

Pharmacokinetic assessment of subcutaneous rituximab hyaluronidase among Ugandan adults with CD20⁺ diffuse large B-cell lymphoma

Kelvin Roland Mubiru,¹ Henry Ddungu,² Scott V. Adams,³ Jacqueline Asea,¹ Benjamin Mwesige,² Rosemary Namagembe,¹ Prossy Namuli,¹ Jackson Orem,² Camille Puroen,³ Thomas S. Uldrick,³ Edus H. Warren,^{3,5} and Manoj P. Menon^{3,4}

¹Hutchinson Centre Research Institute-Uganda, Kampala, Uganda; ²Uganda Cancer Institute, Kampala, Uganda; ³Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA; ⁴Division of Hematology and Oncology, Department of Medicine, University of Washington, Seattle, WA; and ⁵Translational Science and Therapeutics Division, Fred Hutchinson Cancer Center, Seattle, WA

Key Points

- We demonstrate that the C_{trough} was 96.5 µg/mL, with little variation between the 2 groups.

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy worldwide. In high-income countries, treatment outcomes for NHL have dramatically improved over the past 25 years in large parts due to rituximab. However, these same benefits have not been realized in low- and middle-income countries given limited access to monoclonal antibodies. To assess the pharmacokinetic profile of subcutaneous rituximab (sqR) among patients in Uganda, we enrolled 18 newly diagnosed patients with CD20⁺ diffuse large B-cell lymphoma. In cohort 1 (n = 6) IV rituximab was given on day 1 of cycle 1, followed by CHOP (cyclophosphamide, doxorubicin, Oncovin [vincristine], and prednisone) chemotherapy and then sqR and CHOP for cycles 2 to 6. The second cohort (n = 12) received sqR plus CHOP for all cycles. We assessed trough concentrations (C_{trough}) from the plasma, and pharmacokinetic assessments were determined using an enzyme-linked immunosorbent assay. C_{trough} was analyzed descriptively. We demonstrate that C_{trough} provides exposure within the published reference range, was consistent across cohorts and within acceptable limits, and supports the use of sqR in Uganda. Efforts to increase access to monoclonal antibodies, including rituximab, are necessary to reduce health disparities. Subcutaneous formulations are one way forward. This trial was registered at www.clinicaltrials.gov as NCT03864419.

Introduction

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy globally.¹ Although the mortality rate from NHL in high-income countries (HICs) has decreased in the past 25 years, patients with NHL who are treated in low- and middle-income countries (LMICs) continue to have inferior

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In general, beyond the investigators and projects indicated in this proposal, we propose to release unpublished data under the project principal investigator(s). The investigators of the projects that created the requested data will decide if a data request is appropriate. Applicants must identify research goals, funding source(s), study timeline, and data items. The scientific significance of the proposed research, the applicant's scientific credentials, and the ethics of data use will be reviewed.

Data are available from the corresponding author, Kelvin Roland Mubiru (kmubiru@fredhutch.org), on request.

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outcomes, with 12-month overall survival rates typically under 50%.^{2,3} Although there are a host of factors and obstacles responsible for this disparity, including late stage at presentation^{4,5} and limited oncologic infrastructure,⁶⁻⁸ reduced access to therapeutics is potentially most amenable to timely change.^{7,9}

Rituximab, a monoclonal antibody targeting the CD20 antigen, when administered IV and combined with chemotherapy, improves overall survival for a variety of NHL subtypes, including the 2 most common subtypes, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma.¹⁰⁻¹² As such, IV rituximab received regulatory approval from the US Food and Drug Administration (FDA) in 1997 and is included as part of the standard of care for the treatment of CD20⁺ DLBCL in HICs.^{11,13} Despite this regulatory approval and subsequent inclusion in the World Health Organization's List of Essential Medicines, IV rituximab is not readily available in LMICs.⁹ Although local governments in certain LMICs have worked with pharmaceutical companies to reduce the cost of monoclonal antibodies, such as a recent partnership between the Kenyan Ministry of Health and Roche East Africa ([Ministry of Health and Roche Partner to Cut Breast Cancer Treatment Costs by Two-Thirds | Ministry of Health](#)), access is not widespread.¹⁴ The availability of rituximab has been further hampered due to the scarcity of infusion centers, a requirement given the multiple hours required to administer it and the human resources necessary to care and monitor patients.¹⁵ Therapeutics, which overcome these obstacles, including subcutaneous formulations, are warranted.

