Effects of an Ocrevus Rapid Infusion Protocol: A Literature Review and Quality Improvement Project

Courtney Brandt, DNP, APRN, FNP-C

ABSTRACT

The administration of Ocrevus, an infusion therapy for the treatment of multiple sclerosis, is time and labor intensive, leading to poor patient adherence, treatment delays due to scheduling issues, and significant staff workload. This problem worsened during the COVID-19 pandemic, which created scheduling difficulties due to space restrictions. A US Food and Drug Administration-approved rapid infusion protocol for Ocrevus decreases the infusion time by 1.5 hours per patient. The purpose of this project was to complete a literature review on rapid infusion protocols and analyze the effects of the Ocrevus rapid infusion protocol on 2 outcomes of interest: total visit time and infusion reaction rates. Data were collected using retrospective chart review and analyzed by comparing the results of each outcome to the same data points prior to the implementation of the project. Results found a statistically significant decrease in visit time, with no increase in infusion reaction rates. These findings support the implementation of this rapid Ocrevus infusion protocol in the outpatient setting with the potential to improve patient scheduling, patient satisfaction, and nursing workload, while maintaining patient safety.

Key words: clinic management, infusion reaction, multiple sclerosis, Ocrevus, outpatient infusions, rapid infusion, visit time

Ocrevus is an intravenous infusion therapy used for the treatment of multiple sclerosis (MS). The administration of this medication is time and labor intensive, requiring frequent monitoring and titration.[1] The entire therapy currently requires around 6 hours (3.5 hours for the Ocrevus infusion and 2.5 for premedications and observation time), which can create a significant burden on staff and patients.[2] Long infusion times can lead to poor patient adherence,[3] treatment delays due to scheduling issues,[4-5] and significant staff workload.[6-7] As many infusion centers face rising patient volume, staffing shortages, and increased orders for high-acuity medications, the impact of this problem grows. Further, the COVID-19 pandemic has made patient scheduling more difficult and increased viral exposure time dangerous, heightening the importance of reducing infusion times.

Author Affiliations: *Baylor University LHSON, Dallas, TX, and Paragon Healthcare, Dallas, TX.*

Courtney Brandt, DNP, APRN, FNP-C, *is a family nurse practitioner and clinical assistant professor of nursing at Baylor University. She has been practicing in outpatient infusion centers for 4 years and currently works for Paragon Healthcare in Dallas, Texas. She earned her DNP from University of Texas at Arlington in 2021 and her MSN from Texas Tech Health Sciences Center in 2017. She also has previous experience as a family nurse practitioner in asthma/allergy medicine, as well as a nursing background in the pediatric intensive care unit and adult medical/surgical nursing. Her areas of research interest include infusion medicine and nursing education. She lives in Arlington, Texas, with her husband and 4 young children.*

DOI: 10.1097/NAN.0000000000000498

LITERATURE REVIEW

In January 2021, the US Food and Drug Administration (FDA) approved a rapid infusion protocol,[8] which shortens the Ocrevus portion of the infusion visit from 3.5 hours to 2.0 hours (see Table 1 for full protocol). The use of this protocol could help to address the clinical problem identified above. To investigate the potential effects of the rapid protocol, a systematic review was conducted. The inclusion criteria for the search included the following: publication date after 2000 (with preference given to articles published in the past 5 years), English language, study population of patients receiving Ocrevus or other high-acuity infusions in an outpatient setting, and studies regarding impact of infusion times and/or shortened/rapid infusion protocols. Inclusion criteria also included the following outcomes of interest: patient safety (allergic reactions, infusion reactions, and ability to complete infusion), patient satisfaction (reported satisfaction level, cost for patient, anxiety/stress related to infusion, and

TABLE 1

Infusion Protocol for Administration of Ocrevus[a]

Variable		Amount and Volume	Infusion Rate and Duration
Initial dose (2 infusions)	Infusion 1	300 mg in 250 mL	• Start at 30 mL/h • Increase by 30 mL/h every 30 min • Maximum: 180 mL/h • Duration: At least 2.5 h
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent doses (1 infusion every 6 months)	Option 1 Infusion of approx 3.5 h duration	600 mg in 500 mL	• Start at 40 mL/h • Increase by 40 mL/h every 30 min • Maximum: 200 mL/h • Duration: At least 3.5 h
	Option 2 (if patient qualifies for shortened infusion) Infusion of approx 2 h duration	600 mg in 500 mL	• Start at 100 mL/h for the first 15 min • Increase to 200 mL/h for the next 15 min • Increase to 250 mL/h for the next 30 min • Increase to 300 mL/h for the remaining 60 min • Duration: At least 2 h

Abbreviations: approx, approximately; h, hour; min, minute; mg, milligram; mL, milliliter.

