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Best Practices in Alemtuzumab Administration

Practical Recommendations for Infusion in Patients With Multiple Sclerosis

ABSTRACT

With the growing complexity of multiple sclerosis (MS) care, nursing professionals have increasing responsibility in managing clinical disease and treatment. Nursing professionals and other health care providers play important roles in educating patients about disease-modifying therapy options, the course of therapy, and managing potential adverse effects. A panel of nursing and MS experts was convened and used a modified Delphi method to reach consensus on best-practice recommendations for alemtuzumab infusion in MS patients. This valuable clinical resource provides a practical guide for clinicians to optimize patient education and implement strategies for infusion-associated reaction prophylaxis and management when administering alemtuzumab.

Key words: alemtuzumab, multiple sclerosis, infusion, nursing, monoclonal antibodies, neurology, disease-modifying therapies, guidelines

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Multiple sclerosis (MS) is the leading cause of disease-related disability among young people and has a lifetime cost exceeding $1 million.[1] MS is characterized by immune-mediated axonal damage and demyelination caused by a complex interaction of T and B lymphocytes and the innate immune system.[2]

Alemtuzumab is a humanized anti-CD52 monoclonal antibody that has been studied extensively in phase 2 and phase 3 studies as a therapy for patients with relapsing-remitting MS (RRMS).[3-5] Recent phase 3 trials in patients with RRMS have demonstrated efficacy of alemtuzumab across clinical and radiological measures, compared with high-dose subcutaneous (SC) interferon (IFN) beta-1a, along with manageable side effects, safety, and tolerability. Alemtuzumab is currently approved in the United States[6] (for patients with relapsing forms of MS who have had an inadequate response to 2 or more drugs indicated for MS), the European Union (for RRMS patients with active disease defined by clinical and imaging features), and numerous other countries (indications vary by country).[3,4]

CD52 is a cell-surface protein that is expressed on the surface of T and B lymphocytes but not hematopoietic cells of the innate immune system.[7] Alemtuzumab binding to CD52 results in the rapid lysis of circulating T and B cells.[8] The presumed mechanism of action is immune system rebalancing that occurs after depletion and repopulation of circulating T and B lymphocytes. Following alemtuzumab treatment, the number and proportions of some lymphocyte subsets are transiently altered, including an increase in the proportion of regulatory and memory T cells within the overall T cell population.[8-11] This may influence clinical effects that persist long after alemtuzumab is cleared from the circulation.[12]

Therapeutic options for MS have expanded in recent years, offering clinicians and patients greater choices and growing opportunities to optimize disease management. With greater MS care complexity, nursing professionals have increased responsibility in managing clinical disease and treatment. Nursing professionals and other health care providers also play important roles in educating patients about disease-modifying therapy options, therapeutic courses, and managing potential adverse effects (AEs). Best-practice guidelines and evidence-based treatment protocols can guide patient assessment/monitoring and facilitate consistent patient management.[13] Accordingly, a panel of nursing and physician assistant experts was convened to develop best-practice recommendations for alemtuzumab infusion to treat patients with RRMS.

CLINICAL TRIAL EXPERIENCE WITH ALEMTUZUMAB INFUSION

The safety and efficacy of alemtuzumab were evaluated in 3 rater-blinded comparative phase 2 and phase 3 clinical trials: CAMMS223, CARE-MS I, and CARE-MS II.[3-5] Compared with SC IFN beta-1a (44 μg 3 times per week), alemtuzumab significantly reduced annualized relapse rates in all 3 trials, as well as sustained disability risk in CAMMS223 and CARE-MS II.[3-5]

CAMMS223 (NCT00050778) was a 3-year, phase 2 trial of treatment-naive patients with a short duration of disease (≤ 3 years), low-level disability (Expanded Disability Status Scale [EDSS] ≤ 3.0), and active disease (at least 2 relapses within the prior 2 years with gadolinium-enhanced brain lesions on magnetic resonance imaging).[5] Patients were randomized to receive either SC IFN beta-1a (44 μg 3 times per week) or alemtuzumab (12 or 24 mg daily on 5 consecutive days at baseline and on 3 consecutive days at months 12 and 24, the latter course being optional).[5] Compared with SC IFN beta-1a, alemtuzumab reduced the risk of sustained disability by 71% (hazard ratio [HR] = 0.29, 95% CI, 0.16-0.54; $P < .001$) and the annualized rate of relapse by 74% (HR = 0.26, 95% CI, 0.16-0.41; $P < .001$). The mean EDSS score improved from 1.9 at baseline to 1.5 at 36 months in the alemtuzumab group and worsened from 1.9 to 2.3 in the SC IFN beta-1a group ($P < .001$).[5]

CARE-MS I (NCT00530348) was a 2-year, phase 3 trial of treatment-naive patients with disease onset ≤ 5 years before enrollment, EDSS ≤ 3.0, and active disease (≥ 2 relapses in the prior 2 years, with 1 relapse occurring within the previous year).[3] CARE-MS II (NCT00548405) was a 2-year, phase 3 trial of patients with active disease (≥ 2 relapses in the prior 2 years, with 1 relapse occurring within the previous year) who relapsed on previous therapy (IFN-beta and glatiramer acetate).[4] In contrast to CARE-MS I, patients with higher EDSS scores (≤ 5.0) and longer disease duration (≤ 10 years) were eligible to enroll in CARE-MS II. Patients in both trials were randomized to receive SC IFN beta-1a (44 μg 3 times per week) or alemtuzumab (12 mg daily for 5 consecutive days at baseline and again for 3 consecutive days 12 months later).[3,4] In CARE-MS II, an additional group was randomized to alemtuzumab 24 mg, but this dose was discontinued to aid recruitment.