Subcutaneous rituximab (sqR), which can be administered over 5 to 7 minutes, reduces the strain on patients, health care staff, and infusion centers.¹⁶ Multiple studies have demonstrated a similar safety and efficacy profile of sqR compared with IV rituximab and therefore sqR received FDA approval in 2017.¹⁷⁻²¹ However, these studies were all conducted in HICs. Given the lower body mass index and prevalence of malnutrition in LMICs and the potential impact of these factors on drug distribution and elimination, the pharmacokinetic profile, safety, and efficacy may vary among patients in LMICs compared with HICs.²²⁻²⁴

We previously reported the safety and efficacy data of sqR in DLBCL at the Uganda Cancer Institute (UCI), Kampala, Uganda and demonstrated excellent survival results comparable to HICs.²⁵ Here, we report a pharmacokinetic assessment among Ugandan adults with CD20⁺ DLBCL who received a fixed dose of 1400-mg sqR in combination with the standard-of-care chemotherapy backbone.

Study design

This open-label phase 1 nonrandomized study, conducted at the UCI, enrolled patients aged ≥ 18 years with newly diagnosed CD20⁺ DLBCL in 2 cohorts. The sample size ($N = 18$) was predetermined given financial and logistical considerations. As per FDA's prescribing guidelines, cohort 1 ($n = 6$) received IV rituximab, 375 mg/m² on day 1 of cycle 1 plus combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, Oncovin [vincristine], and prednisone) and sqR (1400 mg) for subsequent cycles (ie, cycles 2-6). The second cohort ($n = 12$) received sqR plus CHOP for all cycles. Eligible patients had an Eastern

Cooperative Oncology Group performance status ≤ 2 and measurable disease on computed tomography. People living with HIV infection were eligible if they had a CD4⁺ count of ≥ 200 cells per μL , were on effective antiretroviral therapy, and were not receiving ritonavir or cobicistat.

We collected blood samples on day 1 of cycles 1 to 5 within 6 hours before rituximab administration to measure trough plasma concentrations (C_{trough}). Specimens were processed and stored at -80°C . Rituximab pharmacokinetic assessments were determined using a validated enzyme-linked immunosorbent assay at QPS Netherlands. Calibration, quality control, and study samples were analyzed in duplicates. Pharmacokinetic parameters were assessed using the PKNCA R package version 0.10.2 for Windows.²⁶ The main pharmacokinetic parameter was C_{trough} ; the reference range for C_{trough} was defined as a $25\text{ }\mu\text{g/mL} < C_{\text{trough}} < 400\text{ }\mu\text{g/mL}$ after the first subcutaneous dose.²⁷⁻²⁹ Body surface area (BSA) was dichotomized as "low" if the BSA was $\leq 1.73\text{ m}^2$ and "high" if the BSA was $> 1.73\text{ m}^2$.

Descriptive statistics were used to summarize C_{trough} . All data analysis were performed using R version 4.3.1 (R Core Team, 2023), and the graphs were produced using the package ggplot2.

The study was performed in compliance with the principles of the Declaration of Helsinki and registered with [ClinicalTrials.gov](#) (NCT03864419). The Fred Hutch Cancer Center Institutional Review Board, UCI Research Ethics Committee, Uganda National Drug Authority, and Uganda National Council for Science and Technology each approved the study protocol. All patients signed informed consent in English or Luganda.

