Drug Evaluation

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Subcutaneous rituximab with recombinant human hyaluronidase in the treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia

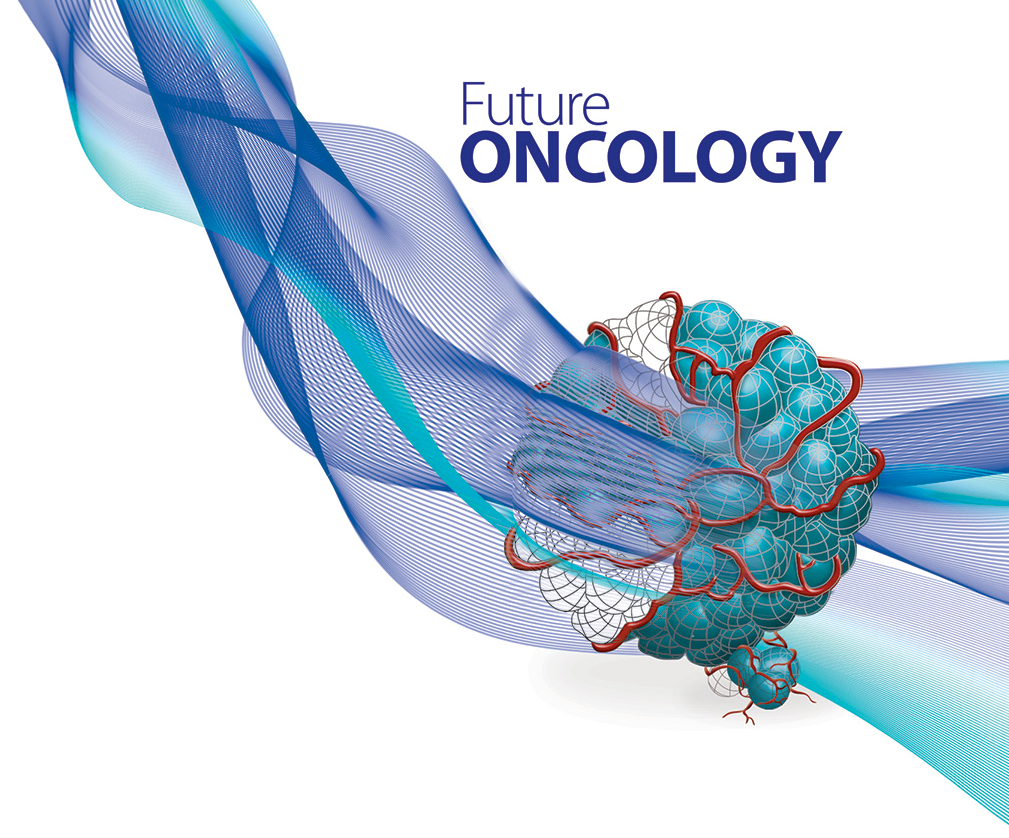
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The anti-CD20 monoclonal antibody rituximab (MabTheraR/RituxanR ) has been proven to improve outcomes in a range of B-cell malignancies. Initially developed as a formulation for intravenous infusion, administration times for rituximab can be prolonged and associated with infusion-related reactions, prompting a combined clinical development program investigating subcutaneous delivery in combination with recombinant human hyaluronidase. As this program comes to fruition, this article reviews the evidence demonstrating subcutaneous rituximab to have noninferior pharmacokinetics when delivered at a fixeddose as well as equivalent clinical outcomes in the treatment of follicular lymphoma, chronic lymphocytic leukemia and diffuse large B-cell lymphoma. This mode of delivery is more preferable to patients and healthcare professionals and is associated with time and cost savings.

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**Keywords:** chronic lymphocytic leukemia • diffuse large B-cell lymphoma • follicular lymphoma • non-Hodgkin lymphoma • rituximab • subcutaneous administration

Since its approval in 1997, the anti-CD20 monoclonal antibody rituximab (MabTheraR/RituxanR ) has become a key drug in treating a variety of B-cell malignancies. So dramatic was the survival advantage observed by adding rituximab to the treatment of high-grade B-cell lymphomas [1,2], it was classed as an essential medicine by the WHO in 2015 [2,3]. Rituximab is now a key component in the treatment for diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL), both in first-line and in relapsed disease [4–7]. It is also widely used to treat a range of other B-cell malignancies and autoimmune conditions [7].