In the CARE-MS I trial, alemtuzumab demonstrated a 55% reduction in relapse risk compared with SC IFN beta-1a (HR = 0.45, 95% CI, 0.32-0.63; $P < .0001$) at 2 years after treatment initiation. The cohort proportion that demonstrated sustained disability accumulation was 8% in the alemtuzumab group and 11% in the SC IFN beta-1a group at 2 years (HR = 0.7, 95% CI, 0.4-1.23; $P = .22$) (Table 1).[3] This difference was not significant.[14] In CARE-MS II, alemtuzumab demonstrated a 49% reduction in relapse risk (rate ratio = 0.51, 95% CI, 0.39-0.65; $P < .0001$) and a 42% reduction in the risk of sustained disability accumulation compared with SC IFN beta-1a at 2 years (HR = 0.58, 95% CI, 0.38-0.87; $P = .0084$) (Table 1).[4]

Adverse events of interest associated with alemtuzumab treatment include autoimmune disorders, infusion-associated reactions (IARs), and infections. In CARE-MS I and CARE-MS II, 16% and 18% of patients, respectively, who were treated with alemtuzumab 12 mg developed autoimmune thyroid disease at 2-year follow-up. Thyroid function tests are to be performed every 3 months until 48 months from last infusion. Immune thrombocytopenic purpura (ITP) occurred in 3 patients who received alemtuzumab in CARE-MS I and 5 patients in CARE-MS II; however, ITP has been reported in 1.5% of all patients in the overall alemtuzumab clinical trial program (core and extension [NCT00930553]). The fatal ITP index case and 2 additional ITP cases in the CAMMS223 phase 2 study led to the development of a safety monitoring program for early ITP detection. All subsequent cases were identified by monthly platelet or symptom monitoring. The majority of confirmed ITP patients responded to first-line therapy (corticosteroids or intravenous [IV] immunoglobulin), while some patients required further treatment with second-line therapies (eg, rituximab).[5] Nephropathies are rare and may occur months or years after alemtuzumab treatment. Although no antiglomerular basement membrane nephropathy cases were reported in the 2-year CARE-MS I and II trials (Table 1), the incidence of glomerular nephropathies in MS patients treated with alemtuzumab in Genzyme clinical trials (core and extension) was 0.3%. All cases were detected by the safety monitoring program, and none resulted in renal failure.[15] Complete blood counts for monitoring of ITP and nephropathies are recommended monthly for up to 4 years from last infusion.

Infections were more common in the alemtuzumab group compared with the IFN beta-1a group, although they were predominantly mild or moderate and responded to conventional therapy; serious infections in the CARE-MS trials ranged from 2% to 4% in patients receiving alemtuzumab 12 mg.[3,4]

INFUSION EXPERIENCE

In CAMMS223, IARs were defined as any AE, whether drug related or not, occurring during or within 48 hours of infusion.[5] IARs were reported in 106/108 (98.1%) of patients randomized to alemtuzumab 12 mg. Most IARs were mild; only 3 patients (1.4%) experienced events that qualified as serious. The most common IARs, affecting more than 20% of patients, were rash, headache, urticaria, pyrexia, pruritus, and nausea.[5]

In CARE-MS I and CARE-MS II, IARs were defined as any AE, whether drug related or not.[3,4] The time frame was broad, with an onset during or within 24 hours of alemtuzumab infusion. Reactions were considered serious if they resulted in death, required or prolonged hospitalization, were life threatening or disabling, or represented an important medical event according to the investigator.[16] In both CARE-MS I and CARE-MS II, IARs were usually mild to moderate and occurred in 90% of patients receiving alemtuzumab 12 mg. Serious IARs occurred in 3% of those receiving alemtuzumab (Table 2).[3,4] Reactions were less common during the second treatment course (Figure 1).[16] The number of IARs generally decreased with each day of infusion.

All patients in each of the 3 clinical trials received 1 g/d of IV methylprednisolone on 3 consecutive days for each treatment course, as required by study protocols.[3-5] Methylprednisolone was infused during the 1-hour period prior to administering alemtuzumab. Patients with IARs were treated with concomitant medications at the treating neurologist's discretion. Concomitant medications used to manage IARs by ≥ 15% of patients receiving alemtuzumab included antipyretics and analgesics (acetaminophen and ibuprofen), H_1-receptor antagonists (diphenhydramine, cetirizine, loratadine, promethazine), H_2-receptor antagonists (ranitidine, famotidine), chloropyramine, and hydroxyzine.

EXPERT PANEL RECOMMENDATIONS AND PRACTICAL GUIDELINES

Methods

Clinicians with expertise in MS patient care and infusion nursing (12 nursing professionals and 1 physician assistant) developed and reviewed a series of protocols implemented by some clinical trial investigators for treating IARs occurring after alemtuzumab infusion. These protocols were based on infusion nursing considerations for administering alemtuzumab and other monoclonal antibodies, MS patient care, and best practices in IAR prevention and management. The panel convened to discuss these practices and reached consensus on a series of best-practice recommendations.

