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ORIGINAL RESEARCH ARTICLE

Assessment of Self-Administration of Romiplostim in Patients with Immune Thrombocytopenic Purpura after Receipt of Home Administration Training Materials: a Cross-Sectional Study

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Abstract

Introduction Romiplostim is a subcutaneously administered thrombopoietin-receptor agonist approved in the European Union for self-administration (or administration by a caregiver) in selected adult patients with chronic primary immune thrombocytopenia refractory to other treatments. To mitigate the risk of medication errors due to self-administration, the manufacturer has implemented additional risk minimisation measures (RMM) in the form of a Home Administration Training (HAT) pack to support the training of both healthcare professionals (HCPs) (guide and checklist for patient selection and training) and patients (a preparation mat, quick guide booklet, step-by-step guide, self-administration diary and DVD/video).

Objective The primary objective was to estimate the proportion of patients/caregivers who administered romiplostim correctly after HAT pack training.

Methods A multicentre observational study was conducted to evaluate the effectiveness of the HAT pack by recording data on a standardised collection form during direct observation of patients/caregivers in the act of administering romiplostim at the first standard-of-care visit 4 weeks after training with the HAT pack.

Results Among the 40 patients/caregivers enrolled across 12 study centres in eight European countries, 35 [87.5%; 95% confidence interval (CI) 73.9–94.5] administered romiplostim correctly, and five (12.5%; 95% CI 5.5–26.1) did not.

Conclusion The correct administration of romiplostim by most patients/caregivers supports the effectiveness of the HAT pack as an additional risk minimisation tool in the population and setting of this study.

Key Points

Patients with chronic primary immune thrombocytopenia may be selected by their healthcare professional (HCP) as candidates for home administration of romiplostim, a medication that increases platelet counts.

These selected patients or their caregivers must undergo Home Administration Training (HAT) designed to minimise risk of administration errors, and must demonstrate competence before being permitted to home administer romiplostim.

This study showed that most patients or caregivers (87.5%) correctly administered romiplostim while under direct observation of an HCP, showing that the HAT pack was effective in minimising the risk of patient/caregiver errors in the population studied.

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1 Introduction

Primary immune thrombocytopenia (ITP) is a rare disorder characterised by a low platelet count and a tendency for increased bleeding [1]. The incidence of adult ITP ranges from an estimated 1.6 to 3.9 per 100,000 persons per annum in the European Union (EU) [2–5]. Current international standards for first-line treatments for primary ITP include steroids and intravenous immunoglobulin, while second-line treatments include splenectomy, immunosuppressants, vinca alkaloids, rituximab and thrombopoietin-receptor agonists [6].

Romiplostim (Nplate®; Amgen Europe B.V.) is a subcutaneously administered thrombopoietin-receptor agonist approved for use in the EU for patients with chronic ITP refractory to other treatments [7]. Romiplostim was first approved for administration at weekly intervals by healthcare professionals (HCPs) in the EU in 2009 using a multistep process that includes dose calculation based on the patient's weight and platelet count response, reconstitution of drug (supplied as vials containing 250 or 500 µg of active ingredient in the form of a sterile, preservative free, lyophilised solid white powder), measurement of volume to be injected as per the physician's prescription and subcutaneous injection.

To provide patients with a more flexible alternative to clinic visits for injections, the manufacturer developed an additional kit for self-administration. Approval for romiplostim self-administration by selected patients or their caregivers was granted in December 2012 [7]. Candidates for self-administration, as specified in the Summary of Product Characteristics (SmPC) [7], include adult chronic ITP patients with stable platelet count $\geq 50 \times 10^9$/L for ≥ 4 weeks without dose adjustment and their caregivers. Romiplostim was then also supplied in reconstitution packs that contain 250 or 500 µg of romiplostim powder in a vial and sterile water (0.72 or 1.2 mL) in a prefilled syringe. The packs also include a plunger rod for the prefilled syringe, sterile vial adapter, sterile safety needle, sterile 1-mL Luer lock syringe, and alcohol pads. While the dose calculation is performed by the prescribing physician, self-administration steps completed by the patient or caregiver include reconstitution of drug, measurement of volume to be injected as per the physician's prescription, and subcutaneous injection. Self-administration provides the opportunity for selected patients to transition from clinic to home settings, without loss of efficacy [8]. Hence, self-administration has the potential to save resources and improve patient quality of life by allowing patients to take greater control of their disease management.

