Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase

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Background: Rituximab and trastuzumab were the first therapeutic monoclonal antibodies (mAbs) approved in oncology. Both antibodies are delivered by the intravenous (IV) route, but recently subcutaneous (SC) formulations have been developed. Subcutaneous administration of mAbs can offer substantial patient and resource benefits compared with IV, but SC administration of some mAbs can be limited by drug volume. Recombinant human hyaluronidase (rHuPH20) temporarily degrades hyaluronan, allowing SC delivery of drug volumes that might not otherwise be feasible.

Methods: Clinical trials assessing coformulation of rituximab or trastuzumab with rHuPH20 for SC administration were reviewed.

Results: Phase I trials of rituximab SC maintenance therapy in patients with follicular lymphoma and trastuzumab SC in healthy volunteers and patients with early breast cancer have demonstrated substantially shorter administration times and comparable tolerability and pharmacokinetics compared with IV formulations. Rituximab SC 1400-mg and trastuzumab SC 600-mg doses were identified for further study. Phase III clinical data for rituximab SC 1400 mg have shown comparable efficacy to rituximab IV, and initial clinical data suggest comparable efficacy of trastuzumab SC 600 mg and the IV formulation.

Conclusion: Coformulation with rHuPH20 may enable effective, well-tolerated, cost-effective, and convenient SC administration of rituximab and trastuzumab. Additional studies are ongoing.

INTRODUCTION

Rituximab and trastuzumab were the first monoclonal antibodies (mAbs) approved for the treatment of cancer (US FDA, 2011) and have since become the standard of care (Vogel, 2010; National Comprehensive Cancer Network, 2012). Rituximab targets CD20 and is indicated for patients with non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia (F. Hoffmann-La Roche, 2008). Trastuzumab is targeted to HER2 (human epidermal growth factor receptor 2) and is indicated for the treatment of HER2-positive early and metastatic breast cancer and metastatic gastric cancer (F. Hoffmann-La Roche, 2011). In oncology, mAbs are typically administered by intravenous (IV) infusion; however, this administration route faces some challenges (Vogel, 2010; Haller, 2007; Sehn et al, 2007; Vescia et al, 2008), including:

- The need for trained personnel, dedicated infusion facilities, dose calculation, aseptic preparation of required infusion volumes, and extended post-infusion observation;
- Long infusion times and slow workflow for medical staff;
- Potential difficulties with IV catheter placements;
- Risk of infusion-related reactions and complications (e.g. relevant thromboembolic events, infections), leading to hospitalisation and additional costs;
- Costs associated with the placement of permanent IV lines.

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Subcutaneous (SC) administration can potentially overcome many of these challenges (Haller, 2007; Bookbinder et al., 2006). Although administration-associated reactions (AARs) may occur with SC administration, they are likely to be less severe than IV-associated infusion-related reactions, given the more gradual absorption of the SC formulation. SC formulations may be more convenient for patients, offering potential improvements in quality of life and treatment adherence (Bookbinder et al., 2006; Haller, 2007). In oncology, SC administration of mAbs has been shown to reduce administration times (Salar et al., 2010; Wynne et al., 2013) and health-care costs relative to IV infusion (Lundin et al., 2002; Stilgenbauer et al., 2009). However, this delivery method is challenged by limitations on drug volume (Bookbinder et al., 2006; Haller, 2007). This article will review how recent technological advances can potentially make SC administration of mAbs more feasible and more beneficial than IV formulations in the oncology setting.

**Subcutaneous Administration of mAbs**

Clinical development programmes exploring SC formulations of rituximab or trastuzumab coformulated with rHuPH20 are underway. These programmes are underpinned by pharmacokinetic studies: the clinical benefit of rituximab IV and trastuzumab IV is assumed to be dependent on serum concentrations of the respective antibodies (Mager and Jusko, 2001; Yin et al., 2010). As serum trough concentrations (C_{trough}) reflect the degree of accessible target site saturation, it is hypothesised that attaining C_{trough} levels with SC dosing that are at least as high as those of approved IV doses will provide comparable saturation of target sites and, thus, comparable efficacy. It has been shown that rHuPH20 improves the bioavailability of coadministered SC drugs. With rHuPH20, it may be possible to achieve serum concentrations equivalent to those seen with IV formulations (Bookbinder et al., 2006; Haller, 2007; Thomas et al., 2007; Thomas et al., 2009; Vaughn et al., 2009; Harb et al., 2010).