The panel identified 2 core objectives for alemtuzumab infusion recommendations. The first goal was delivery of patient-centered care and education in a manner that encourages a high-quality patient infusion experience, enhances patient knowledge, facilitates communication, and promotes follow-up. The second area for recommendations was alemtuzumab infusion best practices and processes for clinicians. This included potential IAR prevention and management through (1) establishing consensus recommendations on patient preparation and prophylaxis during the preinfusion period; (2) patient monitoring, ongoing nursing care, and IAR interventions during infusion; and (3) postinfusion management, discharge, and follow-up.

Best-practice guideline implementation improves the quality of health care delivery and patient outcomes.[17,18]

TABLE 1

Summary of CARE-MS I and CARE-MS II Clinical Trials of Alemtuzumab in Patients With RRMS

	CARE-MS I Treatment-Naive		CARE-MS II Relapsing on Therapy	
	IFNβ-1a (n = 187)	Alemtuzumab 12 mg (n = 376)	IFNβ-1a (n = 202)	Alemtuzumab 12 mg (n = 435)
Baseline characteristics				
Age, mean years (SD)	33.2 (8.5)	33.0 (8.0)	35.8 (8.8)	34.8 (8.4)
Female,%	65	65	65	66
EDSS, mean score (SD)	2.0 (0.8)	2.0 (0.8)	2.7 (1.2)	2.7 (1.3)
Disease duration, mean years (SD)	2.0 (1.3)	2.1 (1.4)	4.7 (2.9)	4.5 (2.7)
Number of relapses in past year, mean (SD)	1.8 (0.8)	1.8 (0.8)	1.5 (0.75)	1.7 (0.9)
T_2 MRI hyperintense lesion volume, cm^3, mean (SD)	7.3 (9.9)	7.4 (9.0)	9.04 (10.42)	9.94 (12.25)
Proportion with gadolinium-enhanced lesions, %	51	46	44	42
Coprimary end points				
Annualized relapse rate	0.39	0.18	0.52	0.26
Relative reduction vs IFN beta-1a		55% ($P < .0001$)		49% ($P < .0001$)
Patients with SAD, %	11	8	21.1	12.7
Relative reduction vs IFN beta-1a		30% ($P = .22$)		42% ($P = .0084$)
Safety summary				
Patients with AEs, n (%)	172 (92.0)	361 (96.0)	191 (94.6)	428 (98.4)
Patients with SAEs, n (%)	27 (14.4)	69 (18.3)	44 (21.8)	85 (19.5)
AEs causing study discontinuation, n (%)	11 (6.0)	5 (1.0)	15 (7.0)	14 (3.0)
AEs of interest, n (%)				
Infections				
Any associated events	85 (45.5)	253 (67.3)	134 (66.3)	334 (76.8)
Serious AEs	2 (1.0)	7 (2.0)	3 (1.0)	16 (4.0)
Thyroid				
Any associated events	12 (6.4)	68 (18.1)	10 (5.0)	69 (15.9)
Serious AEs	0	4 (1.0)	0	2 (< 1.0)
ITP	0	3 (0.8)	0	3 (0.9)
Anti-glomerular basement membrane	0	0	0	0

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; IFN, interferon; SD, standard deviation; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; SAD, sustained accumulation of disability; AE, adverse effect; SAE, serious adverse effect; ITP, immune thrombocytopenic purpura.

To craft guidelines that are practical for clinicians while being scientifically rigorous, the panel reviewed evidence from publications, abstracts, reviews, and clinical trial experiences, as well as expert opinion.[19] A modified Delphi method was used to reach consensus.[20] The process began by assessing an initial series of recommendations based on the management protocols employed in alemtuzumab clinical studies. Individual recommendations were critically assessed by information gathering, discussion, refinement, and anonymous voting. This process was repeated as many times as needed until consensus was reached, defined by more than 80% agreement. The internationally recognized standards of the Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration were used as a framework for assembling and reporting the results.[21] The AGREE instrument provides a series of criteria that characterize high-quality clinical practice recommendations, including scope and purpose, stakeholder involvement, rigor, clarity, applicability, and independence.

TABLE 2

Prevalence of Most Frequently Reported Infusion-Associated Reactions (Affecting > 10% in the 12-mg Dose Alemtuzumab Group) and Serious Infusion-Associated Reactions[3,4]

Infusion-Associated Reaction	CARE-MS I (n = 376)	CARE-MS II (n = 435)
Events affecting > 10% in alemtuzumab group, n (%)		
Headache	160 (43)	188 (43)
Rash	155 (41)	168 (39)
Nausea	51 (14)	72 (17)
Pyrexia	125 (33)	69 (16)
Urticaria	43 (11)	64 (15)
Pruritus	36 (9.6)	50 (11)
Flushing	43 (11)	NA
Chills	38 (10)	32 (7)
Insomnia	NA	44 (10)
Fatigue	NA	39 (9)
Serious adverse events, n (%)		
Cardiovascular		
Atrial fibrillation	2 (1)	NA
Bradycardia	1 (< 1)	NA
Sinus bradycardia	1 (< 1)	NA
Sinus tachycardia	1 (< 1)	NA
Tachycardia	1 (< 1)	NA
Pulmonary/thoracic		
Dyspnea	NA	1 (< 1)
Hemoptysis	NA	1 (< 1)
Pleurisy	1 (< 1)	NA
Cough	NA	1 (< 1)
Throat tightness	1 (< 1)	NA
Chest pain	NA	1 (< 1)
Noncardiac chest pain	NA	1 (< 1)
Chest discomfort	1 (< 1)	1 (< 1)