[a]Data from: Genentech. Infusion rate tables. Infographic. Ocrevus.com. Published 2020. Accessed April 20, 2021. https://www.ocrevus.com/content/dam/gene/ocrevus/hcp/pdfs/OCREVUS-multiple-sclerosis-dosing-and-administration-guide.pdf.[28]

willingness to remain on therapy), and clinic management (reports of nursing workload, nurses' reports of stress level, number of patients scheduled per day, delays in treatment, and cost/profit for infusion center). Exclusion criteria for the systematic review included: patients less than 18 years of age and inpatient infusion settings.

The databases utilized for the review were PubMed/MEDLINE, CINAHL, and Cochrane Database of Systematic Reviews. Search terms included: rapid infusion, shorter infusion, high-acuity infusion, Ocrevus, rituximab, infusion center management, nursing workload, patient safety, patient satisfaction, cost, and treatment delays. Rituximab was chosen as a specific search term due to its similarities to Ocrevus and longer history of rapid infusion protocols. Both rituximab and Ocrevus are anti-CD20 monoclonal antibodies that target B-cells in the immune system.[1,9] Also, both medications have very similar safety profiles and infusion protocols.[1,9] However, Ocrevus was only approved for use 3 years ago, with a rapid infusion protocol approved in December 2020,[8] whereas rituximab was approved for use in 1997, with a rapid infusion protocol approved in 2012.[9] Hence, more research has been conducted on rituximab rapid infusion and, due to the extreme similarities between the medications, this research is highly relevant to the clinical problem.

RESULTS OF THE REVIEW

Utilizing these search terms and databases, 887 results were found. However, after inclusion and exclusion criteria were applied and the articles were examined for applicability to the clinical problem, the results were narrowed to 11 studies, which are synthesized in the following sections. Overall, the studies consistently provided statistically significant results. Three themes emerged upon analysis of these studies: rapid infusions are safe, rapid infusions positively impact clinic management, and rapid infusions positively impact patient satisfaction.

General Overview

There were multiple types of studies in this review, including randomized controlled trials (n = 1), prospective interventional cohort studies (n = 7), and retrospective cohort studies (n = 3). All studies utilized quantitative methodologies and provided good- or high-quality evidence, ranging from level I to level IV (see Table 2).

Patient Safety

The most common topic of the literature was patient safety—specifically, infusion reaction rates. *Infusion reactions* are defined as a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.[10] Most commonly these reactions are non-immunoglobulin E (IgE) mediated, although their presentation often looks very similar to an allergic reaction. Infusion reactions occur most frequently during the first exposure to the medication, in contrast to IgE-mediated allergic reactions, which do not occur with initial exposure. Infusion reactions typically resolve quickly when the infusion is stopped or slowed, sometimes requiring further symptomatic treatment with antihistamines or steroids. However, infusion reactions do have the potential to become severe, requiring emergent respiratory or cardiac support, and can even result in death. Infusion reactions often improve over time with repeated exposure to the medication.

It is not surprising that the rate of infusion reactions is an important factor in the analysis and implementation of rapid infusions, as even standard infusion protocols of Ocrevus and rituximab can yield high reaction rates. Also, faster administration time makes infusion reactions more likely to occur.[10] Therefore, it is easy to see the

TABLE 2

Levels of Evidence Defined and Identified for Each Article in Systematic Review

Levels of Evidence Defined[25]

- Level I: Systematic review and meta-analysis of randomized controlled trials; clinical guidelines based on systematic reviews or meta-analyses
- Level II: One or more randomized controlled trials
- Level III: Controlled trial (no randomization)
- Level IV: Case-control or cohort study
- Level V: Systematic review of descriptive and qualitative studies
- Level VI: Single descriptive or qualitative study
- Level VII: Expert opinion

Article	Level of Evidence
Pritchard C, Greenwald M, Kremer J, et al. (2014)[2]	Level III
Sehn L, Donaldson J, Filewich A, et al. (2004)[7]	Level III
Hartung HP, Berger T, Bermel RA, et al. (2020)[11]	Level II
Rath L, Bui MV, Ellis J, et al. (2020)[15]	Level III
Vollmer TL, Cohen JA, Alvarez E, et al. (2020)[16]	Level III
Ursu SG, Rinchuse DL, Lister J. (2020)[17]	Level IV
Dotson E, Crawford B, Phillips G, et al. (2016)[18]	Level III
Fenton TT, Crawford BS, Bullington SM. (2020)[19]	Level IV
Modelevsky L, Tizon R, Reiss SN, et al. (2018)[20]	Level IV
Patel J, Ho M, Ho V, et al. (2013)[21]	Level IV
Swan JT, Zaghloul HA, Cox JE, et al. (2014)[22]	Level III

importance of ensuring that a rapid infusion protocol does not significantly increase infusion reaction rates.

