

A Canadian perspective on the subcutaneous administration of rituximab in non-Hodgkin lymphoma

D. MacDonald MD,* T. Crosbie BScPharm ACPR,[†] A. Christofides MSc RD,[‡] W. Assaily PhD,[§] and J. Wiernikowski RN(EC) MN NP-Adult CON(C)^{||}

ABSTRACT

Rituximab is widely used for the treatment of non-Hodgkin lymphoma, being a key component in most therapeutic regimens. Administration of the intravenous (IV) formulation is lengthy and places a significant burden on health care resources and patient quality of life. A subcutaneous (sc) formulation that provides a fixed dose of rituximab is being examined in a number of studies. Results indicate that the pharmacokinetics are noninferior and response rates are comparable to those obtained with the IV formulation. Moreover, the sc formulation is preferred by patients and health care providers and reduces administration and chair time. Additional advantages include a lesser potential for dosing errors, shorter preparation time, reduced drug wastage, and fewer infusion-related reactions. Despite the success of the sc formulation, correct administration is needed to reduce administration-related reactions. By using a careful procedure, 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 Rituximab (subcutaneous), lymphoma, non-Hodgkin lymphoma

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in Canadian adults, accounting for 4.5% of all new cancer cases in men and 3.8% in women in 2015¹. Among the B-cell NHLs, the most prevalent subtypes include diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, with follicular lymphoma representing up to 35% of all cases in North America².

Significant progress has been made since the 1980s in the treatment of NHL, with one of the most important advances being the addition of rituximab to chemotherapy. That new approach has been shown, in a number of randomized studies involving patients with NHL, to significantly improve overall response, duration of response, and overall survival³.

Rituximab is currently approved by Health Canada for the treatment of patients with NHL⁴, including

- relapsed or refractory NHL;
- DLBCL [in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy];
- previously untreated stage III or IV follicular lymphoma [in combination with CVP (cyclophosphamide, vincristine, prednisone) chemotherapy];
- follicular lymphoma (as maintenance treatment for patients who respond to induction therapy with CHOP or rituximab-CHOP); and
- advanced follicular lymphoma with a high tumour burden (as single-agent maintenance treatment for previously untreated patients who have responded to induction therapy with rituximab-CHOP or rituximab-CVP).

Health Canada has also approved rituximab treatment for other disease states such as chronic lymphocytic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis.

Subcutaneous Rituximab

Despite the success of rituximab for the treatment of NHL, the intravenous (IV) formulation involves dose calculations, aseptic preparation of infusion fluids, long infusion durations, and titration of the infusion rate according to tolerability. In addition, IV administration can result

in improper catheter placement and toxicities such as infusion-related reactions, with potential negative consequences for patients and health care providers. To provide a faster and easier administration method, a subcutaneous (sc) formulation was developed that provides a fixed dose of rituximab.

Although sc administration of therapeutic agents can offer a number of advantages over IV administration, the technique is limited by the interstitial matrix, which physiologically restricts both the rate of delivery and the volume that can be injected⁵. To overcome that barrier, the sc formulation of rituximab is highly concentrated to reduce the volume to 11.7 mL and contains 8-recombinant human hyaluronidase alfa, an enzyme that temporarily degrades the extracellular matrix to facilitate the absorption of large volumes^{5,6}. The degradation of the extracellular matrix is temporary and allows for the injection of rituximab with minimal tissue distortion, edema, or tissue irritation⁵. Any changes to the extracellular matrix are reversible within 24 hours after the injection.

The sc formulation of rituximab was examined in a number of clinical trials, leading to its approval by the European Commission in March 2014 for use in patients with follicular lymphoma and DLBCL⁷. Health Canada subsequently approved the sc formulation of rituximab in September 2016. The sc formulation offers a number of potential advantages, such as a lower cost of administration, increased capacity for administration units by reducing chair time, and a lesser burden on patients.

The purpose of the present review is to discuss the use of sc rituximab as a potential alternative to the IV formulation in Canada; included is an in-depth review of key published papers and abstracts for the treatment of DLBCL and follicular lymphoma acquired through a literature search of PubMed and online meeting abstracts and presentations. A discussion of the use of sc rituximab for the treatment of other hematologic cancers such as chronic lymphocytic leukemia is beyond the scope of the review.