Results and discussion

Between 25 October 2019 and 7 October 2022, 18 eligible patients were enrolled, with 6 (33%) in therapy group 1 (IV/SqR) and 12 (67%) in therapy group 2 (SqR only). The median age was 36.5 years (interquartile range, 25.2-50.0), 10 (56%) were men, and 10 (56%) had advanced-stage (III/IV) disease ([Table 1](#)). Three participants were excluded from the pharmacokinetic analysis because they lacked measurements for 3 treatment cycles, leaving 15 evaluable patients. Quantification values $< 0.5\text{ }\mu\text{g/mL}$ were treated as 0.

[Table 2](#) presents geometric mean values (95% confidence interval [CI]) of C_{trough} . All 15 evaluable participants achieved C_{trough} within the predefined therapeutic range (25-400 $\mu\text{g/mL}$) from cycles, cycle 3 day 1 (C3D1) to C5D1, whereas 12 of 15 (80%) were within this range at C2D1. At the final treatment cycle (C5D1), the overall geometric mean C_{trough} was 96.5 $\mu\text{g/mL}$ (95% CI, 77.5-120.1), well within the target range ([Table 2](#)). Therapy group 2 (SQ only) had a lower geometric mean C_{trough} than therapy group 1 (89.2 $\mu\text{g/mL}$ [95% CI, 67.1-118.5] vs 108.5 $\mu\text{g/mL}$ [95% CI, 76.3-154.3]), although both remained within the therapeutic range. Likewise, participants with a BSA $\leq 1.73\text{ m}^2$ had a geometric mean C_{trough} of 99.6 $\mu\text{g/mL}$ (95% CI, 80.7-122.9). Across all measured cycles, trough concentrations remained within the target range, with comparable C_{trough} values regardless of whether the first dose was administered IV (BSA-based) or subcutaneously (fixed dose; [Table 2](#); [Figure 1A](#)). The

Table 1. Participant baseline characteristics

Characteristics	Therapy group 1 (IV/SqR; n = 6)	Therapy group 2 (SqR only; n = 12)	Total (N = 18)
Age, median (Q1-Q3)	43.0 (33.8-50.8)	35.0 (24.0-50.0)	36.5 (25.2-50.0)
Sex (female)	2 (33)	8 (67)	10 (56)
HIV status (positive)	1 (17)	2 (17)	3 (17)
Stage (DLBCL)			
I	0 (0)	2 (17)	2 (11)
II	2 (33)	4 (33)	6 (33)
III	4 (67)	4 (33)	8 (44)
IV	0 (0)	2 (17)	2 (11)
BSA, median (Q1-Q3)	1.7 (1.7-1.8)	1.7 (1.6-1.8)	1.7 (1.6-1.9)
Cycles completed, median (Q1-Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)

Q, quartile.

observed variability in C_{trough} between cohort 1 (IV then SQ) and cohort 2 (SQ only) is likely explained by the pharmacokinetic differences inherent to switching the routes of administration. SQ absorption is slower, incomplete ($\approx 65\%$ bioavailability), and more variable than direct IV delivery. In addition, residual drug levels from prior IV cycles in cohort 1 confound the SQ-specific exposure measurement.³⁰

BSA ranged from 1.4 to 2.2 m² (interquartile range, 1.7-1.9), with a median of 1.7 m² in both cohorts; C_{trough} was comparable across BSA subgroups. In cohort 1, patients with low BSA (≤ 1.73 m²; n = 4) had a geometric mean C_{trough} of 108.1 $\mu\text{g/mL}$ (95% CI, 67.4-173.3) vs 109.4 $\mu\text{g/mL}$ (95% CI, 53.2-224.9). In cohort 2, patients with low BSA (n = 5) had a geometric mean of 93.3 $\mu\text{g/mL}$ (95% CI, 82.1-105.9) vs 84.3 $\mu\text{g/mL}$ (95% CI, 43.1-165.0) (Table 2; Figure 1B).