Infusion Reaction Rates With Standard Protocols

Clinical trials have shown that approximately 26.9% to 39.9% of patients experienced infusion reactions during the administration of Ocrevus at the standard infusion rate.[11-13] Clinical trials also show rituximab has a similar reaction rate of 25% to 30% when using the standard infusion protocol,[9] but some studies demonstrate even higher infusion reaction rates of up to 77%.[14] Most of these reactions are mild (throat irritation, flushing, and generalized pruritis) and do not require interruption of the infusion.[11-14] However, up to 10% of patients may progress to a more serious grade III or grade IV reaction that involves respiratory or circulatory compromise.[13-14]

Infusion Reaction Rates With Rapid Ocrevus Protocol

Infusion reaction rates of a rapid Ocrevus protocol were identified as an outcome in 3 of the 11 studies in this review. The results in this area, specifically for Ocrevus, are slightly limited due to the very recent FDA approval of this protocol.[8] Further support is found in the literature regarding rituximab, which is shown in the next section. The review showed that shortening the Ocrevus infusion time to 2 hours did not increase infusion reaction rates compared to the standard 3.5-hour time.[11,15-16] One randomized controlled trial was found in which researchers directly compared patients receiving the 2.0-hour Ocrevus infusion with patients receiving the standard 3.5-hour Ocrevus infusion and found infusion reaction rates to be 28.8% and 26.5%, respectively.[15] In other studies ($n = 2$), reaction rates of patients receiving the 2-hour Ocrevus infusion were compared with reaction rates of the standard infusion protocol in published data.[11,16] Results showed that reaction rates were not statistically higher when utilizing the shorter protocol. No patients experienced severe or life-threatening reactions.[11,15-16] The researchers in all the above studies concluded the 2-hour Ocrevus infusion time was safe for their patients.

Infusion Reaction Rates With Rapid Rituximab Protocol

Infusion reaction rates with a rapid rituximab protocol were analyzed in 7 of the 11 studies in this review. The rapid infusion protocol for rituximab decreases the infusion time from 3 hours to 90 minutes,[17] a reduction similar to the new Ocrevus protocol. Rapid rituximab infusions were found to be very safe throughout this literature, with multiple prospective, interventional studies finding no statistically significant increase in reaction rates.[2,7,18-19] In each of these studies, qualifying patients (those who had not experienced a severe infusion reaction in the past) were changed to the rapid rituximab protocol, and their rates of infusion reaction were compared with other patients in the same

clinic who received the standard protocol or with their own previous infusions with the standard protocol.[2,7,18-19] Three retrospective cohort studies further support these findings. Utilizing chart review to analyze infusion reactions with the rapid protocol, none of the studies found a statistically significant increase in reaction rates when compared to patients receiving the standard protocol.[17,20-21] Interestingly, many of the studies within this review found reaction rates to be lower with the rapid protocol than with the standard protocol,[17,19,21] with 2 of the studies showing zero infusion reactions with the rapid protocol.[18,20] This evidence overwhelmingly supports the idea that rapid rituximab infusion is safe. Furthermore, the evidence will help to support the literature regarding shorter Ocrevus infusion, due to the extreme similarities between the 2 medications discussed above.

Clinic Management

The effect of rapid infusions on the management of outpatient infusion clinics was another important outcome of interest. Seven of the 11 articles utilized in the review focused on some aspect of clinic management, including infusion time,[7,16-19,22] overall clinic visit time,[19,22] and nursing satisfaction/workload.[7,15,18,22] Exposure time to COVID-19 during the pandemic was another applicable outcome studied.[15] Overall, every study showed positive effects of rapid infusion protocols on every aspect of clinic management, discussed in further detail below.

Infusion Time

Several of the studies in this review highlight the impact that long infusions have on workload, patient satisfaction, patient adherence, and scheduling.[7,15-19,22] Therefore, decreasing the time of infusion utilizing rapid infusion protocols is a highly anticipated outcome, with many researchers predicting the multiple positive ways it could impact clinic management. Utilizing a review of medical records, the studies found that rapid infusion protocols of either rituximab or Ocrevus saved 0.75 to 3.00 hours, depending on the drug, the exact protocol utilized, and infusion reactions.[16-19,22] The researchers in these studies consistently noted the positive effects the decreased infusion time had on the clinic, including improved nursing satisfaction/workload,[7,18] increased appointment availability,[19] decreased overall clinic visit time,[22] decreased exposure to COVID-19,[15] and improved patient satisfaction.[7]

Overall Clinic Visit Time

Two studies discussed the impact that rapid infusion protocols had, not only on infusion time, but on the time of the entire patient visit. One study found that utilization of a rapid rituximab infusion protocol decreased clinic visit time by 92 minutes per patient encounter, resulting in a reduction of 255 to 299 visit hours per year for the entire clinic.[22] It is easy to see the great impact this could have, not only for rituximab or Ocrevus patients, but also for other patients in the clinic. This improvement would allow for more scheduling flexibility for other patients and improved patient flow in the clinic (decreased wait times, etc). Another study highlighted this point when researchers found that implementing rapid rituximab infusions allowed their clinic to see at least 1 more patient, on average, per day.[19]