USE OF SC RITUXIMAB

Clinical Evidence

Pharmacokinetics

Growing evidence supports the idea that body weight has minimal influence on the variability of exposure to monoclonal antibodies⁶. In addition, prior studies have reported no dose-limiting toxicities for rituximab up to 5000 mg, suggesting that patients with a low body surface area (BSA) should not experience dose-limiting toxicities⁸. The sc formulation of rituximab is therefore amenable to a fixed dose, allowing for more convenient dose preparation, with fewer errors. To obtain clinical activity comparable to that of the IV formulation, a pharmacokinetic bridging approach was taken, with the idea that the C_{trough} concentration is related to the saturation of CD20 receptors, which is necessary for optimal efficacy⁶. Therefore, the correct dose of the sc formulation would be that which achieves at least the same pharmacokinetic profile as the IV formulation. Thus, patients with a higher BSA should receive a dose sufficient for saturation of CD20 receptors.

The phase IB SparkThera trial used a 2-stage design to examine the pharmacokinetics and safety of the sc compared with the IV formulation of rituximab as maintenance therapy for follicular lymphoma (Table 1)⁶. In the first stage, 124 patients were randomly assigned to sc rituximab at various doses based on BSA or to IV rituximab at the standard dose of 375 mg/m². Results of the first stage predicted that a fixed sc dose of 1400 mg rituximab would achieve a C_{trough} similar to that achieved with the IV formulation dosed at 375 mg/m². The second stage confirmed that the sc 1400 mg dose resulted in a C_{trough} noninferior to that achieved with the standard IV dose given at 2- to 3-month intervals. After sc rituximab, the area under the curve was at least as high as that after administration of the IV formulation.

Subsequently, the SABRINA study compared induction and maintenance therapy using sc rituximab 1400 mg compared with the standard 375 mg/m² dose of the IV formulation in 127 patients with untreated follicular lymphoma^{12,a}. Again, the pharmacokinetic profile of sc rituximab proved to be noninferior to that of the IV formulation with respect to the geometric mean C_{trough} concentrations measured after the first 7 cycles. In the SABRINA study, a sub-analysis that categorized patients by BSA [high: >1.9 m² ($n = 59$); medium: 1.7–1.9 m² ($n = 46$); low: <1.7 m² ($n = 53$)] did not suggest any notable differences in efficacy outcomes between the IV and sc rituximab groups. In addition, both regimens demonstrated similar variability of C_{trough} (approximately 40%), meaning that BSA-based dosing did not optimize the pharmacokinetic exposure.

Based on the results of the foregoing studies, a fixed sc dose of rituximab 1400 mg was determined to be optimal for the treatment of follicular lymphoma.

Response Rates

In addition to noninferior pharmacokinetic outcomes, similar response rates with the sc and IV formulations of rituximab have also been shown in a number of studies. The SABRINA study reported investigator-assessed overall response rates of 84.4% and 83.4% with the IV and sc formulations respectively and complete response (CR) or unconfirmed CR (CRU) rates of 31.7% and 32.7% (Table 1)^{12,a}. The ongoing MABEASE study randomized 576 patients with untreated DLBCL 2:1 to receive either sc rituximab or IV rituximab at standard doses, plus 6–8 cycles of CHOP¹³. Preliminary data presented at the European Hematology Association meeting in 2015 showed comparable CR rates of 52% with the sc formulation and 51% with the IV formulation. Moreover, no differences in the occurrence of CR or CRU were observed by BSA category [high (>1.9 m², $n = 128$): 49.2%; medium (1.7–1.9 m², $n = 113$): 53.1%; low (<1.7 m², $n = 101$): 54.5%]. In addition, after a median follow-up of 24 months, progression-free survival was comparable in the treatment arms.

^a Davies A, Merli F, Mihaljevic B, Mercadal S, Solal-Céligny P. Subcutaneous rituximab and chemotherapy achieves similar overall response rates to intravenous rituximab in first-line follicular lymphoma: efficacy and safety results of the phase III SABRINA study [abstract S652]. Presented at the 2014 European Hematology Association Congress; Milan, Italy; 12–15 June 2014.

