Pharmacy Operationalization of the Intralesional Oncolytic Immunotherapy Talimogene Laherparepvec

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Abstract

Objective: Oncolytic immunotherapy involves the use of viruses to target and destroy cancer cells and to induce immune responses for an enhanced antitumor effect. Talimogene laherparepvec, a genetically modified herpes simplex virus type 1 (HSV-1) that selectively replicates in tumors to induce lytic cell death, tumor antigen release, and the local production of granulocyte–macrophage colony-stimulating factor (GM-CSF), has been approved for the treatment of a defined population of patients with metastatic melanoma. Talimogene laherparepvec is administered as a series of intralesional injections, and specific procedures are implemented to minimize the risk of viral exposure. Because talimogene laherparepvec represents a novel therapeutic modality, its preparation, administration, and handling requirements differ from current therapies; pharmacists have an important role in developing new procedures to incorporate it into clinical practice. **Methods:** In this review, pharmacists with experience dispensing talimogene laherparepvec, in the clinical trial setting and/or as a commercially available product at US academic institutions, synthesized their personal experiences through group discussions to provide insights on the ordering, receipt, storage, preparation, administration, and handling of talimogene laherparepvec. **Results:** Suggestions for patient education and practical guidance to assist hospital pharmacists and decision makers with implementing talimogene laherparepvec at their institutions are provided. **Conclusion:** These insights may further inform the development of policies or procedures to incorporate talimogene laherparepvec into clinical settings and improve patient outcomes.

Keywords

clinical services, dispensing, oncology

Introduction

As diverse and innovative therapeutic agents continue to enter the oncology clinic through both investigative trials and regulatory approvals, hospital practices must continuously keep step to implement these new therapies. In many instances, these therapies differ from previous cancer treatments in aspects that affect both clinical and pharmacy practices. These differences can include novel mechanisms of action, storage requirements, safe handling considerations, and modes of administration, each of which carries implications for a hospital's practical operations.

Oncolytic immunotherapies present an illustrative case study of the unique challenges that such new agents may present for pharmacists, who must be flexible and adaptable to ensure that new agents are appropriately incorporated into clinical practice and patient care. Oncolytic immunotherapy is a form of anticancer therapy in which viruses directly target and destroy cancer cells, and subsequently induce systemic immune responses to further enhance the antitumor

effect. The preparation, administration, and handling procedures for oncolytic immunotherapies for pharmacists and/or practitioners are different from those for other immunotherapies. For example, because oncolytic immunotherapies are replication-competent viruses, they are associated with additional safety concerns, such as possible secondary transmission. Furthermore, the viral nature of oncolytic immunotherapies prompts consideration of protecting the integrity of the virus during preparation so that it retains its activity for patient treatments.

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Figure 1. Talimogene laherparepvec mechanism of action.

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Note. GM-CSF = granulocyte-macrophage colony-stimulating factor.

Among the first oncolytic immunotherapeutic agents to be developed is talimogene laherparepvec (IMLYGIC®; Amgen Inc.), a genetically modified oncolytic virus approved for the local treatment of unresectable, cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.¹ Talimogene laherparepvec is designed to selectively replicate in tumors, while leaving normal tissues unharmed, and to express granulocyte-macrophage colony-stimulating factor (GM-CSF; Figure 1).^{1,2} For some institutions and health care professionals unfamiliar with talimogene laherparepvec, the path to operationalization may raise certain challenges and questions. Furthermore, as familiarity with the product grows, experienced sites may also wish to revisit their initial protocols to better optimize operations.

This article presents an overview of the preparation and handling process of talimogene laherparepvec (Figure 2), drawing on multi-institutional experience from US pharmacists, to provide practical insights that will assist hospital pharmacists and decision makers with implementing talimogene laherparepvec in their institutions.

Talimogene Laherparepvec: Mechanism of Action and Clinical Outcomes

Talimogene laherparepvec is a recombinant oncolytic virus created by genetically modifying the herpes simplex virus (HSV) type 1 to enable selective replication in tumor cells, resulting in lytic cell death, tumor antigen release, and the local production of human GM-CSF, which enhances the antitumor immune response.³ The general properties of HSV-1 make it amenable for use as an oncolytic immunotherapy. From a safety perspective, the replicative biology and lipid bilayer envelope of the virus render it susceptible to