Another important consideration regarding total visit time is amount of viral exposure during the COVID-19 pandemic. Exposure is especially important for rituximab and Ocrevus patients who are immunocompromised and receiving treatments in an open, multipatient space. In 1 study, researchers implemented a rapid Ocrevus infusion protocol and highlighted the positive impact it had on exposure time for their patients during the pandemic.[15]

Nursing Satisfaction and Workload

Another important consideration associated with clinic management is nursing satisfaction and workload. Many researchers found it essential to look at the impact of rapid infusion protocols on the work of nurses, as they are the main operators and caregivers in any outpatient infusion center. Four of the 11 studies reviewed included nursing workload or satisfaction as a measured outcome.[7,15,18-19] In 2 of the studies, chart review showed a decrease in nursing workload, measured by nurse contact time and documentation acuity.[7,15] Other studies examined nurse-reported comfort level and satisfaction level with rapid rituximab infusion protocols.[18-19] By surveying nurses, these researchers found very positive results when nurses expressed the effect rapid infusion protocols had on their stress level, workload, and ability to care for all of their patients.

Patient Satisfaction

Patient satisfaction is a very important aspect to consider in health care, especially regarding infusion medications for chronic illnesses. Long infusion times can have a significant effect on patients' medication adherence and persistence. Clinical practice guidelines on the treatment of MS strongly recommend early treatment of MS with a disease-modifying therapy (DMT) such as Ocrevus.[23] The guidelines also suggest that adherence to DMTs is a common issue with MS patients, and every effort should be made to remove barriers to adherence when possible. With this information in mind, it becomes clear that efforts to improve patient satisfaction regarding Ocrevus therapy are an important part of best practice.

One study in this review emphasized the negative effects that long infusions have on different aspects of a patient's life.[24] Researchers surveyed patients receiving rituximab infusions using 19 questions that evaluated the impact of infusion-visit time on stress, employment, caregiving, and work-related responsibilities. Results showed that 35% of patients felt stressed about their long infusion visit, all patients missed at least 1 whole day of work due to the infusion, and 75% of patients reported that a reduction in infusion time would have a moderate or major impact on their life.

Two of the 11 studies analyzed patient satisfaction with rapid infusion protocols. Rath et al[15] utilized a 4-question survey to gain information on patient experience with the implementation of a rapid Ocrevus infusion protocol during the COVID-19 pandemic. They found that all patients reported a positive and impactful experience. Sehn et al[7] also reported a positive patient experience when implementing a rapid rituximab infusion protocol, but these researchers were less specific on how patient experience was measured. Overall, patient satisfaction seems to increase with the utilization of rapid infusion protocols, although more research in this area would be beneficial.

METHODS

The literature review revealed clear themes showing that the rapid Ocrevus infusion protocol could positively affect clinic management and patient satisfaction, while maintaining patient safety. After completion of the review, a quality improvement project was designed to fully implement and measure the impact of this protocol on visit time and infusion reaction rates in 2 outpatient infusion center locations. These infusion centers administer many specialty intravenous medications and are staffed by registered nurses (RNs) and nurse practitioners (NPs).

Intervention

The project was implemented over a 10-week period, which was followed by a period of data collection utilizing retrospective chart review. Prior to the implementation period, education was provided to the infusion center staff on the rapid infusion protocol and the use of the protocol for all qualifying patients. Some of the staff at the centers were already aware of the protocol, as it has been approved by the FDA since January 2021.[1] The clinical staff had permission to utilize this protocol; however, before this project, the use of the protocol had been inconsistent, especially in patients with a history of any infusion reactions.

When the 10-week implementation period began, each Ocrevus patient was evaluated by the RN at their appointment for possible use of the rapid infusion protocol. All patients receiving Ocrevus in either of the 2 centers were considered. To qualify for rapid infusion, patients had to be receiving a subsequent Ocrevus dose (not their initial dose: see Table 1, for details). The patient must also have had no history of a severe or life-threatening reaction (grade III or IV) to Ocrevus. This was determined with the National Cancer Institute Common Terminology Criteria for Adverse Events grading system[27] (see Table 3) discussed under the Measurement Methods section below. Patients with a history of grade I or II reactions could receive the rapid infusion protocol, while patients with a history of grade III or IV reactions were excluded and received the conventional protocol.

If any questions arose regarding patient qualification, the RN clarified with the NP on duty. If the patient was determined to be eligible for the rapid infusion protocol, the new protocol was explained to the patient by the RN. If the patient agreed, the rapid infusion protocol was utilized. During the infusion, the RN monitored the patient's vital signs and symptoms according to protocol. Blood pressure, respiratory rate, O_2 saturation, heart rate, and temperature were taken prior to the infusion and after the 1-hour post-infusion observation time. During the Ocrevus infusion, the blood pressure, respiratory rate, and heart rate were taken every 15 minutes for the first hour and then every 30 minutes for the remainder of the infusion. The RN also asked the patient to report any symptoms (eg, itching, lightheadedness, rash, scratchy throat, trouble breathing) at each vital signs check. This monitoring and observation schedule for the rapid protocol is the same as was used for the conventional protocol. However, fewer checks were required if the rapid infusion protocol went as planned, due to the decreased infusion time. All vital signs, patient symptoms, intake times, and discharge times were documented by the RN in the electronic health record (EHR).