Rituximab is licensed for use in combination with traditional cytotoxic medications for treatment of DLBCL, most commonly cyclophosphamide, doxorubicin and vincristine plus prednisolone (R-CHOP), but also with other agents [5]. It is recommended alongside chemotherapy in previously treated and untreated individuals with FL. Following successful induction treatment, rituximab may also be used for maintenance treatment in FL for up to 2 years to prolong progression-free survival [6]. CLL represents a malignancy of the clonal mature peripheral B lymphocytes. Rituximab is routinely used as first-line treatment or for relapsed disease in CLL, either in combination with fludarabine and cyclophosphamide (FCR) or with other agents such as chlorambucil [4].

A chimeric murine/human monoclonal antibody, rituximab targets an epitope on the extracellular domain of CD20 [8]. Expressed first on pro-B cells, this nonglycosylated phosphoprotein is increasingly expressed in maturing B cells, but not on pro-B lymphocytes, plasma cells, hematopoietic stem cells or other healthy tissues. By targeting CD20, present in 95% of B-cell lymphomas, the immature lymphocytes and mature plasma cells remain relatively unscathed.

Rituximab has been shown to have numerous mechanisms of action. The antibody’s Fab domain is specific for CD20 allowing the Fc domain to interact with a host of immune effector cells and molecules. This results in target cell depletion via antibody-dependent cell death through the recruitment of granulocytes, natural killer cells and

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macrophages to the Fc domain. The Fc domain also recruits the complement cascade by binding C1q, initiating complement-dependent cytotoxicity. Antibody binding to CD20 is also considered to have a direct apoptotic effect on its target cell [9]. Increased sensitivity of malignant B lymphocytes to rituximab has been observed when used in parallel with traditional cytotoxic agents [10].

Initially formulated and marketed for intravenous (iv.) infusion, administration times for rituximab vary and can be lengthy. Infusion-related reactions (IRRs) are common with first exposure necessitating slow administration of the first dose [7]. Subsequent treatments can be more rapid but administration typically takes between 1.5 and 6 h [7,11] but can still be prolonged. As such intravenous dosing is associated with significant costs, in terms of prolonged time in chemotherapy day units and management of reactions, as well as placing a burden on patients and carers. Dosing by body weight increases preparation time by pharmacy services and introduces possibility of dosing errors at the time of prescription or while in dispensing [12,13].

Subcutaneous (sc.) administration of monoclonal antibodies has been proven to be quick and efficacious in the context of trastuzumab for HER2-positive breast cancer, paving the way for the development of a sc. rituximab formulation [14,15]. There has been a strong patient preference for subcutaneous administration of trastuzumab compared with intravenous dosing, a sentiment that was expected to be replicated in patients receiving rituximab [16,17].

The subcutaneous preparation of rituximab as MabThera for subcutaneous injection contains rituximab at 120 mg/ml, a 12-fold increase in concentration when compared with the intravenous preparation. The total dose of rituximab per vial is 1400 mg (11.7 ml) which is combined with recombinant human hyaluronidase (rHuPH20) [7]. rHuPH20 is a recombinant human enzyme that acts to transiently depolymerize interstitial hyaluronan allowing rapid dispersion and absorption of subcutaneously administered medication. Hyaluronan is an important component of subcutaneous extracellular matrix and provides resistance to large volume subcutaneous infusion [18]. Depolymerization by rHuPH20 is rapid but transient with a half-life of 30 min and resynthesis of hyaluronan in 24–48 h [18–20]. This causes decreased resistance to injection and allows larger volumes that would normally be tolerated to be given subcutaneously.

rHuPH20 is typically well tolerated and has long been used in the palliative care setting. It does not tend to cause any local side effects or lasting tissue damage, and does not interact with rituximab [19,21–22]. There appears to be very little in the way of systemic dispersion. This approach of combining rHuPH20 with monoclonal antibodies to facilitate subcutaneous administration has been successfully adopted in the formulation of subcutaneous trastuzumab, licensed for use in HER-2-positive breast cancer treatment.

Given the prolonged intravenous infusion times observed with rituximab and the complications associated with dosing by body surface area (BSA), a move to subcutaneous administration would save considerable time and resources in increasingly busy hematology and oncology departments. A move to single-dose administration may also reduce the risk for practitioner error.