antiviral medications as well as lipid solvents and disinfectants.^{4,5} In addition, HSV-1's natural cell entry mediators are sometimes overexpressed on the surface of cancer cells compared with normal cells.⁶ To enhance the tumor-specific replication of talimogene laherparepvec, genetic alterations were made (1) to attenuate the natural neurovirulence of the virus (which enhances the preferential killing of tumors and diminishes replication in normal tissues, effectively increasing both the safety and the tumor specificity of the virus when injected into patients); (2) to permit proper antigen presentation on the surface of virally infected cells (which would normally be inhibited); (3) to allow for the upregulation and earlier expression of the HSV-1 *US11* gene (which results in increased replication efficacy and enhanced tumor killing in tumor tissue); and (4) to express GM-CSF in the tumor microenvironment (to enhance the antitumor response through recruitment of and activation of antigen-presenting cells).^{3,7} In preclinical testing, the expression of GM-CSF resulted in enhanced tumor shrinkage in noninjected tumors when compared with a viral construct that lacked the gene for this cytokine.³

To maximize the local effect in tumors, talimogene laherparepvec is administered as a series of intralesional injections into cutaneous, subcutaneous, and nodal melanoma lesions. First, an initial lower dose of 10^6 plaque-forming units per milliliter (PFU/mL) is given to minimize the symptoms associated with seroconversion for patients who are HSV-1 negative. The second and all subsequent doses are administered at a concentration of 10^8 PFU/mL every 2 weeks.¹ Talimogene laherparepvec is injected uniformly throughout the selected lesion using a single needle insertion point. However, if the tumor radius exceeds the reach of the needle, multiple insertion points may be used.^{1,8} To avoid possible bacterial infection, the needle should be changed for

Figure 2. Diagram of author-recommended best practices for talimogene laherparepvec storage, preparation, and administration. Note. BSC = biosafety cabinet; HCP = health care provider; PPE = personal protective equipment; USP = US Pharmacopeial Convention.

each new needle entry point.^{1,8} The total delivered dose volume for each treatment must not exceed 4 mL, distributed amongst all injected lesions. The volume injected into each selected lesion is dependent on the size of the lesion.⁸

The clinical use of talimogene laherparepvec is supported by the data collected during the randomized, phase 3 pivotal trial in melanoma—the OPTiM trial. In OPTiM, 436 patients with injectable, unresectable regionally or distantly metastatic melanoma were randomized 2:1 to receive either talimogene laherparepvec ($n = 295$) or subcutaneous GM-CSF ($n = 141$).² The primary endpoint was durable response rate (DRR; defined as the rate of objective response [ie, complete response or partial response] lasting at least 6 months continuously and beginning within the first 12 months of treatment); secondary endpoints included best overall response and overall survival (time from randomization to death).² Patients with extensive visceral disease burden were excluded.² The DRR was significantly higher with talimogene laherparepvec (16.3%; 95% confidence interval [CI], 12.1%–20.5%) than with GM-CSF (2.1%; 95% CI, 0%–4.5%; unadjusted odds ratio, 8.9%; 95% CI, 2.7%–29.2%; $P < .0001$).² In an exploratory subgroup analysis, the difference in DRR between treatment arms was more pronounced in patients with stage IIIB–IVM1a disease (25.2% vs 1.2%; $P < .0001$). In the intent-to-treat population, the overall response rate (95% CI) was also greater in those who received talimogene laherparepvec (26.4%; 21.4%–31.5%) than in those who received GM-CSF (5.7%; 1.9%–9.5%; $P < .001$), and treatment with talimogene laherparepvec resulted in a median (95% CI) overall survival of 23.3 (19.5–29.6) months compared with 18.9 (16.0–23.7) months with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62–1.00; $P = .051$).² Responses were seen in both injected nonvisceral lesions and noninjected visceral lesions, suggesting local injection could elicit an overall systemic response.²

In the OPTiM study, adverse events of any grade that occurred more frequently with talimogene laherparepvec than with GM-CSF were expected based on the viral nature of the agent, and included fatigue (50% vs 36%), chills (49% vs 9%), fever (43% vs 9%), nausea (36% vs 20%), influenza-like illness (30% vs 15%), and injection-site pain (28% vs 6%).² Grade ≥ 3 adverse events occurred in 36% of patients treated with talimogene laherparepvec and 21% of patients treated with GM-CSF; only cellulitis occurred in $\geq 2\%$ of talimogene laherparepvec treated patients (2.1% vs $<1\%$).