If the patient began to experience any symptoms concerning for a possible infusion reaction (eg, pruritis, flushing, rash, hives, dizziness, headache, nausea, chest pain, scratchy throat, or shortness of breath), the protocol for rate modifications due to an infusion reaction was followed (see Table 4). Additional medications (eg, corticosteroids, antihistamines, or intravenous fluid) for symptomatic treatment were at the discretion of the NP on duty. This was the same procedure already in place for

TABLE 3

National Cancer Institute Common Terminology Criteria for Adverse Events: Tool for Grading of Infusion-Related Reactions[26]

Term	Grade I	Grade II	Grade III	Grade IV	Grade V
Infusion-related reaction	Mild, transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment	Prolonged (not rapidly responsive to medication or interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

TABLE 4

Protocol for Responding to Infusion Reactions[29]

Mild-to-moderate	Severe	Life-threatening
Reduce the infusion rate to half the rate at onset of the reaction and maintain reduced rate for at least 30 minutes. If this is tolerated, increase the rate as described in Table 1 above.	Immediately interrupt the infusion and administer appropriate supportive treatment. Restart the infusion, after all symptoms have resolved, at half the rate at the onset of the reaction. If this is tolerated, increase the rate as described in Table 1 above.	Immediately stop and permanently discontinue Ocrevus if there are signs of a life-threatening reaction. Provide supportive treatment as necessary.

treating infusion reactions associated with the conventional protocol. Thorough documentation of the symptoms and treatment was completed by the RN and NP.

After the 10-week implementation period, data on all patients treated with the rapid infusion protocol were collected from the EHR and stored in a dashboard. This dashboard contained basic patient demographics, such as an assigned case number for project organizational purposes, age range, and gender. The dashboard also included total visit time, occurrence of infusion reactions, and grade of infusion reactions.

The objectives of this project required the comparison of the rapid infusion data (infusion reaction rates and total visit time) to the same data prior to the implementation of the rapid infusion protocol. As these data were not currently available within the company system, they were collected as part of the project to provide baseline statistics. This collection was done by EHR review during the project implementation period. All patients receiving a subsequent dose of Ocrevus utilizing the conventional protocol in the 2 months prior to project implementation were reviewed to develop these baseline data.

Measurement Methods

Two outcomes were measured within this project: infusion reaction rates and average total visit time for Ocrevus therapy. The average visit time was determined utilizing EHR review of documentation of check-in time and discharge time for every patient who received the rapid Ocrevus infusion protocol during the 10-week period. Total visit time was chosen as a measured outcome over infusion time for several reasons. Total visit time includes the time from check-in to discharge (initial intake, premedications, Ocrevus infusion, and observation time), whereas infusion time is only the time the Ocrevus is infusing. With the utilization of the rapid infusion protocol, the nurse may have taken extra time during the intake period to determine if the rapid protocol could be used. Also, the potential for infusion reactions could have required pausing the infusion, administering additional medications for the reactions, and increasing observation times. Due to these factors, it was determined that total visit time would give a more accurate depiction of the effect of the new protocol than would infusion time.

Infusion reactions were measured by reviewing nursing documentation to identify any abnormal patient symptoms that indicated an infusion reaction during the infusion or the 1-hour postinfusion observation time. Each incidence of an infusion reaction was graded utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which is an open access tool.[26] This is the standard tool utilized to grade and report infusion reactions to monoclonal antibodies such as Ocrevus (see Table 4). It was utilized in the initial clinical trials on the rapid Ocrevus infusion, which led to the development and FDA approval of the protocol used in this project.[11] It has also been used in subsequent research on rapid Ocrevus infusions.[16] No specific research can be found on the validity and reliability of this tool. However, since it is the only grading tool utilized in all current research on Ocrevus infusion reactions, and is the tool referenced in the FDA-approved rapid infusion protocol, it was used to ensure that the terminology and processes in this project followed the approved guidelines.

RESULTS

Over the 10-week project implementation period, 40 patients received an Ocrevus infusion using the rapid infusion protocol. Of these patients, 35 were female and 5 were male. The frequency distribution of age ranges was as follows: 20 to 30 years (7.5%), 30 to 40 years (17.5%), 40 to 50 years (20.0%), 50 to 60 years (20.0%), 60 to 70 years (32.5%), and 70 to 80 years (2.5%). To establish baseline data points for comparison, 49 patients who received an Ocrevus infusion using the conventional protocol between November 2020 and December 2020 were analyzed. Of these patients, 37 were female and 12 were male. The frequency distribution of age ranges was as follows: 20 to 30 years (2.0%), 30 to 40 years (20.4%), 40 to 50 years (30.6%), 50 to 60 years (28.6%), 60 to 70 years (14.3%), and 70 to 80 years (4.1%).