TABLE 1 Clinical trials examining subcutaneous rituximab

Reference	Population	Treatment	Notes
Rule <i>et al.</i> , 2013 ⁹ at ASH 2013; De Cock <i>et al.</i> , 2013 ¹⁰ at ASH 2013; Rule <i>et al.</i> , 2014 ¹¹ at ISPOR 2014 MABCUTE (NCT01461928)	Patients (n=216) with relapsed or refractory INHL treated with rituximab plus CHOP or CVP or bendamustine	1400 mg SC	<p>Patient satisfaction:</p> <ul style="list-style-type: none"> ■ Demonstrated consistent patient satisfaction and preference for SC administration <p>Time savings:</p> <ul style="list-style-type: none"> ■ Health care professional time reduced by 6.8–38.4 minutes with SC administration (compared with real-world data for IV administration) ■ Mean chair time saved was 64%–91% (SC compared with IV administration) <p>Safety:</p> <ul style="list-style-type: none"> ■ Administration-related reactions in 41% SC vs. 28% IV, but were transient and mild to moderate
Salar <i>et al.</i> 2014 ⁶ SparkThera (NCT00930514)	Patients with untreated follicular lymphoma receiving rituximab as maintenance after rituximab induction (stage 1: n=124; stage 2: n=154 additional)	1400 mg SC vs. 375 mg/m ² IV	<p>Pharmacokinetics:</p> <ul style="list-style-type: none"> ■ C_{trough} with SC administration noninferior to that with IV administration <p>Safety:</p> <ul style="list-style-type: none"> ■ Similar for SC and IV administration ■ Administration-related reactions^a more frequent with SC administration
Davies <i>et al.</i> , 2014 ¹² ; Davies <i>et al.</i> , 2014 ^b at EHA 2014 SABRINA (NCT01200758)	Patients with untreated follicular lymphoma receiving rituximab plus CHOP or CVP followed by rituximab maintenance (stage 1: n=127; stage 2: n=283)	1400 mg SC vs. 375 mg/m ² IV	<p>Pharmacokinetics:</p> <ul style="list-style-type: none"> ■ Profile of SC administration noninferior to that of IV administration ■ Body surface area and sex did not influence results <p>Efficacy:</p> <ul style="list-style-type: none"> ■ Overall response rate of 83.4% with SC administration vs. 84.4% with IV administration ■ Complete response or unconfirmed complete response of 32.7% with SC administration vs. 31.7% with IV administration <p>Safety:</p> <ul style="list-style-type: none"> ■ Similar for SC and IV administration ■ Administration-related reactions more frequent with SC administration (47% vs. 33% with IV administration), mainly grade 1
Lugtenburg <i>et al.</i> , 2015 ¹³ at EHA 2015 MABEASE (NCT01649856)	Patients (n=576) with untreated diffuse large B-cell lymphoma receiving rituximab plus CHOP	1400 mg SC vs. 375 mg/m ² IV	<p>Efficacy:</p> <ul style="list-style-type: none"> ■ Complete response rate of 52% with SC administration vs. 51% with IV administration <p>Safety:</p> <ul style="list-style-type: none"> ■ Overall adverse event rate of 92% with SC administration vs. 91% with IV administration ■ Slight increase in adverse events with increasing SC dose ■ Higher frequency of administration-related reactions^a with SC administration
Rummel <i>et al.</i> , 2015 ¹⁴ at ASH 2015; Rummel <i>et al.</i> , 2016 ¹⁵ at EHA 2016 PrelMab (NCT01724021)	Patients (n=743) with untreated follicular lymphoma or diffuse large B-cell lymphoma receiving rituximab plus CHOP or CVP or bendamustine	Two different sequences of SC and IV cycles (1400 mg SC, 375 mg/m ² IV)	<p>Patient satisfaction:</p> <ul style="list-style-type: none"> ■ SC administration preferred by 80% of patients; IV administration, by 10%; 10% had no preference <p>Reasons included</p> <ul style="list-style-type: none"> ■ less time in clinic (68%) ■ more comfortable during administration (37%) ■ mean administration time of 865 ± 401 minutes IV vs. 37 ± 100 minutes SC ■ time taken with SC administration was just right (>70% patients) <p>Safety:</p> <ul style="list-style-type: none"> ■ Similar for SC and IV administration ■ More gastrointestinal adverse events with IV administration (55% vs. 31%) in follicular lymphoma

TABLE 1 Continued

Reference	Population	Treatment	Notes
Irwin <i>et al.</i> , 2016 ¹⁶ at EHA 2016	Patients (n=92) with follicular lymphoma or diffuse large B-cell lymphoma in a single centre in the United Kingdom	SC administration as part of routine therapy	<p>Savings:</p> <ul style="list-style-type: none"> ■ Drug cost savings estimated at UK£20,000 ■ Pharmacy time reduced by 160 hours annually ■ Chair time reduced by 842 hours annually <p>Safety:</p> <ul style="list-style-type: none"> ■ No increase in adverse events