To assist patients in correctly administering romiplostim outside of healthcare facilities and to mitigate the potential for medication errors associated with self-administration, the manufacturer implemented additional risk minimisation measures (RMM) in the form of a Home Administration Training (HAT) pack to support the training of both HCPs and patients. For HCPs, the HAT pack includes a guide and checklist for patient selection and training. For patients or their caregivers, the HAT pack training materials include a preparation mat (placemat to lay out the administration components), a quick guide booklet, a step-by-step guide, a self-administration diary (log of administration details only), and an instructional DVD/video. Following HAT pack training, patients/caregivers are required to demonstrate to an HCP their ability to self-administer. This process is designed to identify patients/caregivers who are both mentally and physically able to carry out administration (including self-injection where applicable). After being deemed competent to perform all steps of the administration, the patient/caregiver is permitted to administer at home. 4 weeks after HAT pack training, patients and their caregivers, where applicable, are required to visit the HCP for observation while reconstituting and administering romiplostim as an additional check on their self-administration technique. As stated in the SmPC, only patients or their caregivers who demonstrate the ability to correctly reconstitute and self-administer romiplostim are allowed to continue doing so [7].

European pharmacovigilance legislation requires assessment of any additional RMM, and the European Medicines Agency (EMA) has produced guidelines on Good Pharmacovigilance Practices (GVP) [9], which complement a two-part good practice guide on medication errors [10, 11]. As these guidelines were released after the initiation of this study, our study design was based on the approach described by Prieto et al. [12], as a risk minimisation resource for medication errors. Prieto et al. describe a dual evidence study design in which the effectiveness of RMM is evaluated based on both *implementation* (clinical knowledge; clinical behaviour) and *attainment of final objectives* (adverse drug reaction occurrence before and after, or compared to reference value).

The objective of this observational study was to estimate the proportion of patients/caregivers who administered romiplostim correctly while being observed by an HCP. We expected that the results of the study would serve as an indicator for the types of administration errors that might occur in this population, and identify possible opportunities for refinement of the HAT pack.

2 Patients and Methods

2.1 Study Design

This was a multicentre, non-interventional, cross-sectional study in which HCPs observed patients or their caregivers in the act of administering romiplostim at their first standard-of-care visit, which occurred 4 weeks (range 2–8) after training with the HAT pack and subsequent self-administration at home. The primary objective was to estimate the proportion of patients/caregivers who administered romiplostim correctly. The secondary objectives were to estimate the proportion who reconstituted romiplostim correctly, the accuracy of administration of the prescribed dose of romiplostim, and the proportion who injected romiplostim successfully.

Correct administration of romiplostim was a composite endpoint consisting of correct reconstitution, accurate dose delivery, successful injection, and no intervention by the HCP at any point during administration.

- *Correct romiplostim reconstitution* was defined as a multi-step process consisting of use of aseptic technique to prepare the vial, gentle injection of all the sterile water from the syringe into the vial, and ensuring that all romiplostim was dissolved.
- *Accurate romiplostim dose delivery* was defined as a margin of error $\pm 10\%$ between the prescribed and administered doses.
- *Successful romiplostim injection* was defined as a multi-step process consisting of the removal of all air bubbles from the syringe, clinically appropriate use of an alcohol wipe at the injection site, clinically appropriate handling of the syringe to avoid contamination, and clinically appropriate technique of subcutaneous injection.

Centres with clinicians known to treat ITP patients with romiplostim were approached for possible participation in this study. Study centres and countries were selected based on availability and willingness to participate; no minimum number of patients treated with romiplostim, use of self-administration, or other criteria were applied. The study began after the HAT pack became available in the individual countries, beginning with the first country in March 2013.

As part of routine care, patients or their caregivers were given a self-administration kit and a HAT pack. Physicians/HCPs directly observed the patient/caregiver in the act of administering romiplostim at the first standard-of-care 4-week visit and completed a standardised data collection form. As noted earlier, the HCP HAT pack includes guidance on selecting and training patients. Variables collected included demographics of the patient/caregiver performing the administration, the prescribed and administered injection volume per syringe, appropriate alcohol wipe use at injection site, clinically appropriate handling of the syringe to avoid contamination, and clinically appropriate subcutaneous injection technique. Further observations at any subsequent visits to the study centre were also recorded within 16 weeks of enrolment. These additional visits were voluntary and were not required for study participation; they occurred only if the HCP requested them as part of routine clinical practice. Data were also collected from the self-administration diary at the first standard-of-care visit to ensure that there were no problems with administration while not at the clinic.

2.2 Patients/Caregivers

To be eligible for romiplostim self-administration, as per the SmPC, patients were required to be adults (≥ 18 years of age) with chronic ITP with a platelet count $\geq 50 \times 10^9$/L sustained for ≥ 4 weeks without the need for dosage adjustment. The person performing the administration (either the patient or their caregiver) was required to be new to romiplostim administration or to have had at least a 3-month gap between the last administration and enrolment. Patients or their caregivers were enrolled consecutively and provided informed consent.

