Clinical Considerations for Oncolytic Viral Therapies --- a Regulatory Perspective

Author: Ke Liu

Correspondence: Ke Liu, Oncology Branch, Division of Clinical Evaluation, Pharmacology and Toxicology, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration

Building 71, Rm 5264
10903 New Hampshire Avenue
Silver Spring, MD 20993

Telephone: 240-402-8325
Email: ke.liu@fda.hhs.gov

Word counts for the introduction: No introduction. This article is a commentary.

Word counts for the manuscript as a whole: 1719 (including references, but not including this title page)

The number of references: 10

The number of figures: none

The number of tables: none

Key Words: Oncolytic Viral Therapy, FDA, Clinical Consideration, Trial Design

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/cpt.640

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Ke Liu

Oncology Branch, Division of Clinical Evaluation, Pharmacology and Toxicology, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration
ke.liu@fda.hhs.gov

Introduction

The US FDA approved the first oncolytic viral therapy (OVT), Imlygic (talimogene laherparepvec), in October 2015 for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery, although talimogene has not been shown to improve overall survival or have an effect on visceral metastases (1).

This approval represents an apex of intensive scientific and clinical research on OVT (2). Oncolytic viruses (OVs) are characterized by the potential to kill cancer cells while sparing normal cells. These agents include diverse RNA and DNA viruses, which can target a variety of tumor types. In some cases, genetic modifications have been designed to improve the potential efficacy or safety of these viruses. For example, an oncolytic virus can be modified to express a transgene that has direct cytotoxic activity or enhances the immune response. In Imlygic, the attenuated herpes simplex virus type 1 (HSV-1) is genetically modified to express human granulocyte-macrophage colony-stimulating factor (huGM-CSF) (3). These OVs can be administered locally (e.g., intratumorally) or systemically by intravenous infusion.

Still, many regulatory challenges exist in the development of OVT, including, but not limited to, challenges in clinical trial design and manufacturing of OVs. For example, it is essential to have a manufacturing process, along with associated test methods and control measures, that is capable of...
yielding an OV product with consistent quality characteristics. This commentary focuses on some clinical considerations that are unique to OVT.

1. Efficacy evaluation

a. Assessment of systemic effect from OVT as part of providing primary evidence of effectiveness

One important consideration for intratumorally administered OVT is whether such a treatment would or would not have any systemic treatment effect. Most OVT trials use OV injected intratumorally, and the primary endpoints of these trials are usually tumor response rates. Because of this route of administration, such a treatment would be expected to have a local treatment effect, i.e., tumor responses would be expected in the tumors that are injected with OV. This mechanism of action is distinguished from that of systemically administered agents such as chemotherapy or biologic therapy. For a systemic therapy, tumor responses occur or are expected to occur not only in the target tumor lesion that can be visualized but also in subclinical micrometastases. Although in some instances, especially in the setting of rare cancers, FDA has considered tumor response rate as evidence of clinical benefit itself, the tumor response rate is typically considered in the context of a systemic therapy in solid tumors, and most commonly used as an Accelerated Approval endpoint, which is intended to predict a clinical benefit such as symptomatic relief or survival (4). In addition, most local therapies in oncology, such as palliative radiation therapy or bone-seeking radioisotopes, have used trials with a symptom endpoint (e.g., pain relief) rather than a tumor response endpoint. Therefore, it is challenging to interpret the
tumor response rate when the OVs are injected into local tumor(s) in the setting of treated or untreated systemic diseases.

Thus, one important factor to consider in the efficacy evaluation for OVT is the evidence whether OVT has a systemic effect in mediating the regression of tumor lesions that are not injected. In the setting of metastatic diseases, such an abscopal effect would be contingent upon immune responses elicited by the treatment of injected lesions with OVT. One approach to address this issue is to monitor these immune responses. Knowledge of such responses could provide supporting evidence regarding whether or not an OVT could have a systemic effect. However, assays for such immune monitoring may not be available, or may not be standardized, which could pose important challenges for this approach.