(continues)

TABLE 2

Prevalence of Most Frequently Reported Infusion-Associated Reactions (Affecting > 10% in the 12-mg Dose Alemtuzumab Group) and Serious Infusion-Associated Reactions[3,4]
(Continued)

Infusion-Associated Reaction	CARE-MS I (n = 376)	CARE-MS II (n = 435)
Vascular/renal		
Hypotension	2 (1)	NA
Gastrointestinal		
Nausea	1 (< 1)	1 (< 1)
Vomiting	NA	1 (< 1)
Nervous systems		
Headache	1 (< 1)	NA
Migraine	1 (< 1)	NA
Status migrainosus	NA	1 (< 1)
Pyrexia	1 (< 1)	2 (< 1)
Brain stem syndrome	1 (< 1)	NA
Skin and subcutaneous, musculoskeletal		
Urticaria	1 (< 1)	NA
Angioedema	1 (< 1)	NA
Myalgia	1 (< 1)	NA
Endocrine		
Hypothyroidism	NA	2(< 1)
Other and miscellaneous		
Incorrect dose	2 (1)	NA
Infusion related	NA	1 (< 1)
Anaphylactic shock[a]	1(< 1)	NA

[a]*Classified during infusion; later reclassified by investigator as nonanaphylactoid hypotension.*
Abbreviation: NA, not applicable.

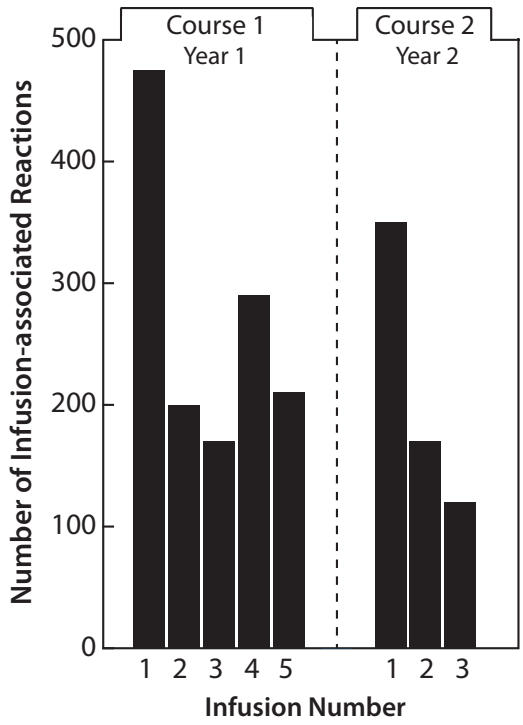

Figure 1 Incidence of infusion-associated reactions in CARE-MS I. The incidence of infusion-associated reactions decreased with successive infusions.

Final anonymous voting revealed 100% consensus on all recommendations detailed here.

Recommendations and Nursing Considerations

Before infusion

Optimal nursing care begins before the day of infusion. Clinician and patient preparedness, laboratory testing completion, premedication administration, and other steps are necessary and integral to optimizing patient education and readiness for infusion.

During the week before infusion, clinicians should confirm the medication order and assess patient readiness for infusion. Objective considerations before infusion day include assessment of baseline MS symptoms, presence of any infections, immunization status, and current medications. Any needed vaccination series should be completed 6 weeks before alemtuzumab treatment. Ordering laboratory tests, including a pregnancy test for women, should be confirmed and the results reviewed. Current medications should be reviewed to identify potential drug interactions or contraindications between MS medications and concomitant medications given before, during, or after alemtuzumab infusion. Medications may be checked in consultation with a pharmacist when appropriate. In preinfusion discussions, the health care provider confirms that the patient understands the need for antiviral prophylaxis (eg, acyclovir). These and any additional medications should be available before the first day of infusion. The availability and contents of an emergency kit in the infusion area should be confirmed by nursing staff, and any needed drugs or equipment should be obtained before the first infusion day.

The location of infusion will vary by institution, country, and local regulations. In the United States, alemtuzumab must be administered in a setting with appropriate equipment and personnel to manage serious infusion reactions.

The patient will often be evaluated by the provider in the MS clinic before infusion. Once at the infusion area, the patient should receive written instructions about expectations, potential AEs, and preparation requirements for infusion days. The infusion procedure and timing should be clearly outlined with the patient, as well as the possible need to maintain vascular access (heparin or saline lock) between infusions, if vascular access is maintained between infusions. Patients should be reminded to bring all medications, including an inhaler if the patient has asthma. The patient's plan for the infusion with regard to necessary logistics, transportation, caregivers, child care and/or work arrangements, and items needed to remain comfortable or occupied during the infusion period should also be reviewed. The provider should confirm and document that the patient is using appropriate contraception, which can be reinforced by nursing staff.

It is important to educate the patient about the potential of transient MS symptom worsening that may occur during or after infusion. In pilot studies, some patients experienced a Uhthoff's-like syndrome during or soon after alemtuzumab infusion. Uhthoff's phenomenon is a disease-specific transient worsening of MS symptoms that occurs when body temperature increases, such as during exercise, a hot bath, or with fever.[2] This phenomenon occurs when heat disrupts demyelinated nerve impulse conduction.[22] The occurrence of Uhthoff's phenomenon following alemtuzumab infusion may be associated with cytokine-release syndrome (CRS). The cytokines trigger biologic responses, such as fever, fatigue, and hypotension.[23] Patients should be educated about CRS, its transient nature, and approaches to reversing symptoms (ie, cooling the core body temperature).