2.3 Statistical Analyses

The sample size was selected to achieve adequate precision for the estimation of the primary endpoint and taking into account the infrequency of ITP. Additionally, given the need for the patient to be capable of self-administration or to have a caregiver capable of giving the injection, and the limitations imposed by reimbursement restrictions for romiplostim, we predicted that the number of patients/caregivers available was likely to be of the order of several hundred across Europe. With a sample size of 40, if 90% of participants were found to self-administer correctly, the 95% confidence limits would be 77–96%.

All analyses were descriptive, and no formal hypothesis was tested. The primary endpoint was the proportion of patients/caregivers who correctly administered romiplostim at the first 4-week visit based on 'yes' or 'no' according to the criteria listed in Sect. 2.1, and secondary endpoints included the proportion of patients/caregivers who reconstituted romiplostim correctly based on a 'yes' or 'no' answer to meeting the criteria for correct reconstitution as defined in Sect. 2.1; the percentage difference between the prescribed and administered dose of romiplostim; and the proportion of patients/caregivers who administered romiplostim successfully based on a 'yes' or 'no' answer to meeting the criteria for successful administration as defined in Sect. 2.1.

3 Results

A total of 41 patients/caregivers were provided with HAT pack training and were considered eligible for this study. Enrolment began on 7 July 2014, and the last patient's final visit was on 20 November 2015. One patient became ineligible and was excluded from the analysis because the first standard-of-care visit occurred outside the prespecified window (1 week after HAT pack training). The analysis therefore included 40 patients/caregivers at 12 study centres across eight countries: Austria (three patients), Belgium (one patient), France (one patient), Germany (four patients), Greece (four patients/five caregivers), The Netherlands (eight patients/four caregivers), Spain (four patients/two caregivers), and the UK (three patients/one caregiver). Overall, the study population (i.e. the individuals performing the injection) consisted of more patients than caregivers [28 (70%) vs 12 (30%)]. 23 patients/caregivers (57.5%) were women, and the median (range) age was 60 (25–91) years (Table 1).

Table 1 Demographic and baseline characteristics of the patient or caregiver administering romiplostim; characteristics of HCP; number of romiplostim vials

Total no. of patients/caregivers	40
Female gender, *n* (%)	23 (57.5)
Median age, years (range)	60.0 (25–91)
Age group, *n* (%)	
18–64 years	23 (57.5)
≥ 65 years	17 (42.5)
Person administering romiplostim, *n* (%)	
Patient	28 (70.0)
Caregiver	12 (30.0)
Observing HCP, *n* (%)	
Clinician	15 (37.5)
Nurse	25 (62.5)
Same person acting as trainer and observing HCP, *n* (%)	
Yes	38 (95.0)
No	2 (5.0)
Number of vials needed for single administration, *n* (%)	
1	36 (90.0)
2	3 (7.5)
3	1 (2.5)

HCP healthcare professional

35 patients/caregivers (87.5%) (25 patients and ten caregivers) administered romiplostim correctly [95% confidence interval (CI) 73.9–94.5] while being observed at the first standard-of-care visit (i.e. reconstituted romiplostim correctly, administered the prescribed dose within a 10% margin of error, successfully injected romiplostim, and did not require HCP intervention at any point during the administration), and five (three patients and two caregivers) (12.5%, 95% CI 5.5–26.1) did not (Table 2). Of the five patients/caregivers who did not meet the criteria for correct administration, one patient forgot to check that all romiplostim was dissolved, one patient and one caregiver needed verbal encouragement, one patient needed nursing intervention to read the correct dose from the vial due to poor eyesight, and one caregiver needed guidance with the syringe and vial connection (the caregiver connected the syringe with the needle instead of the vial, and broke the needle; a new needle was provided and the caregiver then administered romiplostim correctly). We note that the

Table 2 Direct observation of patients/caregivers administering romiplostim at the first standard-of-care 4-week visit after HAT pack training

Parameter	No. of patients/caregivers (%)	95% confidence interval
Primary endpoint		
Patient or caregiver administered romiplostim correctly	35 (87.5)	73.9–94.5%
Secondary endpoints		
Patient or caregiver reconstituted romiplostim correctly	39 (97.5)	87.1–99.6%
Aseptic techniques used in preparing the vial/s	40 (100)	NA
Gently injected all water from sterile water syringe into the vial/s	40 (100)	NA
Ensured all romiplostim dissolved	39 (97.5)	NA
Difference between the prescribed and administered dose of romiplostim within ± 10%	40 (100)	NA
Patient or caregiver injected romiplostim successfully	40 (100)	91.2–100%
Ensured all air bubbles removed from injection syringe	40 (100)	NA
Clinically appropriate use of alcohol wipe at injection site	40 (100)	NA
Clinically appropriate handling of syringe to avoid contamination	40 (100)	NA
Clinically appropriate technique of subcutaneous injection	40 (100)	NA

HAT Home Administration Training, *NA* not applicable

patient who was excluded from the analysis (because the first standard-of-care visit occurred only 1 week after training with the HAT pack) did administer romiplostim correctly.