Total visit time was calculated in minutes for each patient for the rapid protocol (mean = 269.48, standard deviation [SD] = 22.96) and the conventional protocol (mean = 366.98, SD = 34.65). The results of an independent *t* test comparing these groups showed a statistically significant change in visit time ($t(87) = 15.26$, $P < .001$) with a decrease of 97.5 minutes on mean visit time.

The overall infusion reaction rate for patients who received the conventional protocol was 10.2% (n = 5). Of those reactions, 20% were grade I (n = 1) and 80% were grade II (n = 4). The patient who had a grade I reaction experienced mild oral pruritis, requiring no interruption of the infusion. Three patients who had a grade II reaction experienced moderate oral pruritis, and 1 patient experienced a mild rash. All patients were able to finish the infusion after symptomatic management. No patients had a grade III or IV reaction. For patients receiving the rapid infusion protocol, the overall infusion reaction rate was 2.5% (n = 1). This single reaction was a grade II reaction in which the patient had mild oral pruritis requiring no infusion interruption. No patients had a grade I, III, or IV reaction. Fisher exact 2-sided test was performed on these data, revealing that the difference in reaction rates between the 2 protocols was not statistically significant ($P = .217$). Fisher exact test was chosen due to the small sample size.

DISCUSSION

The rapid infusion protocol utilized in this project resulted in a statistically significant decrease in infusion time with no significant change in infusion reaction rates. This suggests that this intervention can save valuable time without sacrificing patient safety. These findings are similar to several other studies on rapid infusions, discussed above. In particular, the results on infusion reaction rates are comparable to those of the randomized, double-blind ENSEMBLE PLUS study, which was utilized in the initial approval of the rapid Ocrevus protocol.[11] The saved visit time, an average of 97.5 minutes, is beneficial to both the infusion centers and the patients for several reasons.

A primary concern with long infusions is their negative influence on scheduling and center management. When utilizing the conventional protocol, Ocrevus patients had to be scheduled in the morning, as their infusion was too long for an afternoon appointment. However, the rapid infusion will now allow for patients to be scheduled in the afternoon as well. This gives the patient more options and flexibility to accommodate their preferences and their work schedule. It also provides much more flexibility to the center scheduling staff, hopefully decreasing any delay in finding Ocrevus patients an appointment time.

The shorter infusion time will also allow for more patients to be scheduled in the center per day. The average visit time for patients in the center is about 1.0 to 1.5 hours. This means approximately 1 extra patient can be scheduled for every Ocrevus patient who switches from the conventional protocol to the rapid protocol. As the infusion centers continue to face rising scheduling issues, this is a significant change that could decrease treatment delays.

Further, scheduling more patients per day will increase profits for the infusion center. Reimbursement rates for infusion therapy are greater for the first hour of treatment and are reduced for additional hours. For example, Medicare reimbursement rates for 2021 are $71.46 for the first hour of infusion therapy and $22.01 for each additional hour.[27] For this reason, it is more profitable for the center to save the additional 97.5 minutes with the Ocrevus rapid infusion protocol and fill that time with another patient whose infusion takes 1.0 to 1.5 hours.

Nursing workload can also be reduced with the rapid infusion protocol. Ocrevus is a high-acuity infusion, meaning it requires frequent vital signs and monitoring. Ocrevus patients require vital sign checks every 30 minutes and frequent verbal and visual checks of the patient to monitor for reactions, whereas many other therapies given in the center are lower acuity, meaning they have a much lower risk of reaction and do not require frequent vital sign checks. Decreasing the time that a nurse cares for a higher-acuity patient will likely reduce workload and stress, especially because the rapid infusion protocol has not been found to increase infusion reactions.

The Ocrevus rapid infusion protocol can also have a positive impact on patient satisfaction. As discussed above, a significant portion of Ocrevus patients report stress about the long infusion time and missing an entire day of work. They also report a reduction in visit time would have a significant, positive effect in their lives. The rapid infusion protocol offers this reduction without compromising safety. The time saved reduces the visit to a half day, meaning less work time missed. The decrease in infusion time can also result in a cost savings for the patient. Since patients are likely paying for at least a portion of their infusion, each hour saved reduces their out-of-pocket cost. The exact amount would depend on the patient's insurance coverage.

Lastly, the decrease in visit time with the rapid infusion protocol is important during the COVID-19 pandemic, resulting in an average of 97.5 fewer minutes of exposure per visit. As discussed above, this is especially important for Ocrevus patients, who are immunocompromised and particularly susceptible to the virus. Here, it is worth noting the recent trend to move Ocrevus infusions to the home setting, especially during the pandemic. Research has shown that home infusions have similar safety profiles to those conducted in a center.[30] Further, in a recent study, 2-hour home infusions of Ocrevus were found to be safe in 51 patients.[31] Many of the benefits found in this project can be applied to the home setting as well.