Prophylaxis with antihistamines and antipyretics is often recommended to reduce the frequency and severity of infusion reactions.[24-26] Patients may be prescribed premedications that can be taken at home on the morning of alemtuzumab infusion. For example, routine dosages of a nonsedating H_1-receptor antagonist (eg, loratadine or cetirizine), plus an H_2-receptor antagonist (eg, ranitidine or famotidine), and an antipyretic (eg, acetaminophen or ibuprofen), were often recommended and found to be effective by the alemtuzumab study investigators. Acetaminophen and ibuprofen may be

given in a rotating fashion if acetaminophen alone does not adequately reduce fever. Patients should be reminded to record the time when home medications are taken. In some cases, the clinician may consider recommending a prophylactic preinfusion antiemetic drug.

The day of infusion

On the day of the infusion, the infusion nurse should confirm the medication order and patient readiness, which would include ensuring that the medications recommended to be taken after leaving the infusion department are readily available. The patient should be prepared to initiate the antiviral prophylactic regimen (eg, acyclovir) beginning on the first day of infusion and continuing for a minimum of 2 months following treatment with alemtuzumab or until the CD4 lymphocyte count is $\geq$ 200 cells/μL, whichever occurs later. The patient should understand what to expect in relation to potential side effects of steroid and alemtuzumab infusions. In particular, education should include patient awareness of potential CRS symptom development.

Premedication such as antihistamines, antipyretics, and antiemetics can be considered if these were not taken at home. Baseline patient assessment should include vital signs, skin evaluation, and any other relevant exams, such as evaluation for infections. An infusion of 1000 mg of methylprednisolone should be administered before alemtuzumab. Patients should be asked about any physical needs and comfort considerations before starting the infusion. The catheter patency must be maintained and the catheter flushed between medications. Vital signs should be reassessed and recorded after completing the steroid infusion. An IV fluid bolus is recommended if the patient's hydration status is suboptimal. It should be noted that alemtuzumab should be administered using an infusion pump.

During infusion

Recommendations for preparation of alemtuzumab are summarized in Table 3. Best practices in infusion nursing include maintaining aseptic technique, recording relevant patient and procedural information, and following drug handling and storage recommendations. Alemtuzumab can be combined with sterile 0.9% sodium chloride or 5% dextrose in water, and solutions can be stored at room temperature or refrigerated. Alemtuzumab vials and solutions should not be frozen. Infuse alemtuzumab over 4 hours starting within 8 hours after dilution. Alemtuzumab can be prepared while methylprednisolone is being infused.[27] Alemtuzumab must also be protected from light, which may be accomplished by covering the drug infusion bag with foil or other opaque material.

Patient monitoring during infusion

Notify the patient and record the starting time when alemtuzumab infusion begins. The patient should be monitored by the infusion staff continuously where feasible for vital signs, IV site assessment, and skin assessment. Other AEs, such as pyrexia and headache, should be recorded at least hourly. The patient should be encouraged to promptly report any emergent symptoms, such as shortness of breath, diaphoresis, or dizziness.

Consider interventions when vital signs or symptom changes suggest an impending IAR that warrants management. Infusion reactions are managed by concomitantly administering appropriate medications or by slowing or temporarily stopping the alemtuzumab infusion. When slowing the infusion, the rate may be decreased by any extent. The expert consensus was to initially decrease the infusion rate by 50% and evaluate

TABLE 3

Preparation of Alemtuzumab for Infusion

Alemtuzumab Dilution and Admixture
DO
✓ Maintain aseptic technique throughout alemtuzumab preparation and administration.
✓ Discard used vial, syringe, and any unused drug portion.
✓ Record mix time and label IV bag with patient's name, drug, dose, date, and time. Cover with an opaque bag.
✓ Store alemtuzumab solutions at room temperature (15°C-30°C) or in refrigerated conditions (2°C-8°C).
DON'T
✗ Shake alemtuzumab vial.
✗ Freeze alemtuzumab. Do not use alemtuzumab if vial has been frozen.
✗ Expose alemtuzumab IV admixture to excessive light.
INSTRUCTIONS
1. Inspect vial for visible particulate matter or discoloration before dilution. If particulate matter is present or the solution is discolored, do not use vial.
2. Insert needle into vial and withdraw 1.2 mL of alemtuzumab into syringe.
3. Inject alemtuzumab into 100-mL sterile 0.9% sodium chloride (normal saline) or 5% dextrose in water (USP).
4. Invert the bag gently to mix the solution.

Abbreviations: IV, intravenous; USP, United States Pharmacopeia.

symptom abatement; if symptoms are relieved, the rate can be increased again, as tolerated by the patient. If the infusion must be entirely stopped, it can be resumed at 50% of the previous rate for 15 minutes and increased thereafter as tolerated.

To aid in efficiency, consistency, and recall, the salient features of nursing management are conceptualized as 3 steps before and during infusion, which are summarized in Table 4. These are to (1) *verify* (readiness, orders, premedications, vaccines, etc); (2) *inquire* (patient preparedness and clinical status); and (3) *prepare* the patient (before infusion) or *proceed* (day of infusion). These steps can be remembered easily using the mnemonic acronym VIP.