For the secondary endpoints, 39 patients/caregivers (97.5%) reconstituted romiplostim correctly, 40 (100%) patients/caregivers performed the injection of romiplostim successfully, and romiplostim dose accuracy was within the predefined 10% margin of error for all patients [the mean (standard deviation) percentage difference was 0.16% (1.01%) and the median percentage difference was zero]. There was a single case of dose preparation inaccuracy where a caregiver prepared a dose of 250 µg instead of 235 µg; however, as the difference was within the 10% margin of error, the criterion for dosage accuracy was met.

Five patients and one caregiver (15% of participants) had additional follow-up visits for further observation as requested by the HCP. Romiplostim was administered correctly on each of these visits. Three patients were assessed during their first standard-of-care visit and at three subsequent monthly routine visits. One patient was assessed during the first standard-of-care visit and at one subsequent monthly routine visit. One patient and one caregiver were assessed at the first standard-of-care visit and during an additional monitoring visit because they previously required verbal encouragement from the HCP.

A total of 18 patients/caregivers (45%) brought their self-administration diary to the first standard-of-care 4-week visit. Of these, two patients recorded that they had administered one of the doses earlier (1 week) or later (1 day) than prescribed. Both then administered romiplostim correctly at the first 4-week visit.

4 Discussion

The objective of this study was to estimate the proportion of patients/caregivers who administered romiplostim correctly while being observed by an HCP. We report that 87.5% of patients/caregivers completed all steps of the process correctly while under observation of an HCP 4 weeks after completing training with HAT pack RMM and demonstration of competence. Instances where the HCP had to intervene to correct an error during administration by the patient/caregiver included failure to check that all romiplostim was dissolved, incorrect attachment of the syringe and vial, incorrect preparation of dose, inability to read the dose correctly due to poor eyesight, and need for verbal encouragement. Given that the HCP interventions to correct a potential administration error were associated with addressable factors which can be managed by training with the current HAT pack materials, we did not find a cause in the limited context of the population studied to refine the HAT pack. While the optimal evaluation of the effectiveness of the HAT pack in reducing errors would have involved assessment pre- and post-training, this was not possible since romiplostim self-administration kits were accompanied by the HAT pack materials from the initiation of marketing. As noted by Prieto et al., if before and after testing of RMM is not possible, the study should measure the outcome that the measures are intended to avoid [12]. No adverse drug reactions were reported during the current study.

Literature searches did not uncover similar articles on home administration of other medications requiring reconstitution and injection; however, some studies have evaluated home administration with prefilled syringes or automatic injectors. Nearly all patients (73 of 75; 97%) successfully injected themselves with an adalimumab autoinjector [13]; 98% of patients successfully injected themselves with an etanercept autoinjector [14]; and 89% of patients with multiple sclerosis injected themselves successfully with a prefilled syringe [15]. We also identified two studies comparing the success of self- versus HCP administration. Successful administration of lanreotide Autogel, as measured by growth hormone control, was achieved for 14 out of 15 self-administering patients and 14 out of 15 patients receiving HCP administration in a non-randomised study [16]. Home versus HCP injection of contraceptive were associated with similar success rates based on continuation (71% self vs 63% HCP), where patients performing home injection had to demonstrate proficiency with injection to receive additional medication [17]. In general, the paucity of information on evaluation of RMM to support home administration for injectable medications, despite the increasing number of medications available for self-injection, indicates a need for further research in this area.

Medication errors are a source of health risk, particularly where medication administration involves multiple steps such as preparation, dose measurement and injection. Self-administration of such medications by the patient or caregiver produces an additional level of risk. The EMA guidelines describe the process of risk management and types of activities that should be undertaken to identify potential medication errors associated with dispensing and administration of a product [9–11, 18]. Identified risks should be mitigated through additions to the product labelling as well as the creation of additional RMM such as explanatory leaflets and training materials directed toward HCPs, patients and caregivers. RMM directed toward patients using plain language were more effective than those with medical language and have been shown to increase patient understanding of self-administration of biologic drugs [19].

