21].

### Home Administration

Although at the time of writing home administration was not approved in any country, the safety and tolerability of a home administration protocol for SC trastuzumab is being examined in the BELIS study[28] (Table VII). The BELIS study is the first to examine the use of SC trastuzumab in a home-based setting. In the trial, 102 Belgian patients with HER2-positive EBC who had previously completed 6 cycles of IV trastuzumab received 12 additional cycles of trastuzumab (600 mg) administered at home by a HCP. Interim results presented at the 2016 SABCS meeting showed that a total of 91 patients (89%) reported 549 all-grade AEs, 194 of which (35%) were considered to be treatment-related. In addition, 8 serious AEs were reported in 8 patients. The authors concluded that the home administration protocol of SC trastuzumab was not associated with any new safety signals and was considered to be beneficial by patients and HCPs. During the hospital administration phase, 99% of patients were satisfied with both the SC and the IV formulations. However, during home administration, all patients (100%) reported that receiving treatment at home was beneficial to a "large" or "very large" extent. Moreover, all HCPs considered the SC administration method, compared with the IV method, to be faster and to require fewer resources for preparation.

## DISCUSSION

Data from IV and SC comparative trials demonstrate that the two formulations have equivalent pharmacokinetic profiles and efficacy (Tables III–VII). In addition, although some studies suggest a slightly higher frequency of AEs with the SC formulation, those AEs are mostly low-grade ISRs and ARRs. Education about proper administration techniques, as described in Table II, should aid in further reducing the risk of local reactions. Moreover, once the AEs are removed from the analysis, the safety profiles of the two formulations appear comparable.

In recent years, the number of chemotherapies being delivered intravenously have increased, which has led to a shortage of infusion chairs for patients. A SC formulation therefore reduces the need for infusion chair time, leaving greater availability of chairs for patients requiring other IV therapies. In addition, the shorter administration time provides greater flexibility for scheduling appointments, relieving pressure on the clinic at peak times. Finally, shorter preparation and administration times reduce the resources needed, increasing efficiency and reducing costs to health care centres.

A number of additional factors that could affect patients, pharmacists, and nurses should also be considered

**TABLE VII** Home administration studies examining subcutaneous (SC) trastuzumab

| Reference (trial name) | Patient | | Treatment | Median follow-up | Patient satisfaction | Safety |
|---|---|---|---|---|---|---|
| | *(n)* | Characteristics | | | | |
| Cocquyt *et al.*, 2017[28] [BELIS (NCT01926886)] | 102 | ■ HER2-positive early breast cancer<br>■ Completion of 6 cycles IV trastuzumab | ■ 3 Additional cycles IV trastuzumab in the hospital (standard dosing)<br>■ Followed by 3 cycles SC trastuzumab (600 mg) in the hospital<br>■ Followed by 6 cycles SC trastuzumab (600 mg) administered at home by a health care practitioner | 4 Weeks from last treatment | ■ 99% of patients satisfied to large or very large extent with IV and SC at hospital<br>■ 100% of patients satisfied to large or very large extent with SC at home<br>■ 100% of patients thought that SC at home was beneficial<br>■ Health care practitioners felt that the SC route was quicker and required less preparation | ■ All-grade AEs: 89%<br>■ No new safety signals<br>■ Treatment-related AEs: 35% of all-grade AEs<br>■ 8 SAEs |

HER2 = human epidermal growth factor receptor; IV = intravenous; AEs = adverse events; SAEs = serious adverse events.

when comparing the SC and IV formulations of trastuzumab. Those factors are presented in Table VIII and are discussed in the subsections that follow.

## Effect for Patients

The time required for patients with BCA to undergo IV therapy is substantial, taking time away from work, family, and other commitments. The commitment required for caregivers to support patients who are receiving IV therapy is often similarly significant. From the patient's perspective, the shorter administration time and greater scheduling flexibility with the SC formulation offer clear benefits, with a positive effect on quality of life. Another negative factor for patients is the invasive procedure of having a central line inserted for IV therapy, which is mandated in certain Canadian centres. In centres that do not mandate a central line, patients could be subjected to multiple cannulations with the IV formulation. As shown in clinical trials, factors such as pain, discomfort, and bruising are reduced with the SC formulation, offering an additional benefit. However, patients will have to be comfortable with injections into the thigh, and it would be helpful to educate patients about clothing selection for easier access to the injection site. In the long term, some patients might experience some discomfort in the thigh area from multiple injections; however, that adverse effect is unlikely to result in treatment discontinuation. It is important, however, to ensure that patients adhere to treatment, given any scheduling changes that would occur with the SC formulation.