This article will review the outcomes of the coordinated clinical development program to investigating the feasibility and efficacy of delivering rituximab as a subcutaneous formulation, in combination with rHuPH20, in the treatment of FL, DLBCL and CLL. In particular, the outcomes of the SparkThera, SAWYER and SABRINA studies are reviewed as the basis for the pharmacological and clinical equivalence of subcutaneous administration. The safety and tolerability as well as the benefits to patients and healthcare providers of moving to this mode of treatment are also discussed.

# Pharmacology

The development of a sc. rituximab formulation drew upon the knowledge and experience gained during its initial investigation as an intravenous preparation. It was considered that an equivalent serum rituximab level achieved subcutaneously as intravenously would result in an equal degree of target-site saturation. This in turn was expected to result in equal efficacy given the active compound, the monoclonal antibody, was identical in both preparations, all be it at a higher concentration when given subcutaneously.

A pharmacokinetic (PK)-based clinical bridging program was initiated, with parallel studies investigating the effects of a switch to subcutaneous administration in FL, DLBCL and CLL. These studies assessed the PK noninferiority, safety profile and subsequently clinical efficacy of this delivery method. Information was also gathered on the acceptability of subcutaneous administration of rituximab to patients.

## Initial considerations

In order to achieve noninferiority with subcutaneous administration, the bridging studies utilized the rituximab serum trough concentration (Ctrough) as a marker of target exposure. Representing the minimum concentration in a defined treatment cycle, this reflects the duration of target exposure. Working on the assumption that peak efficacy is achieved when all target sites are saturated, it was expected that similar Ctrough following subcutaneous administration would result in comparable pharmacodynamic effects. Ctrough along with estimation of area under the concentration over time curve (AUC) has been shown to correlate with disease response in FL, where these two measures have also been shown to correlate with each other [23,24]. As such they were chosen as the primary and secondary end points in the bridging studies.

The peak serum rituximab concentration (Cmax) is not considered a relevant PK parameter. This occurs later, after 3 days, and is less pronounced, in subcutaneous compared with intravenous administration. The high Cmax observed with intravenous administration may account for some of its propensity to produce IRRs [23].

Switching to subcutaneous administration of rituximab has also allowed a shift to fixed (flat) dosing. Such a change would be expected to allow ready-to-use formulation, reducing drug preparation time in pharmacies, reducing waste and reducing the risk of dosing errors. Following on from the traditional dosing of chemotherapies by BSA, rituximab as the first anticancer monoclonal antibody treatment was initially dosed in a similar fashion. Subsequent assessment has revealed that monoclonal antibodies in contrast to most cytotoxic chemotherapies have a wide therapeutic index and wide variability in concentrations achieved in individuals regardless of BSA. In fact other factors, including gender, disease burden and bone marrow involvement, have all been shown to significantly affect the Ctrough levels [24]. It has been shown that variations in PK would be no greater with fixed dosing for rituximab, as well as numerous other therapeutic monoclonal antibodies, than if BSA-based dosing schedule were applied [25].

The wide therapeutic index associated with monoclonal antibodies allows a dose large enough to achieve an acceptable Ctrough in individuals with a high BSA to be given to the whole population. This allows those who would experience a lower exposure to the drug with fixed dosing to be adequately treated, while also keeping potential toxicities to a minimum in smaller individuals.

A similar approach had been successfully deployed to develop a subcutaneous preparation of trastuzumab. A Phase I study utilizing both healthy male volunteers and patients with HER-2-positive early breast cancer found single dose subcutaneous administration could result in Ctrough and AUC levels equivalent to those achieved with the conventional intravenous dosing regimen [14]. The findings of this early phase study were consolidated by a Phase III study showing noninferiority of a fixed subcutaneous dose in terms of clinical efficacy [15].

## Preclinical studies

The first preclinical studies showed good dispersal of rituximab with rHuPH20 when administered subcutaneously to mini pigs and also in mouse studies, in keeping with previous research into sc. trastuzumab. Maximum absorption was achieved at doses at or below 6000 u/ml rHuPH20 in a number of studies [26].

Subsequent studies utilizing a human tumor xenograft model and cynomolgus monkeys added further evidence to sc. rituximab having equivalent PK effects when compared with intravenous administration. These studies also demonstrated pharmacodynamic similarities in rituximab bioavailability and target cell depletion in both the peripheral blood as well as in the lymphoid tissues [27].