Here, we demonstrate that the C_{trough} , which can be used as a proxy to achieve exposure within the published reference range, was 96.5 $\mu\text{g/mL}$, with little variation between the 2 cohorts. This is similar to a recent study of previously untreated patients with CD20⁺ DLBCL receiving sqR in China³¹ as well as a host of additional studies of rituximab for various indications,^{20,32,33} In addition, there were no clear differences between the high- and low-BSA groups.

Multiple studies in HICs have demonstrated the benefits of subcutaneous formulations of therapeutics, in terms of costs and health care use, to the patient and the health care system; these benefits are likely magnified in LMICs. Although the direct drug

costs of IV and SQ formulations of rituximab are comparable in HICs, with intercountry variability, the total costs of SQ administration may be reduced given the decreased staffing needs and infusion times. The increasing availability of biosimilars have potentially reduced the costs of IV monoclonal antibodies; however, their use also remains limited in LMICs. Therefore, cost-analysis studies in LMICs are warranted.

Severe and fatal reactions to rituximab are rare. To mitigate the risk of an infusion reaction, the first dose of rituximab is typically administered at a slow rate with gradual titrations (eg, 50 mg/h increments every 30 minutes), although updated guidance from the manufacturer allowed for a more rapid infusion.³⁴ SQ rituximab is currently approved for use after a patient receives at least 1 dose of IV rituximab. The study suggests that initiating therapy with sqR at cycle 1 could mitigate the challenges of IV therapy in LMICs.

Although our study demonstrated the clinical utility of C_{trough} for Ugandan patients with DLBCL receiving sqR, it has potential limitations. It was a single-institution, nonrandomized study with a median participant age of 36.5 years and therefore may limit generalizability to older populations. In addition, 44% of participants had limited stage disease. However, staging, reflective of current practices in LMICs, did not use positron emission tomography, which might have revealed a more extensive disease. Nonetheless, the findings are consistent with the clinical care of patients with DLBCL in LMICs.

Hematologic malignancies, particularly aggressive B-cell lymphomas, significantly affect LMICs, in part due to restricted access to new treatments. Improving access to therapeutics within the constraints of the health care system is essential. This study indicates that sqR, which has been previously demonstrated to be advantageous in terms of patient preference and health care resource use in HICs,^{35,36} can effectively be used in LMICs. Furthermore, this study highlights the feasibility of conducting clinical trials with translational end points in LMICs.²⁵ Cooperative group studies in LMICs could further validate the use of sqR for inclusion in the World Health Organization's List of Essential Medicines. Public-private partnerships, and other such mechanisms, are recommended to enhance access to sqR and other monoclonal antibodies. Clinical outcomes for aggressive

Table 2. Pharmacokinetic analysis

	N*	C_{trough} , geometric mean (95% CI), $\mu\text{g/mL}^\dagger$
Overall	15	96.5 (77.5-120.1)
Therapy group		
Therapy group 1 (IV/SqR)	6	108.5 (76.3-154.3)
Therapy group 2 (SqR only)	9	89.2 (67.1-118.5)

*Three participants were excluded from this analysis due to incomplete pharmacokinetic data.

†Last observed concentration per patient (cycle 5).