## Effect for Pharmacists

Considering the variation in administration methods (SC versus IV), dosing schedules (weekly versus every 3 weeks), and formulations (trastuzumab emtansine versus trastuzumab alone), avoiding medication errors is a key concern. Setting up a standardized computer system and protocols for proper storage, selection, and dosing are therefore crucial to avoid errors. However, once selected, the SC formulation is convenient and easy to prepare, being provided in a ready-to-use vial that requires no dose calculation, preparatory compounding by the pharmacy, or IV bag preparation—thus reducing potential dosing errors and waste[10]. In addition, the syringe is stable for 48 hours at a temperature of 2°C to 8°C and for 6 hours at ambient temperature (30°C maximum), allowing for convenient storage and use, and the potential to prepare multiple syringes at one time.

## Effect for Nurses

The injection of SC trastuzumab into the thigh creates a need for education about patient privacy and clothing selection. In addition, the large injection volume of the SC formulation might create some concerns for nurses in regard to repetitive motion injuries and back strain. There is therefore a need to educate nurses in proper body mechanics and administration techniques to reduce the chance of injuries. In addition, policy statements will be needed that can cover the large-volume SC injections and changes in patient scheduling. However, the availability of other SC therapies such as rituximab should aid in the training and scheduling process.

The advantage of the SC formulation is that nurses would be able to book more patients into the same time slot that would typically have been used for a single IV administration. Additionally, elimination of the need for proper catheter placement should reduce placement errors and allow for vein preservation.

**TABLE VIII** Comparison of the subcutaneous (SC) and intravenous (IV) formulations of trastuzumab

| Factor | Formulation | |
|---|---|---|
| | Subcutaneous | Intravenous |
| Dosing | ■ No IV bag preparation<br>■ No preparatory compounding needed<br>■ Ready-to-use vial<br>■ Fixed dose requiring no calculations<br>■ No loading dose required | ■ IV bag preparation<br>■ Bodyweight-based dosing calculations might increase errors<br>■ Loading dose required |
| Wastage | ■ None | ■ Potential leftovers in vial |
| Administration | ■ About 2–5 minutes<br>■ Less pain, discomfort, bruising for patients<br>■ Greater vein preservation because of lack of need for IV catheter<br>■ Potential repetitive injuries and back strain with large-volume injections<br>■ Patient privacy and clothing related to thigh injections<br>■ Increased availability of infusion chairs | ■ About 30–90 minutes<br>■ More pain, discomfort, bruising for patients<br>■ IV catheter placement errors<br>■ Fewer infusion chairs available |
| Safety | ■ More injection site reactions or administration-related reactions | ■ Slightly better safety profile |
| Chair time | ■ 55–57 Minutes shorter for SC | |
| Health care practitioner time | ■ 13–17 Minutes shorter for SC | |

## Home Administration

The fact that trastuzumab is considered to be nontoxic suggests that home administration could be feasible when performed by a HCP; however, at present, such a protocol is purely hypothetical given that it is not yet funded anywhere in the world and that it would take careful planning. As described in the BELIS study, home administration might be advantageous for patients and could further reduce the burden on infusion clinics[28]. Such an option might be particularly valuable for maintenance dosing in the adjuvant or metastatic setting by reducing the number of hospital visits. However, should such an option become available, protocols for safe administration and management of potential toxicities would have to be implemented. Furthermore, patients would have to be educated about possible adverse events, and a system for home monitoring of toxicities would have to be created. It might be advisable to give the first 2 cycles in a hospital setting before moving to home-based administration. Protocols for drug preparation, stability, and patient access should also be established. Should a home administration protocol of SC trastuzumab be approved by Health Canada, funding for such a system would also have to be implemented. Currently, a home administration protocol is purely theoretical; however, it could prove advantageous in the future.

## SUMMARY

Trastuzumab has dramatically improved the outcome of patients with HER2-positive BCA and is the standard of care in Canada. However, its IV administration is time-consuming, using valuable health care resources and infusion chairs. The SC formulation of trastuzumab has proved to be noninferior to the IV formulation with respect to pharmacokinetics and efficacy, and its safety profile is similar to that for the IV formulation, with the exception of mild ISRS and ARRS. In addition, the SC formulation is preferred by patients and HCPS, saving time and valuable resources.

The shorter preparation and administration time for the SC formulation provides benefits for patients, HCPS, and health care centres. Given the shorter delivery time and lack of need for dedicated infusion facilities, the SC formulation could improve convenience and quality of life for patients. Ultimately, a SC formulation would simultaneously improve efficiency and reduce the burden on health care systems.

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