Because HSV-1 is transmitted primarily through direct interpersonal mucosal contact,⁹ a phase 2 study was designed to evaluate the biodistribution and shedding pattern of talimogene laherparepvec in patients with melanoma. The results of this study indicated that talimogene laherparepvec viral DNA was transiently detected in the blood (98%), urine (32%), or on the surface of injected lesions (100%) of treated patients ($n = 60$) yet secondary transmission via close contact or interaction with injected persons has not been recorded.¹⁰ In addition, live virus was not detected on the exterior

surface of the occlusive dressings at any time point during the phase 2 study, suggesting that the dressings established an effective barrier. Nevertheless, there is a theoretical possibility for the virus to be transmitted to individuals who are immunocompromised or who have open skin lesions, as well as health care providers (HCPs) and close contacts, pregnant women, and newborns; thus, certain precautions are recommended when preparing, administering, and handling the virus.⁸

Pharmacy Experience With Talimogene Laherparepvec

Talimogene Laherparepvec Ordering

In the typical experience of the authors, orders for talimogene laherparepvec, including the number of syringes needed and the total volume per syringe, are submitted electronically to the pharmacy on the day of treatment. In many instances, the total dose volume needed and the volumes for the individual lesions to be injected are determined by the physician and communicated to the pharmacy when the order is placed. The dose to be injected—as well as the dimensions of the lesions, when possible—is entered into the electronic medical record (EMR); in some cases, EMR structure and institutional process may dictate whether to create one electronic order that documents all lesions or to create one order for each lesion. In addition, the order or comment field should note that the total injected volume should not exceed 4 mL. In some cases, a paper record noting this information is also submitted. The availability of 2 concentrations of talimogene laherparepvec (10^6 and 10^8 PFU/mL) introduces the potential for error in ordering stock, provider ordering, and preparation of syringes. Those individuals in charge of ordering must know the number of vials of each concentration to stock, based on expected new starts and follow-up doses. It is also very important to integrate ordering procedures with the materials or instructions provided by the prescribing practitioners. For example, images of the lesions are often included in the actual note in the EMR. In these images, the lesions are often numbered, and the amounts needed for injection are listed; thus, if syringes are being prepared in the pharmacy, it is beneficial to correlate the identification of the syringes ordered with the lesions identified.

Reception and Storage

Once received by the pharmacy, vials of talimogene laherparepvec must be protected from light and stored at -90°C to -70°C (-130°F to -94°F), either in an ultra-cold freezer or for up to 96 hours in the provided shipping container until preparation/administration.¹ Use of a manual-defrost freezer is preferred to avoid fluctuations of internal temperature that would be expected with an auto-defrost freezer. Shared use of the freezer with other agents is possible. Contrary to

routine practice with other agents, talimogene laherparepvec containers must not be opened until just prior to use. Because freezer temperatures can fluctuate rapidly when the door is opened, it is recommended to set the freezer to -80°C . If space allows, vials containing the 2 different drug concentrations may be stored separately. It is helpful to note the exact location of the vials on the outside of the freezer, so that vial removal is more efficient, and to note that the 10^6 PFU/mL vial differs in appearance from the 10^8 PFU/mL vial, to ensure that the correct vial(s) is removed. It is also recommended that talimogene laherparepvec be stored within additional containers within the freezer for added protection and that a backup plan be devised for instances of freezer failure (eg, power outages, ruptured pipes, compressor failure). This plan should include the use of backup freezers or backup energy sources.

No formal hazard classification for talimogene laherparepvec has been designated in the National Institute for Occupational Safety and Health 2016 List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.¹¹ To date, the level of hazard and associated precautions are determined by each institution for its own practice. On one hand, talimogene laherparepvec is a virally based oncologic therapy, and there are theoretical concerns regarding secondary transmission from inadvertent contact with the virus (eg, needle sticks, interactions with fluids from injected patients). On the other hand, it is attenuated, tumor cell-specific, and highly susceptible to surface inactivation.³⁻⁵ Given the unfolding implementation of the recent US Pharmacopeial Convention 800 requirements and the absence of specific conventions on the handling of oncolytic viral therapies, guidelines for reception, storage, and preparation continue to be developed at the institutional level. In some cases, procedures similar to those required for other oncology therapies are observed in the case of talimogene laherparepvec.