## Early clinical development

A coordinated approach of clinical studies was adopted to identify the optimal dosing for subcutaneous administration of rituximab in the treatment of non-Hodgkin lymphoma and CLL. This was followed by three parallel studies to assess the PKs, clinical efficacy and safety of the doses established for use in treatment of FL, DLBCL and CLL.

## Dose-finding studies

The first clinical dose-finding study was the Phase IB SparkThera study. This study of patients in the maintenance phase of treatment for FL had the primary objective of identifying a subcutaneous dose of rituximab that would reliably result in a Ctrough equivalent to an iv. dose given at 375 mg/m2. The PKs, safety and tolerability of subcutaneous administration was also assessed. Patients selected had already achieved at least a partial response to

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| Table 1. Overview of the studies comparing subcutaneous to intravenous administration of rituximab in non-Hodgkin lymphoma and chronic lymphocytic leukemia. |
| **Study Study design Patient population Number of patients Treatment regimen Overall response Ref. rate** |
| SparkThera Phase IB, open-label, Previously treated – Stage 1: n = 124 – Stage 1 dose finding: on completion [28] multicenter, or untreated FL – Stage 2: n = 154 of induction treatment including  international two-part, rituximab and chemotherapy. Single dose-finding and cycle of R-sc. (375, 625 or 800 mg/m2) dose-confirmation versus R-iv. (375 mg/m2) followed by  study 2 years R-iv. maintenance  – Stage 2 dose confirmation: R-sc.  1400 mg every 2 months or 3 months for 2 years versus R-iv. every 2 months for 2 years |
| SABRINA Phase III, multicenter, Previously – Stage 1: n = 127 – Induction with 6–8 cycles of R-sc. R-sc.: 84.4% [29,30] international, untreated FL – Stage 2: n = 283 1400 mg + CHOP or CVP versus 6–8 (95% CI: 78.7–89.1)  randomized, two-part cycles of R-iv. 375 mg/m2 + CHOP or versus study CVP (first cycle R-iv. in both arms) R-iv.: 84.9%  – Maintenance with R-sc. 1400 mg (95% CI: 79.2–89.5) every 8 weeks in those with at least PR versus R-iv. 375 mg/m2 every 8 weeks  for 2 years |
| SAWYER Phase IB, multicenter, Previously – Stage 1: n = 64 – Stage 1: dose finding. Single cycle R-sc.: 85% [31,32] international, untreated CLL – Stage 2: n = 176 R-sc. (1400, 1600 or 1870 mg) with FC (95% CI: 76–92) randomized two-part, at cycle 6. PK comparison with cycle 5 versus  dose-finding and R-iv. 500 mg/m2 with FC R-iv.: 81%  dose-confirmation – Stage 2: dose confirmation. R-sc. (95% CI: 71–88%) study 1600 mg with FC versus R-iv.  500 mg/m2 (first cycle R-iv. in both arms) |
| MabEase Phase IIIB, multicenter, Previously n = 576 8 cycles of R-sc. (1400 mg) with CHOP R-sc.: 82% [33] open-label randomized untreated DLBCL (first cycle R-iv.) versus 8 cycles R-iv. (95% CI: 78–86%)  efficacy and safety (375 mg/m2) with CHOP versus  study R-iv.: 78%  (95% CI: 71–84%) |
| PrefMab Phase IIIB, multicenter, Previously n = 743 All patients first cycle R-iv. Arm A: 94% [34] international, untreated DLBCL or (375 mg/m2) with 6–8 cycles of CHOP (95% CI: 90–96%) open-label randomized FL or CVP. Then either Arm A: 3 cycles versus Arm B: 92% crossover study R-sc. (1400 mg) followed by 4 cycles (89–95%)  R-iv. (375 mg/m2) or Arm B: further 3 cycles R-iv. (375 mg/m2) followed by 4  cycles R-sc. (1400 mg) |
| CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisolone; CLL: Chronic lymphocytic leukemia; CVP: Cyclophosphamide, vincristine and prednisolone; DLBCL: Diffuse large B-cell lymphoma; FC: Fludarabine and cyclophosphamide; FL: Follicular lymphoma; PR: Partial response; R-iv.: Intravenous rituximab; R-sc.: Subcutaneous rituximab. |