Rituximab SC coformulated with rHuPH20: preclinical and clinical development

**Preclinical efficacy and pharmacodynamics.** For rituximab SC to be efficacious, rituximab must be effectively distributed from a single SC injection site to lymphoid tissues throughout the body. In cynomolgus monkeys given two doses of rituximab SC or rituximab IV (10 mg.kg^{-1}) 7 days apart (Table 1; Del Nagro et al., 2010), C_{trough} levels and the extent of B-cell depletion in distal secondary lymphoid tissues and peripheral blood were similar for both formulations, demonstrating that administration route does not affect non-clinical efficacy (Del Nagro et al., 2010).

In stage 1 of a randomised, dose-finding, open-label, phase Ib trial (BP22333), 124 patients with previously treated or untreated follicular lymphoma who responded to a rituximab-containing induction regimen and had received >1 dose of rituximab IV as maintenance received a single dose of rituximab 375 mg.m^{-2} IV, 375 mg.m^{-2} SC, 625 mg.m^{-2} SC, or 800 mg.m^{-2} SC, with subsequent IV doses (375 mg.m^{-2}) every 2 or 3 months for up to 2 years. Rituximab C_{trough} levels and the extent of serum exposure (bimonthly: area under the curve (AUC)_{0-2y}; trimonthly: AUC_{0-3y}) with SC doses of 625 mg.m^{-2} and 800 mg.m^{-2} were within the range of those in patients receiving rituximab IV 375 mg.m^{-2} (Supplementary Table S1A; Figure 1A). For mAbs, linear pharmacokinetics are observed once accessible target receptors are saturated (Mager and Jusko, 2001; Del Nagro et al., 2010). Pharmacokinetic parameters after a single rituximab SC dose (375, 625, and 800 mg.m^{-2}) were similar for the bimonthly and trimonthly dosing schedules (Supplementary Table S1A; Salar et al., 2010).

Dosing by body surface area has historically been used for cytotoxic agents, which have a narrow therapeutic window. For agents like rituximab, which are well tolerated with a wide therapeutic window, fixed dosing is convenient and minimises error and waste of material (Wang et al., 2009). A flat dose that has undergone rigorous pharmacokinetic and clinical assessment will ensure that target saturation is achieved, even in patients with high tumour burden who may clear antibody more rapidly, and that C_{trough} levels will be maintained throughout the treatment course. To achieve comparable target receptor saturation, and thus comparable therapeutic efficacy, simulations of mean C_{trough} values predicted that a fixed dose of rituximab SC 1400 mg would be...
Rituximab SC 1400 mg was found to be non-inferior to rituximab maintenance cycle (administered bimonthly or trimonthly).

The most common AEs were AARs (atheromatous reactions, rash, erythema, and mild discomfort; these AARs were reversible, related serious AEs, grade 4 AEs, or AEs leading to death, were similar in the two treatment arms. As in the BP22333 study, the proportions of patients with AEs (SC, 92%; IV, 88%), serious AEs (SC, 23%; IV, 22%), and grade ≥3 AEs (SC, 47%; IV, 46%) were similar in the two treatment arms. As in the BP22333 study, the incidence of AEs reported in stage 2 is presented in Supplementary Table S2A (Salar et al, 2012).

The BO22334 (NCT01200758) trial is a two-stage, randomised, controlled, open-label, phase III study of patients with previously untreated follicular lymphoma administered induction chemotherapy plus either rituximab SC 1400 mg or rituximab IV 375 mg m⁻² on day 1 of each maintenance cycle (administered bimonthly or trimonthly). Rituximab SC 1400 mg was found to be non-inferior to rituximab IV 375 mg m⁻², with geometric mean $C_{\text{trough}}$ ratios of 1.24 and 1.12 for the bimonthly and trimonthly regimens, respectively (Salar et al, 2012).

