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Commentary

What goes in the regulatory clinical pharmacology package for an oncolytic virus?

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BRIEF DESCRIPTION OF THE TREATMENT CONCEPT FOR ONCOLYTIC VIRUSES (OVs)

OVs are natural or genetically modified viruses designed to selectively replicate in tumor cells, resulting in tumor cell lysis, that is, a direct oncolytic effect. The destruction of tumor cells leads to the release of viral particles (VPs) that infect surrounding tumor cells and release tumor-derived antigens, which are presented to T-cells. This process results in a cascade of adaptive immune responses (e.g., T-cell activation, memory, migration, infiltration, and T-cell mediated tumor death) leading to a systemic antitumor immune response. OV replication and amplification after administration into the tumor cells are major determinants of tumor eradication [1,2]. The paper aims to guide the readers through the conceptual framework of OV drug development in the current regulatory environment.

COMPARISON OF OV AND TRADITIONAL DRUG APPROVAL

Primary goals of the clinical pharmacology package (CPP)

The main goals of phase I oncology studies are to determine the maximal tolerated dose (MTD), provide recommended phase II dose(s) (RP2D), describe and characterize dose limiting toxicity, and expand understanding of the investigational product [3]. Traditionally, a clinical pharmacology development plan includes studies to characterize the exposure, distribution, metabolism, and elimination of a drug. In addition, factors that affect these characteristics are examined, such as food, drug–drug interaction, intrinsic factors (e.g., polymorphisms contributing to the loss or gain of function of drug-metabolizing enzymes, renal or hepatic impairment), as well as exposure response (efficacy and safety) relationships. A comprehensive CPP helps in predicting, problem-solving, and enabling vital decisions in drug development and enables clinicians to make scientifically informed decisions on the effective and safe use of particular drugs. A well thought-out, preplanned CPP is less likely to leave gaps in data and logic or require additional studies for data that could have been collected in already completed trials.

Conceptually, the CPP for an OV has similar goals, but with nuanced differences because unlike chemical drugs, a virus replicates. For a virus, ‘exposure’ does not mean the

concentration of a parent or metabolites. Instead, exposure represents the number of VPs at the injection-site level, which is intratumoral, as well as at the nontargeted-tissues level. It is possible to measure VPs in blood and tissue at defined time points. However, measurement requires frequent sampling to understand the time–exposure curve, which is clinically infeasible. Moreover, the ability of OV to replicate may vary in different tissue or tumor types. which makes the tipping point for tumor lysis challenging to specifically define without modeling and simulation support.

The CPP for an OV will not characterize pharmacokinetic interactions with other drugs but rather assesses viral activity with a standard of care, characterizing its potential to stimulate the immune system. If the OV is sensitive to an existing antiviral agent (e.g., T-VEC is sensitive to acyclovir), this interaction may interfere with the effectiveness of the treatment. Such product–product interactions should be characterized. Viral biodistribution (BD) and shedding assessments replace the absorption, distribution, metabolism, and elimination study conducted in a traditional CPP. Immunogenicity assessment is also key for OVs as their efficacy depends on their persistence in the patients and their transduction efficiency. Preexisting immunity and the rapid production of neutralizing antibodies may be limiting and lead to a faster clearance of the OV. Thorough QT/QTc study as well as hepatic or renal impairment studies included in classical CPPs are not performed for OV programs. Due their molecular weights, OVs are not expected to interact with ion channels or have their renal clearance impacted by impaired renal function. In addition, OVs are not metabolized by the liver. Note that the regulations for pharmaceuticals are mandated from the Center for Drug Evaluation and Research, whereas OVs fall under the purview of the Center for Biologics Evaluation and Research.