Management of IARs

Any IAR should be treated according to severity and protocol. Although most IARs in patients receiving alemtuzumab infusion are mild to moderate, there is a

TABLE 4

Nursing Considerations for Alemtuzumab Infusion: VIP Approach for Preparation and Day of Infusion

Checklist: Nursing Considerations for Alemtuzumab Infusion Preparation
Before infusion day
Step 1 VERIFY[a]
☐ Confirm alemtuzumab order.
☐ Confirm patient has filled prescription for antiviral and all other prescribed medications.
Step 2 INQUIRE
☐ Assess immunizations and laboratory results, including current pregnancy test and appropriate contraception confirmation, and measure plasma glucose, if needed.
☐ Assess baseline MS symptoms and any concomitant infection.
Step 3 PREPARE
☐ Consider recommending premedications (eg, H_1- and/or H_2-receptor antagonists, antipyretics, antiemetics).
☐ Ensure patient will be well hydrated.
☐ Recommend that the patient bring activities to remain busy during the infusion period.
☐ Encourage a support person (eg, family member, caregiver) to be available during infusion.
Day of Infusion
Step 1 VERIFY
☐ Confirm alemtuzumab order, patient prescription fulfillment, and that any prearrival medications were taken.
☐ Ascertain that the patient has been counseled on expectations for medication side effects, potential cytokine-release syndrome, Uhthoff's syndrome, and any other appropriate information, including the need for antiviral prophylaxis.
Step 2 INQUIRE
☐ Document patient's baseline vital signs and skin evaluation.
☐ Solicit any personal or physical needs to enhance patient comfort during infusion.
☐ Confirm the presence of an emergency kit/team or appropriate supplies, according to organizational protocol.
Step 3 PROCEED
☐ Prepare alemtuzumab as directed (see protocol) or obtain from pharmacy.
☐ Establish vascular access according to protocol and administer 1 g methylprednisolone.
☐ Reassess vital signs after steroid infusion.
☐ Consider premedications (eg, antihistamines, antipyretics) if not yet administered.
☐ Flush catheter with 0.9% sodium chloride (USP) between medications.
☐ Monitor patient hydration and nutritional status.

[a]*The mnemonic VIP may be helpful for recalling the checklist steps: **V**erify, **I**nquire, **P**repare before infusion day and **V**erify, **I**nquire, **P**roceed on infusion day.*
Abbreviations: MS, multiple sclerosis.

wide spectrum of potential reactions that require monitoring and assessment. Infusion reactions occur most often during the first or second infusion in a given consecutive series, with 10% to 30% of reactions occurring during subsequent therapeutic courses.[16] Nevertheless, clinicians should be vigilant with each infusion because IARs occur in as many as 90% of patients and can occur at any point during the alemtuzumab therapy process.

Most alemtuzumab IARs can be managed with interventions such as medication or by slowing or interrupting the infusion. Any IAR-related signs and symptoms that respond to infusion interruption or antihistamine and antipyretic administration may be associated with CRS.[25] Cytokine release from lysed lymphocytes is the most common nonallergic side effect of infusing monoclonal antibodies and can cause a transient inflammatory response similar to an infection or influenza, with symptoms such as fever, chills, headache, nausea, myalgia, and hypotension.[23]

Some reactions to alemtuzumab, such as rash, may be striking but are often not serious and should not be mistaken for anaphylaxis. Although uncommon, an immune-mediated hypersensitivity response can occur in some patients with subsequent infusions. If hypersensitivity symptoms develop, then clinical judgment, experience, and preparation are the best tools to ensure a prompt and appropriate response.[25] In clinical trials, 1 patient had a serious IAR initially recorded as an anaphylaxis event, but on review of the clinical symptoms, the investigator confirmed that the event was nonanaphylactic hypotension.[28]

Clinicians should carefully consider the need for epinephrine during management of serious IARs. Some experts assert that even when doubt is present as to the nature of the reaction, it is better to administer epinephrine than not. This is because underuse or delayed administration of epinephrine can result in poor outcomes, and there is no absolute contraindication in a potentially anaphylactic setting.[29]

Rash was a relatively common IAR in clinical trials. Rash emerging during alemtuzumab infusion may or may not be associated with pruritus or urticaria. Diphenhydramine (or another H_1-receptor antagonist) was an effective intervention for rash. If rash is serious or accompanied by additional signs or symptoms (eg, headache, nausea, fever), then slowing or interrupting the infusion should be considered. Record times that the infusion was slowed, stopped, restarted, and/or increased. In patients with serious rash, the clinician should monitor vital signs, reassess response to interventions, and restart infusion slowly when the patient is stable. Headache and myalgia can be managed with analgesics such as acetaminophen or ibuprofen. Consider alternating between acetaminophen and ibuprofen if fever and myalgia are not responsive to the initial agent. If bradycardia (< 60 bpm) occurs, then consider reducing the rate or interrupting the infusion, according to the severity of symptoms. Asymptomatic, mild bradycardia may be monitored, and ensuring vascular access is an appropriate precaution. If bradycardia is present in a patient without hypotension, monitor vital signs until the patient's heart rate returns to the normal range and then resume infusion. If bradycardia is accompanied by hypotension, chest pain, altered mental status, or other signs or symptoms of worsening IAR, consider additional interventions and notification of the emergency response team or physician/provider, according to individual infusion center protocol. IV fluids (eg, 0.9% sodium chloride) may be provided, supplemented with oral repletion as appropriate.[25] Oxygen saturation can be monitored by pulse oximetry, and if the patient is hypoxic, consider delivering supplemental oxygen by nasal cannula or mask. For severe bradycardia, convert to emergency protocols including using atropine and/or epinephrine, as necessary.