**SAFETY**

Several clinical studies assessing rituximab SC have been completed or are ongoing (Table 1). In stage 1 of BP22333, 157 adverse events (AEs) were reported by 65 patients (52%) following a single dose of rituximab SC. The most common AEs were AARs (n = 30), such as rash, erythema, and mild discomfort; these AARs were reversible, and most were mild in intensity. Mild infections (n = 18) and gastrointestinal disorders (n = 17) were the most common events after AARs for patients treated with rituximab SC. Skin distortion was not observed at the injection site (Figure 2). No treatment-related serious AEs, grade 4 AEs, or AEs leading to death, withdrawal, or treatment discontinuation were reported. Overall, the incidence and severity of AEs associated with rituximab SC (375, 625, and 800 mg m⁻²) were comparable with those known for rituximab IV (Salar et al, 2010). As in stage 1, the most frequently reported AEs in stage 2 were AARs, which occurred in 31% of patients receiving rituximab SC and 4% of those administered rituximab IV. The most frequently observed AARs in the rituximab SC arm were erythema (13%), injection site erythema (5%), and myalgia (5%). An overview of AEs reported in stage 2 is presented in Supplementary Table S2A (Salar et al, 2012).

The BO22334 (NCT01200758) trial is a two-stage, randomised, controlled, open-label, phase III study of patients with previously untreated follicular lymphoma administered induction chemotherapy plus either rituximab SC 1400 mg or rituximab IV 375 mg m⁻². Treatment responders (partial response, complete response) were eligible for maintenance treatment with rituximab SC or rituximab IV monotherapy every 8 weeks for 2 years (US NIH, 2011). In stage 1, participants received cyclophosphamide, doxorubicin, vincristine, and prednisone or cyclophosphamide, vincristine, and prednisone per local practice, and were randomized to 8 cycles of either rituximab SC (n = 62) or rituximab IV (n = 65). Irrespective of randomisation, all patients were given rituximab IV in cycle 1. At a median follow-up of 8.7–8.8 months, the proportions of patients with AEs (SC, 92%; IV, 88%), serious AEs (SC, 23%; IV, 22%), and grade ≥3 AEs (SC, 47%; IV, 46%) were similar in the two treatment arms. As in the BP22333 study, the incidence of AEs was higher with rituximab SC than IV (50% vs 32%) (Davies et al, 2012).
Clinical potential of SC rituximab and trastuzumab

Efficacy

The only efficacy data currently available for rituximab SC derive from the BO22334 trial. Investigator-assessed overall response rates were numerically greater for rituximab SC plus chemotherapy than rituximab IV plus chemotherapy (90.5% vs 84.4%, respectively). In the rituximab SC plus chemotherapy treatment arm, the percentage of patients with a complete response or complete response unconfirmed was 46.0%. The corresponding value in the rituximab IV plus chemotherapy arm was 29.7% (Davies et al., 2012).

Convenience and added value to patients and health-care providers. Rituximab is currently administered IV with infusion times ranging from 90 min (rapid infusion) to 4–6 h (standard infusion) (Salar et al., 2006; Sehn et al., 2007; F. Hoffmann-La Roche, 2008; Vogel, 2010). Rituximab infusion, particularly at the standard rate, can be labour-intensive and be associated with resource costs, including medical supplies and staff for administration and observation time (Haller, 2007; Chan et al., 2009). SC administration is typically more convenient than IV infusion, with reduced administration times and no requirements for dedicated infusion facilities. Rituximab SC can be delivered in ~2–8 min; in a phase Ib study, 4.4–15.0 ml of rituximab SC was administered at an average speed of 1.9 ml min⁻¹ (range: 0.4–3.8 ml min⁻¹; Salar et al., 2010). The rituximab SC 1400-mg dose carried forward to phase III will be delivered in a volume of 11.7 ml.

A survey of oncology practitioners showed that most considered SC administration to be more cost-effective than IV infusion in terms of resource utilisation (Gilbert and Cothran, 2005), suggesting that rituximab SC will have a better cost-effectiveness profile than rituximab IV. Furthermore, SC administration was considered to result in higher patient satisfaction than IV administration (Gilbert and Cothran, 2005). Therefore, SC administration has the potential to improve patient quality of life (Haller, 2007). The BO25341 study, which is due to complete in 2014, will also assess (1) patient and nurse preferences regarding SC vs IV administration and (2) physician and nurse opinions on the time savings and convenience of SC administration (US NIH, 2011).