Another, and perhaps more practical, approach to detect an abscopal effect is to meticulously measure and document the changes in size/volume of tumors that are not injected. If tumors are located in internal organs (e.g., lungs or liver) that are not injected, then measuring these lesions before and after OVT may be the optimal way to observe a systemic effect from a locally-administered OVT. If tumors are not present in internal organs, or are not suitable for definitive measurement, then detailed measurement of non-injected cutaneous, nodal, or other accessible tumors could be crucial. The modalities for such measurement (e.g., clinical assessment, photographic documentation and radiological assessment) need to be utilized consistently at each measurement to avoid assessment bias. Documenting such measurements in the case report forms (CRFs) could provide essential evidence of the presence or absence of an abscopal effect.
Still another consideration is whether progression-free survival (PFS), as assessed by a conventional approach (e.g., Response Evaluation Criteria in Solid Tumors (RECIST)) could serve as an interpretable primary endpoint in the efficacy assessment for the locally administered OVT. Following Imlygic administration (5), some tumor lesions (either injected or non-injected) may initially show progression, but later regress after further treatment. Thus, it can be challenging to interpret PFS results based on the first progression by conventional criteria, since any difference in the observed PFS may not reflect an effect of OVT. Using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) could take such a scenario (i.e., initial progression followed by subsequent regression) into consideration (6). However, the primary endpoint based on irRECIST has not yet been generally accepted to support regulatory approval.

For some locally administered OVTs, the most direct evidence of a systemic effect could be demonstration of an overall survival (OS) benefit. OS is a universally accepted direct measure of benefit, and is easily and precisely measured. However, trials using OS as the primary endpoint may involve larger number of subjects, and interpretation of OS may be confounded by crossover therapy, sequential therapy, and non-cancer deaths (7).

b. Control Considerations

Intratumoral injection could result in tumor regression through a physical effect of the injection procedure (e.g., shearing effect from passing the needles), especially in the setting of multiple injections into a given accessible tumor. If a response is seen in the injected tumor(s), it could be difficult to discern whether the response reflects the effect of the OVT or the effect of the injection procedure. To confirm the effect of the OVT and address this concern regarding any effect from the
intratumoral injection procedure, consideration should be given to a randomized trial design with a concurrent control that is also intratumorally injected. Such a concurrent control could be either a placebo or an active control, depending on the clinical situation (e.g., the availability of alternative available therapies).

2. Safety Evaluation

Almost all OVTs involve live viruses capable of replicating. One safety concern is that such viruses may be shed from the patients who receive such therapy, and then spread to individuals who are in close contact with the patients. Although OVs are often genetically modified to limit the ability of the OV to cause disease, shedding remains possible, particularly for systemically administered OVs.

Therefore, early in the clinical development of OVTs, it is important to consider including plans to monitor for viral shedding into the clinical trial design. Such monitoring serves to safeguard the public health and inform the design of later-phase trials. Yet, it can be challenging to design a development and monitoring program that would fit all OVTs. Therefore, the monitoring approach, with its attendant sample collection, assay methods, cut-off thresholds and their interpretation, should be tailored for the specific OVT. FDA has published Guidance for Industry - Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (8). This guidance can help the sponsor to design the appropriate shedding studies.

3. Combination of OVT with other classes of cancer therapies
One recent advance in immunotherapy is the recognition of the potential power of combination therapies to improve efficacy. Early-phase trials combining Imligic with ipilimumab may suggest that such a combination has a better clinical activity (9) than either product alone. However, in addition to the challenges and considerations described above for using OVT as monotherapy, other considerations include the dose/schedule, sequencing, and safety evaluations of such combined therapies. To address this issue, the FDA has published Guidance for industry - Codevelopment of Two or More New Investigational Drugs for Use in Combination (10). Although this guidance states that it is applicable to the therapeutic biological products that are regulated by the FDA’s Center for Drug Evaluation and Research (CDER), the principles described in this guidance may provide useful information in designing early- or late-phase trials that use both an OVT and another therapeutic agent. Some of these principles include demonstration of the biological rationale for the combination, demonstration of the contribution of each individual new investigational drug in the combination to the extent possible, appropriate designs for early and late clinical trials to provide evidence of the effectiveness of the combination, and optimization of the dose or doses of the combination for Phase 3 trials.

References