Preparation

Before administration, talimogene laherparepvec is thawed (approximately 30 minutes) in the vial carton on a pharmacy bench; some institutions elect to do this within a cleanroom designed to minimize contamination of sterile pharmacy preparations. If the vials were stored in the freezer, the desired vial(s) for thawing should be removed rapidly (ideally in <60 seconds) to minimize freezer temperature fluctuations. In some institutions, the thawing process is undertaken by the pharmacy technician who also prepares the syringes. At one author's site, this procedure is completed in a cleanroom, and standard personal protective equipment (PPE) is used. This includes a double layer of gloves, gown, face-mask, and shoe covers.

After the drug has thawed, syringes for intralesional injection are prepared, preferably in a biosafety cabinet (BSC). The type of BSC is determinable by the institutional standard; the same BSC as that used for the preparation of

antineoplastic hazardous agents is allowed. If multiple hoods are available, pharmacies may consider designating a separate hood for talimogene laherparepvec to further limit the potential for contamination. Prior to syringe preparation, the pharmacy is notified that the patient is present and the person who will inject the lesion(s) is available. The syringes are then placed in bags (eg, biohazard or opaque bags) and transported. If temperature fluctuation is a concern, pharmacies may consider using a cooler with or without freezer packs. If the injection suite is in close proximity to the pharmacy, mid-level staff may transport the syringes with the needle on; however, most institutions send capped syringes to the administration room. Each dose is packaged per syringe and labeled to identify the corresponding lesion to be injected. Syringes should not be sent to the treatment area via a pneumatic tube system.

Although syringe preparation in a pharmacy BSC is preferred by some institutions, the practice at other institutions is to prepare the syringe(s) needed for administration after transport of unopened drug vials to the administration room. In these cases, talimogene laherparepvec vials may be bagged (eg, within a chemotherapy or zip-type light-protective transport bag) before being brought to the administration room for syringe preparation. At one author's institution, vials are thawed in the administration room, and syringes are prepared by the administering nurse team coordinator. If multiple syringes are prepared in the administration room, they should be marked to identify which syringe is being used for which lesion. For example, if two 1-mL syringes and one 2-mL syringe are prepared, the person who will inject the lesions must make sure that the correct lesion is injected with the 2-mL syringe.

As described above, each selected lesion is injected separately, and the total injected dose volume of talimogene laherparepvec for any given treatment session is up to 4 mL.¹ The total injected volume is allocated based on the emergence pattern and size of the prioritized lesions. First, any new lesions are injected; next, the largest lesions are injected, using lesion-specific volumes described in the prescribing information.¹ Typically, the size of the syringe prepared for each injected lesion corresponds with the volume to be injected. Using the smallest and fewest syringes for a given treatment plan will minimize waste. In our experiences, a 3-mL syringe is typically best; however, a 5-mL syringe is suggested for larger volumes, and a 1-mL syringe is advised for volumes <0.8 mL. A 25-gauge safety needle is typically used, with a length of 5/8" for topical injections and a length of 1.5" for deeper injections.

Administration and Handling

Talimogene laherparepvec is often administered on designated treatment days (eg, melanoma clinic days) in a private room by an appropriately qualified and trained HCP. It is

helpful, whenever possible, that the same person carries out or oversees a given patient's injections and measurements each visit, for consistency. Expanded administration and handling guidelines have been published previously.⁸ Briefly, because talimogene laherparepvec is an oncolytic virus, HCPs who handle it should wear appropriate PPE, because there is the theoretical risk for secondary transmission. However, as mentioned, secondary transmission to noninjected persons has not been reported.¹⁰ In addition, the preparation area is cleaned after syringe preparation, and the treatment room surfaces that were exposed to spillage must be sanitized after treatment.

Cleaning and Waste Disposal

During pharmacy cleaning, the BSC or workbench is sanitized per institutional guidelines and/or US Pharmacopeial Convention 797. Cleaning agents must be selected according to virucidal activity, inactivation by organics, residue, and shelf life.¹² For use with talimogene laherparepvec, cleaning agents need to be effective against viruses and safe/compatible with BSC and bench surfaces (eg, 2.5% bleach; 70% isopropanol; 0.8% Vesphene; 0.8% LpH, Steris Life Sciences, Mentor, Ohio; Metriguard, Metrex, Orange, California). Cleaning tools should be sterile, low lint, and preferably composed of synthetic microfibers.¹² Sanicloths with bleach, Surface Safe cleanser, and a fresh 10% bleach solution have also been used. Cleaning implements should also be sanitized after each use and discarded as appropriate.¹² Materials that contact talimogene laherparepvec, such as the syringes used for injection or the injection-site bandages or swabs, should be disposed of according to standard institutional medical waste processes.