conventional rituximab containing treatments in the expectation that the B-cell containing tumor burden would be suitably depleted not to interfere with PK measurement. Individuals who had already had their first maintenance dose were randomized to receive either sc. rituximab at (375, 625 or 800 mg/m2) or rituximab iv. at 375 mg/m2. After a single subcutaneous dose, all patients completed the remainder of their 2-year intravenous maintenance treatment (Table 1). A sc. dose of 1400 mg was identified as having a noninferior Ctrough and AUC as 375 mg/m2 iv. rituximab, whether given 2 or 3 monthly and was chosen for ongoing investigation in patients with non-Hodgkin lymphoma [28].

Data gathered from the SparkThera study were used in modeling to calculate an appropriate starting point for the dose finding element of the SAWYER study, investigating the use of sc. rituximab in CLL. This study of patients with previously untreated CLL receiving treatment with rituximab, fludarabine and cyclophosphamide had the objective of identifying a flat dose of sc. rituximab that was noninferior to the intravenous preparation, delivered in this context as 500 mg/m2 every 4 weeks. The patients received here their final dose of rituximab as either sc. dose 1870, 1400 or 1200 mg with PK data compared with measurements taken during the previous cycle of treatment with rituximab administered intravenously. The outcome was of a sc. dose of 1600 mg rituximab considered noninferior to an iv. dose of 500 mg/m2 when administered every 4 weeks (Table 1) [31].

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| Table 2. Response rates observed during the SABRINA study at the end of induction treatment showing comparable outcomes between intravenous and subcutaneous administrations across all body surface areas. |
| **iv. rituximab sc. rituximab** |
| Low body surface area n = 56 n = 85  Overall response  Complete response |
| Medium body surface area n = 77 n = 58  Overall response  Complete response |
| High body surface area n = 72 n = 62  Overall response  Complete response |
| Response rate shown as percentage of patients and 95% CI. Complete response includes confirmed and unconfirmed complete response at the end of induction chemotherapy. Low body surface area, ≤1.73 m2; medium body surface area, 1.74 to ≤1.92 m2; high body surface area, ≥1.93 m2. iv.: Intravenous; sc.: Subcutaneous.  Reproduced with permission from [30] C Elsevier (2017). |

## Dose confirmation & efficacy studies

Parallel dose confirmation and efficacy studies were performed in patients receiving primary treatment for FL, DLBCL and CLL.

## Follicular lymphoma

The two-stage, Phase III SABRINA study recruited previously untreated patients with FL and randomized them to receive either sc. or iv. rituximab, following an initial dose intravenously, over six cycles in combination with chemotherapy, either CHOP or cyclophosphamide, vincristine and prednisolone. On completion of induction treatment,rituximabandchemotherapytreatmentgiventogaindiseasecontrolandreducethevolumeofmeasurable disease, the participants proceeded to either intravenous or subcutaneous maintenance treatment 2 or 3 monthly (Table 1). The first stage of this international multicenter study recruited 127 patients and assessed Ctrough levels at the end of seven cycles of rituximab. This late assessment of Ctrough was to minimize the effect of target specific elimination on PK data. The outcome of this stage found that a flat dose of 1400 mg to have noninferior PK parameters to BSA-based dosing at 375 mg/m2, this was true across the spectrum of BSA confirming dose selection [29]. In fact, patients with a high BSA were found to have mean Ctrough and AUC measurements higher in the subcutaneous arm when compared with intravenous dosing, a finding replicated in the SAWYER and

SparkThera studies [28–29,31–32].

The second stage of the SABRINA study intended to add to the safety and efficacy data of the first. A further 283 patients were recruited who proceeded in an identical manner to those in the first stage. The pooled data on completion of the second phase demonstrated comparable efficacy with overall response rate of 84.4% (95% CI: 78.7–89.1) in the subcutaneous arm and 84.9% (79.2–89.5) in the intravenous arm (Table 1). On further, scrutiny response rates were comparable across all subgroups including BSA (Table 2), gender and stage disease [30].