In addition to the decrease in visit time, it is important to address the infusion reaction rates with each protocol. While the sample size was small, the data demonstrated the rapid infusion protocol had a lower rate of infusion reactions than the conventional protocol (2.5% and 10.2% accordingly). Here it should be stated this decrease could be due to patients being disqualified from receiving the rapid infusion if they have a history of grade III or IV reactions. This means patients who are most likely to have an infusion reaction (due to their previous reaction history) are receiving the conventional protocol. However, the

difference in reaction rates was not found to be statistically significant, which still suggests the rapid infusion protocol did not compromise patient safety, despite some influence of the selection bias stated above. Also, these findings are in line with previous studies showing no increase in infusion reactions with the rapid protocol. Due to these results and all of the potential positive impacts of the decrease in visit time, infusion centers should not hesitate to adopt this change.

LIMITATIONS

There were a few limitations associated with this project that should be addressed. First, as a quality improvement project, these findings are not considered generalizable outside of this specific entity. The project was not randomized or blinded and had a relatively small sample size. Also, due to time limits on project implementation, long-term effects of the use of the rapid infusion protocol could not be measured (ie, actual profit increase, exact reduction in scheduling delays, or increase in number of patients scheduled per day). However, the decrease in visit time that was measured can be extrapolated to see the potential long-term effects.

CONCLUSION

The growth of infusion medicine, paired with effects of the COVID-19 pandemic, have created stressors on time and space within infusion centers. This project serves as an example of how a rapid Ocrevus infusion protocol can be utilized to save time while maintaining patient safety. The protocol is straightforward and has no associated costs, making it easy to disseminate to other infusion centers and settings. Suggestions for future research in this area include measuring the impact of the rapid protocol on patient satisfaction, profit, and patient scheduling. Research on the implementation of rapid infusion protocols for other high-acuity infusions could be beneficial as well.

REFERENCES

1. Genentech. *Ocrevus prescribing information*. Ocrevus.com. Updated 2021. Accessed January 20, 2021. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf2
2. Pritchard CH, Greenwald MW, Kremer JM, et al. Safety of infusing rituximab at a more rapid rate in patients with rheumatoid arthritis: results from the RATE-RA study. *BMC Musculoskelet Disord.* 2014;15:177. Accessed January 20, 2021. http://www.biomedcentral.com/1471-2474/15/177
3. Zahrani A, Ibrahim N, Eid A. Rapid infusion rituximab changing practice for patient care. *J Oncol Pharm Pract.* 2009;15(3):183-186. doi:10.1177/1078155208100527
4. Aurran-Schleinitz T, Gravis G, Vittot M, et al. One hour Rituxan infusion is safe and improved patient care and outpatient unit management. *Am Soc Hematol.* 2005;106(11):4759. doi:10.1182/blood.V106.11.4759.4759
5. Corey P, Go R, Schaper A. A nurse can safely deliver rituximab over 90 minutes. *Oncol Nurs Forum.* 2007;34(2):493. Accessed January 12, 2021. https://web.b.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=0190535X&AN=28835253&h=XAmK6JrauU5XjfpvE9hkDZghQbZ9hDGPY%2fWaQa49g8fdO%2fX374UYcoHop4rXd5gOudJBAnrXE5YrLdINZ%2fnTZQ%3d%3d&crl=c&resultNs=AdminWebAuth&resultLocal=ErrCrlNotAuth&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d0190535X%26AN%3d28835253
6. Nevidjon B. The challenge of staffing in ambulatory infusion settings. *Clin J Oncol Nurs.* 2018;22(2):2. http://dx.doi.org.ezproxy.uta.edu/10.1188/18.CJON.225-227
7. Sehn L, Donaldson J, Filewich A, et al. Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. *Blood*. 2004;104(11):1407. doi:10.1182/blood.V104.11.1407.1407
8. Roche Group Media Relations. *FDA approves Roche's Ocrevus (ocrelizumab) shorter 2-hour infusion for relapsing and primary progressive multiple sclerosis*. Roche.com. Published December 14, 2020. Accessed January 20, 2021. https://www.roche.com/media/releases/med-cor-2020-12-14.htm
9. Genentech. *Rituxan prescribing information*. Rituxan.com. Updated 2021. Accessed January 20, 2021. https://www.gene.com/download/pdf/rituxan_prescribing.pdf
10. Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. *Clin Transl Immunol.* 2015;4(7):e39. doi: 10.1038/cti.2015.14
11. Hartung HP, Berger T, Bermel RA, et al. Shorter infusion time of ocrelizumab: results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102492. doi:10.1016/j.msard.2020.102492
12. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221-234. doi:10.1056/NEJMoa1601277
13. Mayer L, Kappos L, Racke MK, et al. Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis: results from the phase 3 randomized OPERA I, OPERA II, and ORATORIO studies. *Mult Scler Relat Disord*. 2019;30:236-243. doi:10.1016/j.msard.2019.01.044
14. Levin AS, Otani IM, Lax T, Hochberg E, Banerji A. Reactions to rituximab in an outpatient infusion center: a 5-year review. *J Allergy Clin Immunol Pract*. 2017;5(1):107-113.e1. doi:10.1016/j.jaip.2016.06.022
15. Rath L, Bui MV, Ellis J, et al. Fast and safe: optimising multiple sclerosis infusions during COVID-19 pandemic. *Mult Scler Relat Disord*. 2021;47:102642. doi:10.1016/j.msard.2020.102642
16. Vollmer TL, Cohen JA, Alvarez E, et al. Safety results of administering ocrelizumab per a shorter infusion protocol in patients with primary progressive and relapsing multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102454. doi:10.1016/j.msard.2020.102454
17. Ursu SG, Rinchuse DL, Lister J. Rapid rituximab infusion is safe and well tolerated in malignant and benign disease. *J Oncol Pharm Pract*. 2021;27(8):1919-1922. doi:10.1177/1078155220978450
18. Dotson E, Crawford B, Phillips G, Jones J. Sixty-minute infusion rituximab protocol allows for safe and efficient workflow. *Support Care Cancer*. 2016;24(3):1125-1129. doi:10.1007/s00520-015-2869-4
19. Fenton TT, Crawford BS, Bullington SM. Implementation and evaluation of a 90-minute rituximab infusion protocol at the Richard L. Roudebush VA Medical Center. *Fed Pract*. 2020;37(7):331-335. Accessed January 13, 2021. https://pubmed.ncbi.nlm.nih.gov/32908338/
20. Modelevsky L, Tizon R, Reiss SN, Smith M, Garonce R, Kaley T. Rapid infusion rituximab is well tolerated in patients with primary CNS lymphoma. *CNS Oncol*. 2018;7(3):CNS19. doi:10.2217/cns-2018-0001