^a Includes symptoms such as erythema, pain, swelling, pruritus, rash, bruising, and local myalgia.
^b Davies A, Merli F, Mihaljevic B, Mercadal S, Solal-Celigny P. Subcutaneous rituximab and chemotherapy achieves similar overall response rates to intravenous rituximab in first-line follicular lymphoma: efficacy and safety results of the phase III SABRINA study [abstract S652]. Presented at the 2014 European Hematology Association Congress; Milan, Italy; 12–15 June 2014.
 ASH = American Society of Hematology (annual meeting); ISPOR = International Society for Pharmacoeconomics and Outcomes Research (annual meeting); iNHL = indolent non-Hodgkin lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; SC = subcutaneous; IV = intravenous; EHA = European Hematology Association (annual meeting).

Safety

To date, studies have shown that the safety profiles of the sc and IV formulations of rituximab are similar (Table 1)^{6,9–11,13,14,16,17}; however, studies have reported greater rates of gastrointestinal toxicities with the IV formulation (55% vs. 31%)¹⁴ and of local administration-related reactions (ARRS) with the sc formulation^{6,9–11,13,14,17}. Of patients given the sc formulation, ARRS were reported by 31%–50%; of those given the IV formulation, 4%–32% reported such reactions. The ARRS included erythema, pain, swelling, pruritus, rash, bruising, and local myalgia. Despite the greater rates of ARRS with the sc formulation, the reactions were generally very mild and transient in nature.

Patient Preference and Time Savings

Several studies have collected data on patient preference and time savings associated with the use of the sc rather than the IV formulation of rituximab. The ongoing PrefMab study randomly assigned 743 patients with untreated DLBCL or follicular lymphoma to receive either 1 cycle of IV rituximab and 3 cycles of sc rituximab followed by 4 cycles of IV rituximab, or 4 cycles of IV rituximab followed by 4 cycles of sc rituximab at standard doses^{14,15}. Both groups also received 6–8 cycles of CHOP chemotherapy. Preliminary data presented at the American Society of Hematology meeting in 2015 and at the European Hematology Association meeting in 2016 demonstrated that, of 620 evaluable patients, 495 (80%) preferred sc rituximab after 6 cycles of therapy; only 62 (10%) preferred IV delivery. In addition, 30%–40% of patients felt very strongly and 30%–40% felt fairly strongly that they preferred the sc formulation. The main reasons for preferring sc delivery included less time spent in the clinic and improved comfort during administration. Additionally, more than 70% of patients felt that the time to administer the sc formulation was “just right,” and most did not feel that the shorter administration time negatively affected the time to discuss their illness with the health care team.

A second ongoing trial, MABCUTE, is examining induction with sc rituximab (IV cycle 1; sc cycles 2–8) plus chemotherapy, followed by maintenance with sc rituximab at standard doses in patients with relapsed or refractory indolent NHL⁹. Upon completion of standard maintenance, responding patients will be randomized to receive additional maintenance or observation^{9,10}. Preliminary data from the MABCUTE study presented at the American Society of Hematology meeting in 2013 showed a reduction in chair time of 64%–91% and a savings in physician time of 6.8–38.4 minutes, resulting in an expected annual chair time savings of 105.1–233.4 eight-hour days. An ongoing study using data from the MABCUTE and PrefMab studies is examining scores on the Rituximab Administration Satisfaction Questionnaire to determine patient perceptions of the effect of administration route¹¹. Preliminary results presented at the Annual European Congress of International Society for Pharmacoeconomics and Outcomes Research in 2014 showed improved questionnaire scores for psychological impact, activities of daily living, convenience, and satisfaction with the sc formulation. In addition, approximately 85% of patients preferred the sc formulation to the IV formulation and felt that the time it took to administer the sc formulation was “just right.”

A third ongoing retrospective trial by Irwin *et al.*¹⁶ is examining the cost and time savings of sc compared with IV rituximab in a single centre in the United Kingdom. Preliminary findings presented at the European Hematology Association 2016 meeting showed a drug cost savings of £20,000 with the sc formulation. In total, approximately 160 pharmacy hours were saved per year, and a 842-hour reduction in chair time per year was observed.