Bronchospasm is an infrequent IAR but normally can be managed by reducing the rate of administration or interrupting the infusion. Additionally, clinicians may consider administering additional IV or intramuscular (IM) nonsedating antihistamines. Bronchodilators (β-adrenergic receptor agonists) for bronchospasm and oxygen (2-4 L/min via nasal cannula) may be provided if needed. Patient vital signs should be taken every 2 to 10 minutes as appropriate during the reaction. In severe cases or rapid onset, the emergency response team should be notified according to the infusion center protocol, and epinephrine (0.3-0.5 mg IM anterolateral thigh; EpiPen) may be administered. Table 5 provides a summary of suggested interventions for IARs clinicians may encounter.

Nursing considerations after infusion

Immediately after infusion, patients should be evaluated for any AEs and appropriate treatment considered. Patients should be monitored for 2 hours after infusion completion; during that time, they should be encouraged to maintain adequate nutrition and hydration. Continue to monitor the infusion site for redness, swelling, erythema, pain, and blood return. The infusion site should be changed after 3 days or sooner if needed (Table 6).

An individualized daily discharge sheet should be completed for each patient. Patients may be provided with prescriptions for medications required for rash, fever, or headache. Medications and the use of nonprescription agents should be discussed again, including potential drug-drug interactions and associated risks or AEs. Include a record of when the last dose of all medications was taken.

Before discharge, review and reinforce infusion site management, nutrition, hydration, the importance of completing the antiviral regimen, and any other

TABLE 5
Management of Potential Alemtuzumab Infusion-Associated Reactions

Infusion Reaction	Interventions and Management Options
Urticarial rash	• Reduce infusion rate. Review whether previous antihistamines were taken at home or preinfusion. Infusion rate may be reduced by 50%. • Prolonged reaction may require infusion interruption. Resume at 50% of original rate for 15 minutes and increase, as tolerated. • Consider administration of additional IV or IM nonselective antihistamines. • Monitor vital signs, reassess response to interventions, and restart infusion when patient is stable.
Headache/myalgia (achy fatigue)	• Consider analgesic (eg, acetaminophen or ibuprofen).[a] • For persistent migraine, consider a triptan.[b]
Bradycardia/ hypotension	• Reduce infusion rate or interrupt infusion as above. • Consider a 500-mL IV bolus of 0.9% sodium chloride plus oral repletion. • If bradycardia is accompanied by hypotension, refer to emergency protocol. • Consider epinephrine (0.3-0.5 mg IM; EpiPen).[c] • Monitor vital signs every 2 to 10 minutes, as appropriate.
Bronchospasm or anaphylactoid	• Reduce infusion rate or interrupt infusion, as above. • Consider administration of additional IV or IM nonselective antihistamines. • Consider bronchodilators (β-adrenergic receptor agonist) for bronchospasm. • Consider oxygen (2-4 L/min) if needed.[d] • Monitor vital signs every 2 to 10 minutes, as appropriate. • Administer epinephrine (0.3-0.5 mg IM; EpiPen), if warranted.

[a]Consider alternating between acetaminophen and ibuprofen, if fever or myalgia is not responsive to initial agent.
[b]Exercise of appropriate caution is warranted for coadministration of serotonin agents, such as triptans with antidepressants, opioids (eg, meperidine), CNS stimulants, St. John's wort, dextromethorphan, etc.
[c]Dose for suspected anaphylactic shock. Epinephrine should not be administered as a bolus for hypotensive bradycardia nonresponsive to atropine.
[d]Oxygen can be considered in cases of prolonged reactions, a preexisting hypoxemic state, or in patients with known myocardial dysfunction. Monitor by pulse oximetry.
Abbreviations: IV, intravenous; IM, intramuscular, CNS, central nervous system.

TABLE 6
Nursing Considerations During and After Alemtuzumab Infusion

Checklist: Nursing Considerations During and After Alemtuzumab Infusion
During infusion
❑ Begin alemtuzumab infusion, recording the start time (consider in-bag stability).
❑ Alemtuzumab should be infused 12 mg/d over approximately 4 hours (do not administer as IV push or bolus).
❑ Observe the patient and document hourly assessments of vital signs, infusion entry site, possible signs and/or symptoms of IARs (eg, pyrexia, rash, headache), or worsening of MS signs or symptoms.
❑ Maintain vascular access.
❑ Confirm that emergency practitioner coverage will be promptly available, if needed.
❑ If a change in vital signs or patient status is observed, consider appropriate intervention; extend duration of infusion if not well tolerated.
❑ Ensure fluid intake and patient hydration is appropriate.
After infusion
❑ Observe patient for approximately 1 to 2 hours after infusion; maintain vascular access.
❑ Encourage adequate nutrition and hydration during observation period.
❑ Continue to assess infusion site, and document any changes or concerns (eg, redness, swelling, erythema, pain).
❑ Complete individualized patient discharge form.
❑ Provide patient with prescriptions for an antihistamine, if rash appears, and antipyretic, if fever or headache occurs.
❑ Advise patient on importance of completing the entire month of antiviral prophylaxis.
❑ Provide a summary communication of the alemtuzumab infusion to the prescribing practitioner.