Trastuzumab SC coformulated with rHuPH20: development and clinical experience

Efficacy and pharmacodynamics. To determine the dose of trastuzumab SC that results in an exposure level comparable to the approved dose of trastuzumab IV (6 mg kg⁻¹, given once every 3 weeks following a loading dose of 8 mg kg⁻¹; F. Hoffmann-La Roche, 2011), an open-label, two-part, phase I/Ib dose-finding and dose-confirmation trial comparing the pharmacokinetics of trastuzumab SC vs trastuzumab IV was conducted in healthy male volunteers (HMVs; n = 24) and female patients with early breast cancer (n = 42; Wynne et al., 2013). HMVs received a single dose of trastuzumab IV (6 mg kg⁻¹) or trastuzumab SC (6, 8, or 10 mg kg⁻¹), whereas female patients received a single dose of trastuzumab IV (6 mg kg⁻¹). The pharmacokinetic profile and mean serum exposure of patients and HMVs receiving trastuzumab IV 6 mg kg⁻¹ were comparable (mean Cₘₚₐₓ = 185 µg ml⁻¹ vs 150 µg ml⁻¹, respectively; Figure 2B, Supplementary Table S1B), enabling extrapolation of results in HMVs to patients. In HMVs, mean trastuzumab exposure post dose was similar for trastuzumab
SC 8 mg kg$^{-1}$ and trastuzumab IV 6 mg kg$^{-1}$ (Figure 1B), suggesting that an SC dose of 8 mg kg$^{-1}$ would result in comparable serum exposure to that of the approved IV dose. To confirm this, female patients received a single dose of trastuzumab SC 8 mg kg$^{-1}$; serum exposure was comparable for these patients and those receiving trastuzumab IV 6 mg kg$^{-1}$ (Figure 1B). As trastuzumab IV is administered at a loading dose of 8 mg kg$^{-1}$ (F. Hoffmann-La Roche, 2011), female patients were also exposed to a higher dose of trastuzumab SC (12 mg kg$^{-1}$). Patients who received trastuzumab SC 12 mg kg$^{-1}$ in this study had higher trastuzumab exposure than patients in the Herceptin Adjuvant study, who received a loading dose of 8 mg kg$^{-1}$ IV (60.8 µg ml$^{-1}$ vs 42.9 µg ml$^{-1}$, respectively, 22 days after the first dose; Wynne et al., 2013). Plasma concentrations of rHuPH20 were below the limit of quantification (~3 ng ml$^{-1}$) at all time points, suggesting that rHuPH20 is acting locally and is rapidly eliminated from the body. These data, along with modelling and simulations, were used to calculate a fixed dose of 600 mg for use in phase III trials to further investigate the safety and efficacy of trastuzumab SC (Wynne et al., 2013).

SAFETY

The safety and tolerability profile of trastuzumab SC vs trastuzumab IV was the secondary objective of the phase I/ Ib trial discussed earlier (Wynne et al., 2013). Trastuzumab SC was well tolerated, showing fewer reported AEs vs trastuzumab IV at all dose levels. There was no apparent increase in the incidence or severity of AEs with escalating SC doses (Supplementary Table S2B; Wynne et al., 2013). The most common AEs experienced by patients receiving trastuzumab SC were headache, upper respiratory tract infection, and influenza-like illness, whereas trastuzumab IV was most commonly associated with headache, acne, musculoskeletal pain, diarrhoea, abdominal pain, and IRR. Most of the AEs reported with trastuzumab (IV or SC) were of mild intensity (71–73%). No deaths, serious AEs, AEs leading to withdrawal or dose modification, or clinically relevant changes in any laboratory parameters, vital signs, or electrocardiograms were reported.

Tolerability at the injection site of the SC formulation is important. Among patients who received trastuzumab SC (n = 58), 18 local administration site AEs were reported. Of these, 16 were of mild intensity (erythema, n = 7; discoloration, n = 5; injection site swelling, n = 2; injection site discomfort, n = 1; and injection site reaction, n = 1), and two were of moderate intensity (injection site pain), suggesting that administration site AEs were manageable.