Preparation and Storage

Rituximab for sc administration is provided in ready-to-use, single-dose (1400 mg) vials containing 11.7 mL of sterile, non-pyrogenic, preservative-free solution (no dilution required)^{5,18}. When prepared under aseptic conditions, sc rituximab is physically and chemically stable in a syringe for up to 48 hours at 2°C–8°C or up to 8 hours at room temperature. To reduce errors in selecting the correct formulation, the vials and boxes of the sc and IV formulations should visually differ from each other and be stored in physically separate areas. In addition, proper nomenclature should be used to distinguish between the sc and IV formulations in the computer database, a step that will be important for order entry to ensure that the correct formulation is selected and that label generation for product preparation purposes is accurate. When checking a prepared syringe of sc rituximab in the pharmacy, a second pharmacy technician should check the drug vial to ensure that the sc formulation is chosen.

Administration

The first dose of rituximab should always be given intravenously, with the sc formulation being started from the 2nd cycle only once the patient is seen to be able to receive a complete IV dose^{5,18}. The reasons for that strategy are that ARRs are most likely to occur with the first dose, and the chances of such reactions occurring subsequently are very low. The patient can therefore be monitored over an extended period of time and the infusion can be slowed or stopped if reactions occur. Furthermore, studies of sc rituximab to date have given the first dose intravenously, and evidence that giving the first dose by the sc route is safe is therefore not sufficient.

Detailed notes should be added to the patient's chart after IV infusion to aid in the decision to move to the sc route. Patients should then be counselled on the change in the administration route. Patients who have tolerated their first exposure to the medication can be notified of the change in route toward the end of the IV infusion, being told that they are now able to receive rituximab in a less time-consuming manner. A review of the patient's chart is needed to ensure that the patient tolerated the first IV dose and is ready to proceed to the sc route. The pharmacist or nurse can confirm that cycle 2 has been ordered by the sc route and that the chair time allotted is for a sc injection.

Administration of sc rituximab should always take place by injection into the hypodermis of the abdomen. Because many centres have a maximum volume that can be injected by the sc route, nursing policy and procedures will have to be updated to allow for administration of the 11.7 mL of sc rituximab. Detailed administration instructions are found in Table II.

TABLE II Key steps for administering subcutaneous rituximab^a

- Rituximab should be administered in a setting in which full resuscitation facilities are immediately available.
- Position the patient comfortably in a reclining position with the target region accessible.
- Reassure the patient to help calm anxiety—she or he will need to sit still for 5–7 minutes.
- Attach the appropriate hypodermic needle to the syringe immediately before administration^b.
- Disinfect the target area. Nurse should be sitting comfortably beside patient with feet firmly on floor.
- Do not inject the drug into areas where the skin is red, bruised, tender, or hard, or where moles or scars are present.
- Pinch the skin of the abdomen with one hand to create a skin fold. With the other hand, and using sterile technique, insert the needle at a 45- to 90-degree angle into the skin fold.
- Inadvertent intramuscular injection could result in a more rapid, unwanted systemic exposure. To check for accidental intramuscular injection, draw back on the syringe to ensure that the needle has not entered a blood vessel.
- Release the skin fold and apply pressure on syringe, slowly injecting the drug into the subcutaneous tissue at a constant flow rate over approximately a 5-minute period (approximately 2 mL/min) by applying gentle, even pressure on the syringe with the palm of the hand. To ensure constant flow, position the arm comfortably for the full duration of the injection.
- Have a timing method in place to monitor the rate of administration.
- Ensure that the full 11.7 mL dose is administered to all patients, regardless of body surface area.
- If an injection is interrupted, it can be resumed or continued at another location on the abdomen.
- After administration, the injection site should be covered with a dressing in line with local standards.
- Patients should be observed for at least 15 minutes after each injection session. The observation period should be extended for patients with a history or increased risk of hypersensitivity reactions.
- Patients should be instructed to contact a doctor immediately or go to the emergency department of their nearest hospital if they experience side effects^c.

^a Adapted from Carlson *et al.*, 2015⁵.

^b No recommended needle size; clinical trial investigators use a 25- or 27-gauge needle. Use of a butterfly catheter has not been investigated in clinical trials.

^c Side effects can include severe skin rash, itching, or hives; breathing difficulties, swelling of the tongue or throat; vision loss, associated with headaches, confusion, or seizures; yellowing of skin or eyes; light-coloured bowel movements or dark-coloured urine.

Although ARRs are common after the administration of sc rituximab, such reactions are usually mild and transient. In addition, a number of preventive strategies can be used to reduce the risk of ARRs after administration (Table III). Based on clinical experience, most ARRs require observation only and resolve spontaneously within 1–2 days⁵.