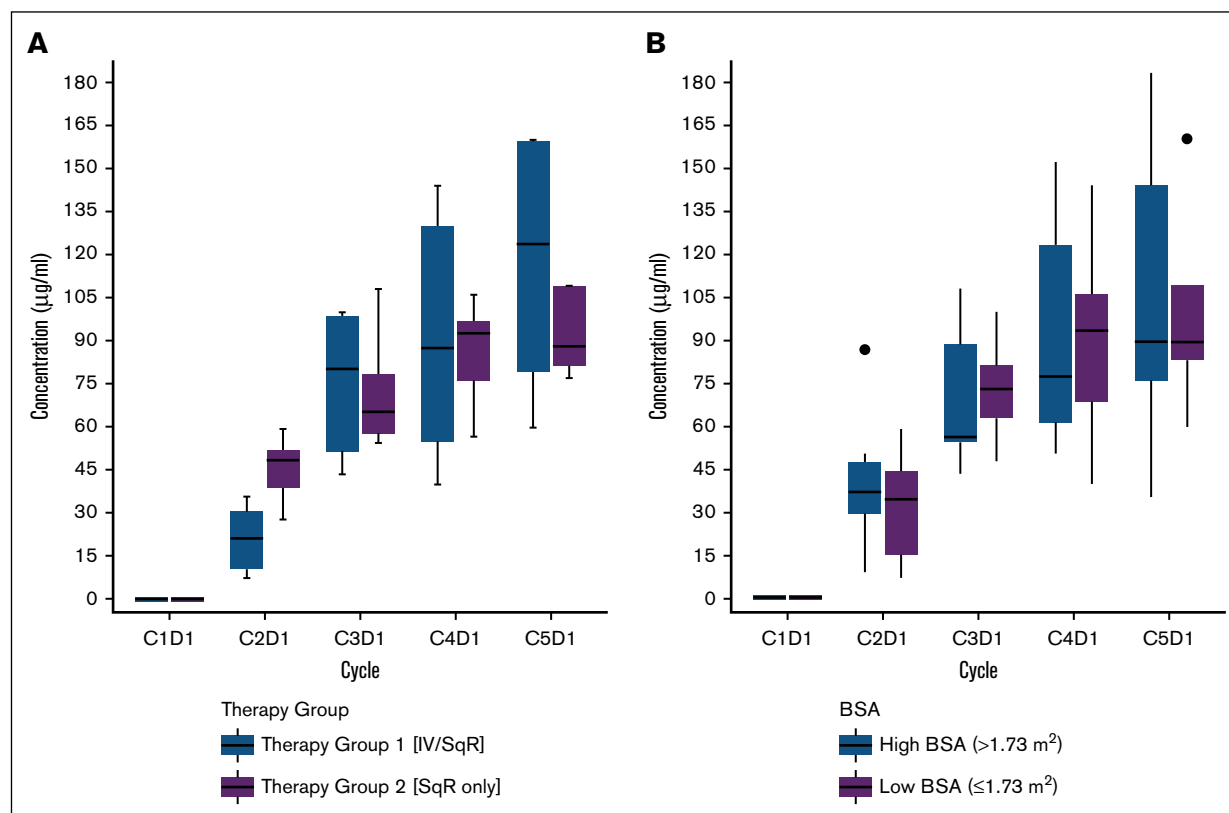


Figure 1. Rituximab trough concentration by (A) therapy group treatment cycle and (B) BSA. Box plots show median (IQR), with vertical lines showing maximum and minimum adjacent values. IQR, interquartile range.

lymphomas in LMICs remain considerably worse than in HICs; continued efforts to reduce this disparity are necessary.

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Authorship

Contribution: H.D., J.O., M.P.M., T.S.U., and E.H.W. contributed to the conceptualization; K.R.M., H.D., R.N., and P.N. contributed to the data curation; K.R.M. and M.P.M. contributed to the formal analysis; M.P.M., T.S.U., and E.H.W. contributed to the funding

acquisition; K.R.M., H.D., B.M., R.N., P.N., J.A., M.P.M., S.V.A., C.P., T.S.U., and E.H.W. contributed to the investigation; K.R.M., T.S.U., S.V.A., and M.P.M. contributed to the methodology; J.O., T.S.U., J.A., M.P.M., and E.H.W. contributed to the project administration; K.R.M. and M.P.M. contributed to the writing of the original draft; and K.R.M., M.P.M., J.A., B.W., T.S.U., C.P., S.V.A., and E.H.W. contributed to the review and editing of the manuscript.

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ORCID profiles: K.R.M., 0000-0001-8647-2399; H.D., 0000-0001-9227-4030; C.P., 0000-0003-3340-360X; E.H.W., 0000-0002-9570-2755.

Correspondence: Kelvin Roland Mubiru, Fred Hutchinson Cancer Research Center, Uganda Cancer Institute, Upper Mulago Hill, Kampala, Uganda; email: kmubiru@fredhutch.org.

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