In the event of accidental eye exposure, the affected eye should be flushed with clean water for at least 15 minutes.⁸ If a needle stick or skin laceration occurs, soap and water or skin disinfectant should be used to clean the wound.⁸ In all instances, it is recommended that an exposed person be monitored by an HCP for any signs of infection and that systemic treatment with antiviral medications such as acyclovir be given if clinically indicated.⁸ As described in the US Prescribing Information and Medication Guide, suspected herpetic lesions should be reported to the manufacturer (Amgen Inc.) for possible additional follow-up testing, which consists of collecting a swab of the suspected lesion for DNA analysis by polymerase chain reaction (PCR). The PCR test is specific for talimogene laherparepvec and distinguishes the oncolytic virus from wild-type HSV-1. Because the sensitivity and accuracy of the PCR test rely on early swabbing of newly developed lesions, the swab should ideally be collected within 3 days of onset; however, swabbing can be conducted at any time when signs or symptoms of infection are present. A testing kit is provided to the supervising HCP as part of the suspected herpetic lesion reporting process.

Reception and Storage	
☐	How will the oncolytic virus be received by the loading dock?
☐	If using just-in-time ordering, where will the cryo-shipping container be stored?
☐	Where will the empty shipping containers be stored and when will they be returned?
☐	How will the 10^6 versus 10^8 concentrations be separated and identified?
☐	Where will the 10^6 and 10^8 concentrations be stored in the freezer?
Transportation and Preparation	
☐	How will the oncolytic virus be transported from the freezer to the BSC?
☐	How is the oncolytic virus prepared and delivered to the treatment administration room? (eg, are the vials sent unprepared, or are the syringes filled ahead of time?)
☐	If the vials are sent unprepared, are they sent fully thawed or frozen?
☐	If they are transported frozen, how do you ensure they are fully thawed before use, and how is the thaw time subsequently tracked?
☐	If prepared first, how will the syringes be transported to the administration rooms?
Handling and Administration	
☐	When is the oncolytic virus to be administered (eg, on designated treatment days)?
☐	What PPE will be required for handling/administration?
Cleaning and Waste Disposal	
☐	How often will the preparation area be cleaned (eg, before/after each use; beginning/end of all preparations)?
☐	What cleaning agents will be used?
☐	How will materials that contact talimogene laherparepvec be disposed?
☐	In the event of accidental exposure, what procedures will be followed?
Patient Education	
☐	How will patients be educated about the injection site care, and procedures to follow if they visit another HCP?
☐	Who will provide patient education?

Figure 3. Items to consider before implementing talimogene laherparepvec in the clinical setting.

Note. BSC = biosafety cabinet; HCP = health care provider; PPE = personal protective equipment.

Patient Education

Because talimogene laherparepvec is a novel immunotherapy, patient education is an important component to the process of operationalization. A 3-pronged approach to patient education is recommended, in which education is provided first by the physician, followed by the nursing staff,¹³ and finally, by the pharmacy.

Patients should be made aware that higher-dose steroids and antivirals (eg, acyclovir) may interfere with the efficacy of talimogene laherparepvec. Steroid use may also theoretically predispose a patient to infection by talimogene laherparepvec. Patients who are being treated with an antiviral agent should notify their physician. Likewise, patients on steroids or other immunosuppressive agents should also inform their providers. Following treatment, patients need to be educated that injection sites should be covered with an occlusive dressing for ≥ 1 week after injection, or longer if the injection site is oozing, and that the dressing should be changed or replaced if it becomes loose or falls off. Furthermore, patients should be counseled on proper disposal procedures; used dressings and cleaning materials should be sealed in plastic bags and disposed of in household waste.^{1,14} Patients are also given information on how to recognize the signs and symptoms of herpetic lesions and how to report suspected herpes infections.

In addition, patients should be advised regarding what processes to follow if they visit another HCP (eg, emergency room, primary care provider). At some authors' sites, patients are given cards or other instructions on how to inform other HCPs about their treatment. For example, patients may be given contact numbers so that if they go to another facility, that facility knows where to call with questions regarding the agent.

Conclusions

Because talimogene laherparepvec is a novel therapy with characteristics that differ from those of current therapies, there are multiple pharmacy-specific procedural considerations involved in its use (Figure 3). However, addressing these is, in general, easily manageable. The experiences outlined here may serve as a guide for the development of policies or procedures that can assist institutions and providers in incorporating talimogene laherparepvec into clinical practice.

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