## Diffuse large B-cell lymphoma

The efficacy in utilizing rituximab subcutaneously in first-line treatment for high-grade B cell lymphomas was explored in the open label MabEase study. This randomized trial of patients with previously untreated DLBCL allocated individuals to receive either sc. rituximab at 1400 mg or iv. rituximab 375 mg/m2 in combination with either six or eight cycles of CHOP chemotherapy every 14 or 21 days. At the end of the induction treatment the complete response rate was similar in both the sc. and iv. rituximab groups at 51 versus 52%, respectively (Table 1). The long-term progression-free survival and overall survival end points have currently yet to be met at 35 months follow-up. Adverse events were comparable between both treatment groups [33].

## Chronic lymphocytic leukemia

Following on from the first stage of the Phase IB SAWYER study, patients were recruited for part two, again with previously untreated CLL and were randomized to treatment with either sc. rituximab at a flat dose of 1600 mg every 4-weeks or iv. rituximab 500 mg/m2, in combination with fludarabine and cyclophosphamide chemotherapy (Table 1). PK noninferiority was confirmed with superior Ctrough levels observed in the subcutaneous arm. The overall response rate at the end of treatment showed comparable efficacy in both subcutaneous and intravenous administration at 85 and 81%, respectively [32]. Treatment with sc. rituximab at the 1600 mg dose has now been approved for use in untreated CLL in the USA [35].

# Safety & tolerability

As stated previously, rituximab is associated with IRRs which can be severe and are usually experienced on first exposure. These reactions can include a combination of cytokine release syndrome, tumor lysis syndrome, anaphylactic and hypersensitivity reactions. Such cytokine release reactions result in a complex of dyspnea, bronchospasm, urticaria and angioedema. This can be accompanied by tumor lysis syndrome, particularly in individuals with high tumor bulk who are considered at higher risk of all such reactions. Rarely such reactions can be associated with respiratory and renal failure and have been documented to be fatal [7].

Reactions associated with cytokine release and tumor lysis syndromes are thought to occur regardless of administration route, providing the rational for the first dose of rituximab being given in a facility equipped to deal with potential complications. Intravenous administration also allows easy discontinuation or alteration of delivery rate to help reduce reaction severity and increase tolerability. It has become adopted practice that patients planning for sc. rituximab infusion are required to have at least one full cycle of treatment administered intravenously prior to switching. In those not able to tolerate their first cycle without significant complications, they should proceed to further administrations intravenously until administration is possible without complication.

The above complications of rituximab are possible regardless of route of delivery to the patient. Sc. rituximab should therefore be administered in a setting with capabilities for delivering emergency resuscitation. Premedication with an antipyretic and an antihistamine should be given and glucocorticoids can be considered in all patients. There is evidence that these can be administered safely as an oral premedication in patients receiving subcutaneous treatment or can even be omitted in certain circumstances. At least 15-min observation should be completed following subcutaneous treatment [29].

Local cutaneous reactions were observed frequently in the SABRINA study participants. In general, these were mild and self-limiting, with injection erythema in 11%, injection pain in 5% and injection site pruritis in 6%. Severe, grade 3 or greater side effects were similarly prevalent in the subcutaneous and intravenous treatment groups at 21 and 26%, respectively [29]. There was no apparent difference in the immunogenicity of rituximab based upon assessment of human antichimeric antibodies and human antihuman antibodies between the two routes of administration [30].

# Benefits of subcutaneous administration

Administration of anticancer treatment is a time and labor intense process, placing a high burden on patients, relatives and healthcare infrastructures. A move to subcutaneous treatment with rituximab had been expected to reduce the treatment burden and be preferable to patients in a similar manner to sc. trastuzumab administration, and so this has been born out in practice.

In the prospective, open-label, randomized crossover PrefMab study, investigating patient preference for either iv. or sc. rituximab, a strong preference was expressed for subcutaneous treatment. The reasons for this were predominantly reduced clinic time, improved comfort and reduction in emotional distress caused by treatment. Higher satisfaction scores were attained in the rituximab-specific treatment satisfaction score when subcutaneous administration was compared with intravenous, with improved convenience being especially highlighted, as well as lower impact on activities of daily living [34,36]. These results were replicated in the MabEase and MabCute studies with a high degree of preference for subcutaneous dosing. Of note, the PrefMab study demonstrated a similarity in the ‘psychological impact’ between intravenous and subcutaneous treatment [33–34,36]. It was felt that the shorter administration times were countered by the feeling of prolonged supervision and contact with healthcare workers. However, the MabEase study demonstrated no difference in the amount of time healthcare professionals were available to patients, rather just an extended amount of time attached to an intravenous infusion [33].