Example regulatory review and approval of Talimogene laherparepvec (T-VEC, Imlygic®)

T-VEC received its initial U.S. Food and Drug Administration (FDA) Biologics License Application (BLA) approval letter in 2015. T-VEC is the only approved OV to date (there are other gene therapy products that use viral vectors such as nadofaragene firadenovec-vncg, which delivers genes that transcribe proteins that help to fight cancer, but are not virus that directly cause oncolysis, so will not be discussed in this commentary). The CPP in T-VEC BLA included the following: viral dose in concentration, BD, and viral shedding. Drug exposure was expressed in terms of viral concentration administered, not the actual viral exposure (which would have increased due to intralesional replication). Regarding viral distribution, the FDA has considered animal models as acceptable surrogate. The nonclinical BD data included assays of viral DNA in various organs following intratumoral administration of T-VEC into a tumor-bearing murine model. Human BD data were assessed in blood and urine using a quantitative polymerase chain reaction assay. Viral shedding was performed from the surface of injected tumors, urine, feces, and an occlusive dressing using swab plaque assays. A more comprehensive shedding study was ongoing at the time of the BLA review to additionally include oral and genital mucosa, as well as new lesions suspected to be of herpetic origin [4].

An FDA reviewer commented that information regarding systemic immune biological responses in humans was not submitted; therefore, the exact mechanism of action is not fully understood. Additional studies were suggested. From the perspectives of clinicians, one of the key pieces of missing information for selecting patients who would potentially benefit from T-VEC was how the host factors might inactivate the virus or cause persistent infection. Early this year, Amgen proposed a viral kinetic mechanistic model. The model parameters

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included: (1) tumor cell growth rate, (2) viral infection rate, (3) death rate of infected tumor cells, (4) viral clearance rate, (5) killing rate of viruses by virus-specific immune cells, and (6) the killing rate of viruses by innate immune cells [5]. Although the model development was guided by limited BD data, it may be a good starting point for future OV development.

Normally, critical information sought by prescribing physicians from clinical pharmacology data includes the dose–exposure–response (efficacy and safety) relationship. This interaction was a bit cloudy for the first OV. In the FDA BLA review, it was noted that in the absence of knowing the dose injected into each lesion, it would not be possible to assess dose dependency. The T-VEC dose administered during clinical trials was highly variable. Although the protocols had defined parameters within ranges, such as the selection of lesions, number of injected lesions, dose per lesion, total dose, and injection frequency, these amounts were set at the investigators' discretion. Moreover, the systemic effect was not well characterized; hence, ae medical recommendation announcing "limitation of use" had to be included in the labeling to state that T-VEC has not been shown to improve overall survival or have an effect on visceral metastases.

CHANGES SINCE T-VEC's INITIAL BLA

Project Optimus

Drug exposure was expressed in terms of VPs administered. No publicly available information reveals whether Amgen attempted to measure viral exposure to reflect intratumoral replication. For clinicians, a remaining question at the time of T-VEC launch was the minimal amount of T-VEC required to be injected into a lesion for tumor lysis. Amgen's position was that because T-VEC is expected to replicate upon intralesional injection, the amount of viral exposure in any individual lesion will vary based on how permissive the tumor is for replication. Thus, a minimal effective dose is difficult to identify. The "drug" (i.e., virus) exposure is further complicated by the interactions between OV, tumor cells, other cells, and innate and adaptive immune responses that have antitumor and antiviral effects.

The FDA recently implemented its Project Optimus, which aims to reform the dose optimization and selection paradigm in oncology. In the past, the therapeutic dose for an oncologic drug was thought to be near the MTD, thus phase 1 studies identified the MTD that enabled a decision on the RP2D. The concept of minimal efficacious dose or the optimal dose (not only focused on longer survival but from a comprehensive benefit-risk assessment) is being applied to oncologic drugs. The guidance document published in January 2023 is not applicable to complex biologics such as cellular or gene therapy products. So whether and how it applies to OVs will require regulatory discussions but this guidance frames the expectation for dose optimization of oncology drugs [6].

Viral shedding guidance

Few guidance documents have been available for gene therapy products released by the FDA since T-VEC, which should be considered in the clinical pharmacology development plan. In August 2015, Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products: Guidance for Industry was released.