21. Patel J, Ho M, Ho V, et al. Rapid infusion rituximab for maintenance therapy: is it feasible? *Leuk Res*. 2013:2013:629283. doi:10.1155/2013/629283
22. Swan JT, Zaghloul HA, Cox JE, Murillo JR Jr. Use of a pharmacy protocol to convert standard rituximab infusions to rapid infusion shortens outpatient infusion clinic visits. *Pharmacotherapy*. 2014;34(7):686-694. doi:10.1002/phar.1420
23. American Academy of Neurology. *Practice guideline: disease-modifying therapies for adults with multiple sclerosis*. Updated September 18, 2021. Accessed January 15, 2021. https://www.aan.com/Guidelines/home/GuidelineDetail/898
24. Fisher MD, Wallick CJ, Miller PJ, et al. Impacts of time spent on rituximab infusion on patient satisfaction, stress, employment, and caregiver burden. *Value Health*. 2018;21(suppl 1):S36. doi:10.1016/j.jval.2018.04.303
25. Melnyk BM, Fineout-Overholt E. *Evidence-based Practice in Nursing and Healthcare: A Guide to Best Practices*. 4th ed. Wolters Kluwer Health; 2019.
26. National Cancer Institute. *Common terminology criteria for adverse events*. Cancer.gov. Published November 27, 2017. Accessed April 20, 2021. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
27. Janssen. *2021 Final Medicare coding and payment*. Janssen Care Path. Published February, 2021. Accessed September 2, 2021. https://www.janssencarepath.com/sites/www.janssencarepath-v1.com/files/medicare-coding-and-payment-drug-admin-services-physician-fee-schedule.pdf
28. Genentech. *Infusion rate tables. Infographic*. Ocrevus.com. Published 2020. Accessed April 20, 2021. https://www.ocrevus.com/content/dam/gene/ocrevus/hcp/pdfs/OCREVUS-multiple-sclerosis-dosing-and-administration-guide.pdf
29. Genentech. *Rate modifications because of IRs*. Infographic. Ocrevus.com. Published 2020. Accessed April 20, 2021. https://www.ocrevus.com/content/dam/gene/ocrevus/hcp/pdfs/OCREVUS-multiple-sclerosis-dosing-and-administration-guide.pdf
30. Polinski JM, Kowal MK, Gagnon M, Brennan TA, Shrank WH. Home infusion: safe, clinically effective, patient preferred, and cost saving. *Healthc (Amst).* 2017;5(1-2):68-80. doi:10.1016/j.hjdsi.2016.04.004
31. Barrera B, Simpson H, Engebretson E, et al. Evaluating the feasibility of pandemic forward, telehealth based home based infusions for ocrelizumab users: measuring patient experiences and safety outcomes. *The Consortium for Multiple Sclerosis Centers Annual Meeting*. Orlando, FL; October 2021.