In accordance with the legislation and guidance documents, the manufacturer of romiplostim provides HAT pack training materials as an additional RMM. Physicians who express an interest in initiating self-administration for specific adult patients receive a HAT pack for those patients.

HAT pack materials for HCPs include a guide for selecting and training eligible patients/caregivers for self-administration, as it is essential that the patients and their caregivers, where applicable, can follow the instructions and properly execute all of the required steps in the self-administration process, and have no physical or mental condition that prevents them from accurately performing these steps. In addition, the HAT pack materials for the patients/caregivers provide instructions and specific wording indicating steps where care needs to be taken to avoid the risk of medication errors (e.g. checking that romiplostim has been reconstituted correctly, preparing the correct dose) and noting the consequences of dosing errors. This is further emphasised by the step-by-step self-administration DVD/video within the HAT pack, which highlights the steps during which medication errors due to self-administration may occur.

Since observations subsequent to the first 4-week visit were voluntary, and because the data collected from these later visits were limited, it is not possible to determine whether all patients/caregivers continued to administer romiplostim successfully after the first standard-of-care visit or whether re-evaluation of the self-administration prescription was required. Of those patients who were repeatedly assessed at subsequent monthly routine visits, all continued to administer romiplostim correctly.

Given that this study was conducted on a convenience sample rather than a random sample of patients, the generalisability of the results may be limited. ITP is a rare disease with an estimated annual incidence in Europe of 3.3 per 100,000 adults [20], only a subgroup of patients receive romiplostim, and a smaller subset of these patients are evaluated and approved by their prescribers for self-administration, leading to a relatively small source population of patients that may be widely dispersed or concentrated in specific institutions. Moreover, the availability of self-administration kits is limited to selected countries because of reimbursement restrictions. Given that the source population in Europe is likely in the order of several hundred, the sample size of 40 reflects a sizeable proportion of the source population.

4.1 Limitations

A new-user (defined as new to romiplostim self-injection or having at least a 3-month gap since the last injection) design was chosen for this study to help avoid any biases identified from historical use and self-administration exposure with romiplostim. However, exposure and familiarity to drug administration devices may vary among the caregivers included in the study as they may be either family/friends who are naïve to such devices or HCPs familiar with such devices but new to the romiplostim self-administration kit. In addition, participants from countries where the drug administrators are mainly limited to HCPs (such as hospital pharmacists and clinicians) may not continue with self-administration. Given the heterogeneous nature of the study population, the variation in health literacy levels, and the differing needs and motivations to adopt self-administration, the study may not be fully representative of the autonomous and caregiver-assisted patients who would self-administer romiplostim and use the HAT pack.

Another limitation of this study is that direct observation can be susceptible to observer bias as well as to the Hawthorne effect, the concept that behaviour changes as a result of observation [21]. For example, participants may have been less confident or nervous while being observed or, alternatively, may have been more careful to follow the administration instructions while under observation. The self-administration diary, which is part of the HAT pack as an aid for the patients but was not specifically designed to capture information in the study, did identify two instances of dosing earlier (1 week) or later (1 day) than planned based on patients' documented log of self-administration. Since this was an observational study, patients were not required to use or to share the diaries. These self-administration logs were therefore not available in most instances, and if available, the data were not complete enough to serve as a control for observation.

Despite its limitations, this study provides valuable information on the effectiveness of the HAT pack in mitigating medication errors in this population of patients/caregivers administering romiplostim at home, and further highlights the importance of such additional RMM in supporting patients and HCPs.

5 Conclusion

Most patients/caregivers who received HAT pack training administered romiplostim correctly [35 patients/caregivers (87.5%) at the first standard-of-care 4-week visit], supporting the use of the HAT pack as an additional risk minimisation tool to mitigate potential medication errors due to self-administration. The results of this study highlight the importance of repeating the supervision of patients/caregivers after the first 4 weeks of self-administration (as required by the HAT pack training materials) and appropriate patient selection by the HCP.

Compliance with Ethical Standards

Conflict of Interest Martin Schipperus and Georgia Kaiafa have no conflicts of interest to declare. Louise Taylor received funding for British Society for Haematology congresses in 2016 and 2017, and funding for the ITP Assembly in 2016 and 2017. Sally Wetten, Georg

Kreuzbauer, Andy Boshier and Anouchka Seesaghur are employees of and hold stock in Amgen.

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Ethical Approval The protocol, proposed informed consent form, and other written subject information were approved by the local investigational review board or ethics committee.

Patient Consent Patients/caregivers provided written informed consent before participation in the study and in accordance with local laws and regulations.

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