As well as improving the patient experience through subcutaneous administration, a number of time and motion studies have demonstrated significant reductions in time spent by healthcare professionals in drug preparation and administration, as well as time spent by patients in the treatment room. This adds up to substantial saving in human resource and other costs associated with rituximab administration [12–13,32,37]. Direct observation during the MabCute study demonstrated a reduction in the active healthcare professional time dedicated to the drug preparation and delivery from 23.7 to 35.0 min. This was accompanied by a substantial fall in the patient chair time within the treatment room, dropping from a mean of 262 to 67 min [37]. The authors have suggested that such time savings could result in 3.5 patients being treated via the subcutaneous route for every one intravenously. This will have significant impact on all healthcare providers, but especially those in a resource limited setting.

It is not only in the treatment room that potential cost saving can be seen. Significant reductions are also noted in pharmacy preparation time with a switch to flat dosing as well as reductions in waste of the expensive compounds [13].

# Conclusion

Rituximab has become an indispensable component of the treatment for non-Hodgkin lymphoma and CLL over the past two decades. Intravenous administration is associated with prolonged treatment times placing a burden on health services as well as patients. A concentrated formulation for subcutaneous administration has been developed in combination with recombinant human hyaluronidase. This has allowed more rapid delivery of rituximab without significant increase in adverse effects and has been demonstrated to achieve similar Ctrough levels when administered at a flat dose across a range of individuals. In addition to PK noninferiority, sc. rituximab administration has been demonstrated to be equally efficacious to intravenous treatment in large and ongoing Phase III studies examining its use in FL, DLBCL and CLL. Treatment by this method has been proven to be tolerable and even preferable to patients as well as delivering cost and time savings to healthcare providers.

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| Executive summary |
| **Background**  Rituximab, an anti-CD20 human/murine chimeric monoclonal antibody, is the first therapeutic anticancer antibody to enter clinical practice.  Licensed for use as a single agent or in combination with chemotherapy in the treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia.  Initially developed for intravenous infusion, administration times can be prolonged and associated with infusion-related reactions.  Successful development of subcutaneous (sc.) administration of trastuzumab with the use of recombinant human hyaluronidase (rHuPH20) has been shown to be cost-effective and increasingly preferable to patients.  Concentrated formulation of rituximab (120 mg/ml) with rHuPH20 has been developed for use in a coordinated development program.  **Pharmacology**  **Preclinical & dose-finding studies**  Rituximab serum trough concentration (Ctrough) considered suitable marker for pharmacokinetic (PK) bridging studies.  Ctrough along with estimation of area under the concentration over time curve has been shown to correlate with disease response in follicular lymphoma.  Fixed dose of 1400 mg sc. rituximab demonstrated to have noninferior Ctrough level to 375 mg/m2 three weekly administration in SparkThera study and confirmed in part 1 of SABRINA study.  **Dose confirmation & efficacy studies**  Noninferior PK profile of sc. rituximab when used to treat follicular lymphoma confirmed in SABRINA study. Equivalent clinical outcomes demonstrated.  SAWYER study demonstrates PK noninferiority of 1600 mg fixed dose of sc. rituximab with intravenous administration at 500 mg/m2 four weekly. Equivalent clinical outcome demonstrated.  Early results from MabEase study suggests equivalent clinical response with use of sc. rituximab alongside chemotherapy in the treatment of diffuse large B-cell lymphoma.  Strong patient preference for use of sc. rituximab in PrefMab study. Subcutaneous delivery also associated with decrease in patient treatment time and preparation time.  Adverse events are comparable in terms of frequency and severity between subcutaneous and intravenous administration of rituximab across clinical studies. Increase in frequency in local skin reactions at injection sites with subcutaneous administration.  **Conclusion**  Subcutaneous administration of rituximab with rHuPH20 is a safe and effective alternative to intravenous administration in the treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia. This is preferable to patients and represents a potential for cost saving, particularly in a resource limited setting. |

Financial & competing interests disclosure

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• **Phase III study demonstrating similar safety and efficacy profile of trastuzumab administered subcutaneously (sc.) versus intravenously (iv.), in combination with chemotherapy in the treatment of early HER-2-positive breast cancer, confirming feasibility of subcutaneous antibody delivery.**

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