In the same study, analyses were performed to evaluate the immunogenicity of trastuzumab SC and rHuPH20. Anti-trastuzumab antibodies were detected in 8 of the 58 patients who received trastuzumab SC and in none of the 12 patients who received trastuzumab IV (Wynne et al., 2013). The presence of anti-trastuzumab antibodies did not correlate with the AE and pharmacokinetic profiles of these patients. At the time of this study, an anti-trastuzumab antibody-neutralising assay was not available; thus, data for neutralising antibodies will be acquired in future studies to further understand the immunogenicity of trastuzumab SC. No patients tested positive for anti-rHuPH20-neutralising antibodies.

Convenience and added value to patients and health-care providers. Trastuzumab IV is administered over 90 min for the loading dose, with subsequent doses infused over 30 min (if the loading dose is well tolerated). The infusion must be administered by a health-care provider, preferably in an outpatient setting, and patients should be observed for 6 h after the start of the first infusion and 2 h after the start of subsequent infusions for infusion-related reactions (F. Hoffmann-La Roche, 2011). As mentioned, long infusion times are associated with increased resource costs, including those for physical space, medical supplies, and qualified staff (Haller, 2007), with additional costs incurred by the need for long observation times in the hospital.

Trastuzumab SC can be given in ~5 min, with a median injection rate of 2 ml min$^{-1}$ and a typical volume of 3.4–11.9 ml (Wynne et al., 2013). Thus, trastuzumab SC has the potential to reduce health-care system burden. The required observation time for trastuzumab SC is under evaluation. The cost-effectiveness of trastuzumab IV is well established in early and metastatic breast cancer (Chan et al., 2009; Perez-Ellis et al., 2009), and it is probable that trastuzumab SC will be associated with additional cost savings over trastuzumab IV.

Ongoing and planned studies with trastuzumab SC. There are a number of studies ongoing with trastuzumab SC (Table 1). The Enhanced Treatment With Neoadjuvant Herceptin study (BO22227; NCT00950300) – a pivotal study comparing trastuzumab SC with trastuzumab IV in the neoadjuvant–adjuvant setting – is evaluating pharmacokinetics, efficacy, and safety. The co-primary end points of efficacy and pharmacokinetics have been met (Ismael et al., 2012). A second study (CP3; NCT01344863) comparing the pharmacokinetics of a trastuzumab SC injection system vs manual injection in HMVs will report results soon (US NIH, 2011). Other studies include Preferences for Herceptin (PrefHer; NCT01401166; US NIH, 2011) and A Safety and Tolerability Study of Assisted- and Self-administered Therapy in Patients With Early HER2-Positive Breast Cancer (SafeHer; NCT01566721; US NIH, 2011). The PrefHer study is a patient preference study on IV vs SC administration and is also assessing health-care provider satisfaction and time savings. The SafeHer study is a global study evaluating the safety of repeated SC injections. Secondary objectives include event-free survival and overall survival; single-use injection device handling; and patient, physician, nurse, and pharmacist perceptions on usage and acceptability. Both PrefHer and SafeHer are assessing the use of an injection system vs manual injection and are due to complete in 2013–2014.

CONCLUSIONS

For patients receiving treatment over prolonged periods, SC administration offers significant benefits over IV administration and is considered convenient. For haematologic malignancies, rituximab is typically given for 6 months as induction therapy and for up to 2 years as maintenance therapy. In the adjuvant setting, trastuzumab is recommended for use for 1 year, whereas some patients with metastatic breast cancer receive treatment for 6–8 years or longer. Conformulation of rituximab or trastuzumab with purified rHuPH20 has the potential to overcome the challenges of SC administration by enabling drug dispersion and absorption at the administration site. Unlike previous preparations of hyaluronidase, rHuPH20 is not associated with the immunogenicity observed with animal-derived preparations, allowing well-tolerated delivery of mAbs. The SC formulations of rituximab or trastuzumab coformulated with rHuPH20 are currently under development, with the aim of demonstrating non-inferiority to IV formulations in terms of pharmacokinetics ($C_{\text{rough}}$), efficacy, and safety. Given the shorter delivery time, comparable safety profile, and lack of need for dedicated infusion facilities, SC formulations of rituximab or trastuzumab can potentially improve convenience and quality of life for patients and provide cost savings to health-care systems.

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