At the time of initial T-VEC BLA submission, The Cellular, Tissue, and Gene Therapies Advisory Committee Oncologic Drugs Advisory Committee expressed concerns about viral

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shedding and potential transmission and latency/symptomatic reactivation, in particular viral exposure of healthcare providers and patient close contacts. At the time, viral shedding study was ongoing, and Amgen proposed a postmarketing study to evaluate transmission of T-VEC to healthcare professionals and close contacts [7]. Early this year, about 8 years after the initial BLA, FDA approved Amgen's sBLA to update the US Prescribing Information to reflect herpetic infection, including disseminated herpetic infection, as an adverse drug reaction with T-VEC [8].

As OVs are replication competent viruses, shedding collections should be performed in Phase 1 trials and continued during Phase 2 and 3 after a dose and regimen have been determined. The matrices (excreta or tissues) to be collected for human shedding evaluation need to be defined based on non-clinical shedding data, route of injection and natural shedding of the viral vector. Monitoring period for shedding would be longer (in order to capture the second peak associated with multiplication) than replication incompetent or deficient products. The guidance document mentions factoring in immune competence is needed especially in cancer patients (may have had immunosuppressive chemotherapy) as immunosuppressed patients may be persistently infected. The shedding sample collection intervals for multiple cycles need to also consider re-introduction of OV may recruit preexisting immunity, thereby shortening the shedding period [9].

Biodistribution (BD) guidance

In September 2021, FDA released a new guidance titled: S12 Nonclinical Biodistribution Considerations for Gene Therapy Products: Draft Guidance for Industry. The guidance defines BD as the *in vivo* distribution, persistence, and clearance at the site of administration, target and nontarget tissues including biofluids such as blood, cerebrospinal fluid, vitreous fluid. BD data should be available to interpret nonclinical pharmacology and toxicology findings as well as inform the first-in-man trial. The guidance also states BD assessments should be conducted in relevant animal species or models and dose levels studied provide sufficient characterization of the BD profile [10]. Based on the guidance, for OVs, the nonclinical BD study would likely involve multiple doses in tumor bearing animals, considering relevant immunological factors.

NONCLINICAL DATA NEEDED FOR CLINICAL PHARMACOLOGY PLANNING

In addition to demonstrating antitumor effects via the proposed mechanism *in vitro* and *in vivo*, nonclinical studies should also provide additional information on immune system effects, viral kinetics in different tumor types to support dose rationale, viral shedding, BD, and stability in body fluids (inactivation by host factors) to define a clinical pharmacology plan.

In the T-VEC nonclinical BD and studies, viral DNA was detected in tumor, blood, lymph nodes, spleen, liver, heart, kidney, lung, and brain. Following administration of T-VEC into the mice footpad the dorsal root ganglia infection was observed. Viral DNA was not detected in bone marrow, eyes, lachrymal glands, nasal mucosa, or feces. The nonclinical BD informed the potential of the OV to spread to uninjected tissues, which should be examined in human subjects. Clinical BD and shedding data were collected from blood and urine up to 30 days after end of treatment, injection site, occlusive dressings, oral mucosa, anogenital area up to 60 days after end of treatment, and suspected herpetic lesions. T-VEC DNA was present in all sites.

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VIRAL SAFETY AND BIOSAFETY

Although not part of the CPP, certain OV-specific data should be collected in phase I studies. As an example, for T-VEC, viral safety and biosafety were crucial aspects discussed during the FDA review as well as throughout the market launch. T-VEC is a genetically modified herpes virus (although attenuated); thus, the possibility of entering into latency and the risks of recombination with wild-type virus were addressed. A systematic preplanned collection of data from healthcare providers and family members who are accidentally exposed is also essential (related to shedding properties).

SUMMARY

In sum, the clinical pharmacology development of an oncolytic virus would contain the following data collection plan:

- BD (inside the body: tumor and other tissues) with multiple doses at several timepoints
- Viral kinetics in blood
- Viral shedding (outside the body) with single and multiple doses (e.g., feces, urine, injection site, occlusive dressing, saliva)
- Exposure–tumor dynamic relationship
- Tumor cell growth rate, viral replication rate, tumor lysis rate, viral clearance rate
- What inactivates the virus
- Antiviral therapies
- Host immune factors
- Immunogenicity
- Interaction with background therapy potential to stimulate the immune system

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