Abbreviations: IV, intravenous; IAR, infusion-associated reaction; MS, multiple sclerosis.

educational points that are necessary to reiterate or discuss. The return visit should be scheduled and the patient reminded about the possibility of delayed IARs, what constitutes a true emergency, and the appropriate response to an emergency. Patients should be told to contact a health care provider if they experience swelling in the mouth or throat, difficulty breathing, weakness, an abnormal heart rate, chest pain, or rash. Particular attention should be paid to patients with cardiovascular disorders.

Also before discharge, clinicians are advised to discuss with the patient delayed IARs and any questions about medication, symptoms, or signs that emerged following treatment. A summary communication of infusion procedures and completed checklists must be provided to the prescribing provider.

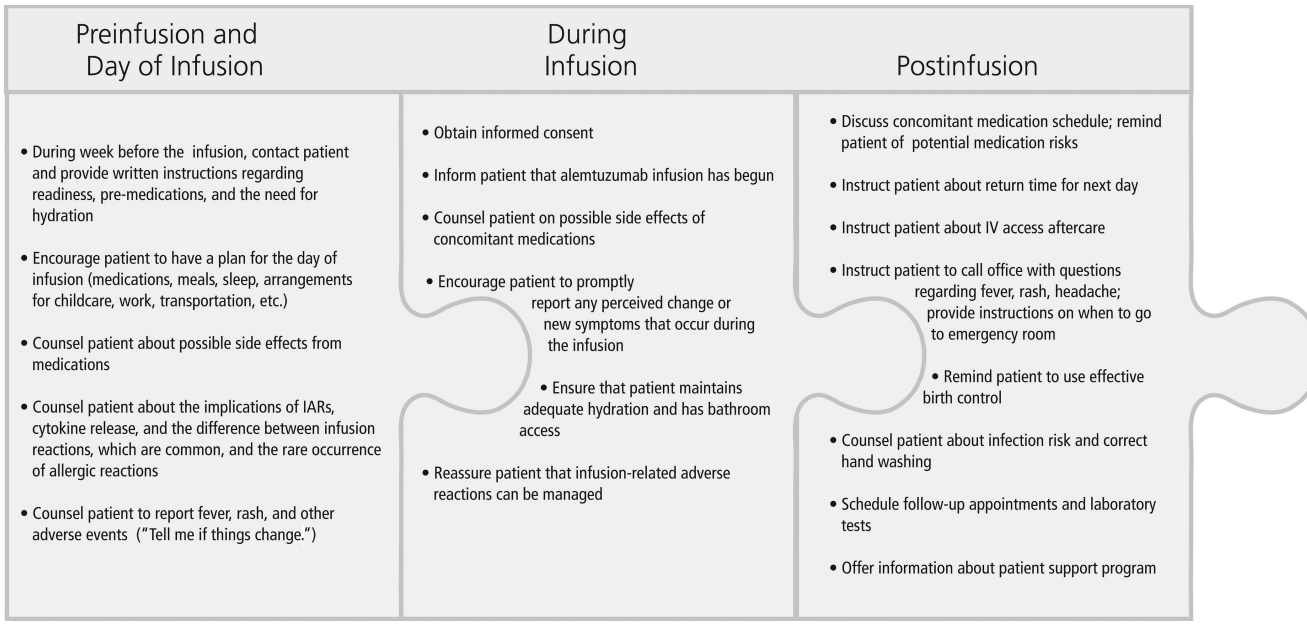

Figure 2 The patient-centered process of education is integrated with the infusion nursing process. *Abbreviations: IAR, infusion-associated reaction; IV, intravenous.*

On the last day of infusion, a final day discharge sheet must be completed. Arrange for follow-up appointments and necessary laboratory tests (eg, monthly complete blood count), or confirm that the patient is aware if laboratory tests have been ordered by the provider. Confirm and document patient use of appropriate contraception. Strategies to decrease infection risk, such as hand washing and food safety, should be discussed. Patients can be offered resources such as MS support program information and other local sources of MS information and patient groups.

CONCLUSIONS

Clinical trials have shown higher efficacy of alemtuzumab compared with SC IFN beta-1a, and alemtuzumab has a consistent safety profile in patients with active RRMS who were treatment-naive or who have relapsed on previous disease-modifying therapy. Efforts to enhance the patient's infusion experience include expanding and reinforcing the practitioner's understanding of the treatment goals; the recognition, prevention, and management of IARs; and proper patient education. Augmenting patient understanding related to the infusion process is an essential component in the successful prophylaxis, identification, management, and aftercare of IARs (Figure 2). These best-practice recommendations, which are based on the best available evidence, expert experience, and clinical trial outcomes, provide a practical resource for clinicians to optimize patient education and infusion experience as well as to implement strategies for IAR prophylaxis and management.

Practice Points for Alemtuzumab Infusion

- The incidence of IARs decreases with use of appropriate premedications (eg, antihistamines, acid blockers); initiate them the day before infusion and use them for as long as 2 weeks after infusion, if needed.
- Adequate hydration to maintain intravascular volume helps prevent hypotension.
- Patient monitoring (vital signs, hydration, etc) is crucial.
- Patients should receive education on medication side effects, expectations for infusion, and optimal aftercare.
- Encouraging communication enhances opportunities for monitoring and optimal nursing care.
- Infusion can be slowed or stopped in the event of an IAR.
- Identify a contact person who can discuss infusion and postinfusion care.
- Patients should take home instructions and a written checklist detailing current and next-dose information, signs and symptoms to watch for (eg, Uhthoff's phenomenon), and health care provider contact information.

Abbreviation: IAR, infusion-associated reaction.

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