Canadian Perspective

Use of a sc formulation of rituximab has a number of key advantages over use of the IV formulation (Table IV). The sc formulation is provided in a ready-to-use vial with a fixed dose, which eliminates dose calculation errors,

preparatory compounding by the pharmacy, waste associated with BSA-based dosing, and IV tubing preparation in the chemotherapy suite. In addition, the administration time required for the sc formulation is approximately 5 minutes compared with the approximately 90 minutes required for IV rituximab. The reduction in required chair time for the sc formulation consequently allows for more patients to receive treatment in a single day and for administration of

other IV therapies. Finally, the shorter administration time not only reduces the burden on health care resources, but is also likely to improve patient quality of life (more time at home and less time in the cancer centre, for instance) and to lower the costs associated with infusion times (for example, because of parking, time off work, and so on).

SUMMARY

Rituximab is widely used in the treatment of NHL and is a key component of most treatment regimens. Despite widespread success, IV administration is lengthy and is associated with a number of potential adverse effects. The sc formulation of rituximab has been proved to be noninferior to the IV formulation with respect to pharmacokinetics, and it is associated with comparable response rates and a safety profile similar to that of the IV formulation, with the exception of mild and transient ARRS. In addition, the sc formulation reduces the administration time and is preferred by patients and health care providers. By following correct administration techniques and using appropriate strategies to prevent and monitor for ARRS, sc rituximab can be given safely and effectively.

Given the shorter delivery time and the lack of a need for facilities that are equipped to give infusions, sc formulations of rituximab could potentially improve patient convenience and reduce the burden on health care resources. The sc formulation achieves an ideal balance between time in the injection clinic, where patient needs can be addressed, and time at home, where quality of life can be the focus.

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CONFLICT OF INTEREST DISCLOSURES

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TABLE III Tips for reducing administration-related reactions^a

- Administer an analgesic or antipyretic (for example, acetaminophen) and an antihistamine (for example, diphenhydramine) 30–60 minutes before each subcutaneous rituximab injection. Those medications could be taken by patients before they arriving for the appointment.
- Consider premedication with systemic glucocorticoids for patients with an increased risk of hypersensitivity reactions.
- Treatment for localized skin reactions could include topical steroid creams in line with local institutional practice, or the use of a cold compress, or both.
- Advise patients to continue monitoring the injection site at home and to report any changes promptly to the clinical team.
- To reduce the severity of injection-site pain, it is recommended that rituximab never be injected in areas where the skin is red, bruised, tender, or hard, or has moles or scars.
- Avoid injecting at the waistband, where pants can press into the injection site.
- Ask the patient to avoid tight clothing and lotions at the injection site.
- In cases of excessive pain on injection delivery, incorrect needle angle or location should be suspected (the needle should ideally be inserted at an angle of 45–90 degrees). In such cases, stop the administration without removing the needle, assess pain severity, and discuss with the clinical team whether to resume the injection or reposition the needle.
- A cold compress might be useful to alleviate pain. If the drug leaks from the injection site, the clinical team should consider removing the syringe and administering the injection at a different abdominal site.
- To reduce skin irritation and minimize drug leakage onto the skin, an air sandwich technique can be considered for the injection.

^a Adapted from Carlson *et al.*, 2015⁵.

TABLE IV Advantages of the subcutaneous compared with the intravenous (IV) formulation of rituximab

Factor	Formulation	
	Subcutaneous	Intravenous
Dosing	Fixed, no dose calculations required	IV bag preparation Dose calculations based on body surface area can be susceptible to error
Pharmacy preparation	Short prep time	Longer prep time, especially for doses >500 mg because multiple vials are required for preparation
Wastage	None	Leftovers in vial cannot be used more than 24 hours after preparation and rely on another patient being booked the same day
Administration	Approximately 5 minutes	90 Minutes
Chair time	Reduced by 64%–91% compared with IV time	—
Health care provider time	Reduced by 7–38 minutes per session compared with IV time	—

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AUTHOR AFFILIATIONS

*Division of Hematology, Dalhousie University, and QEII Health Sciences Centre, Halifax, NS; †The Ottawa Hospital, Ottawa, ON; ‡IMPACT Medicom Inc., Toronto, ON; §Hoffmann–La Roche, Mississauga, ON; ‖The Juravinski Hospital and Cancer Centre, Hamilton, ON.

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