Scientific Abstract

A Phase I/IIA Dose Escalation Trial of Intratumoral Injection with Oncolytic Adenovirus Vector INGN 007 (VRX-007) in Patients with Advanced Solid Tumors

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Adenoviral gene therapy for cancer, especially the use of vectors based on adenovirus serotype-5 (Ad5), has been widely investigated, and numerous gene transfer studies have been performed using replication-defective and conditionally replicating adenoviral vectors. The data suggest that both replication-defective and conditionally replicating adenoviral vectors are safe and well-tolerated ((Lichtenstein and Wold 2004), (Merritt, Roth et al. 2001)). However, their anti-tumor effects have not yet been optimized in the clinic, a situation likely due to a less-than-complete transduction of tumor cells.

To try to circumvent this limitation, the replication-competent therapeutic virus INGN 007 has been developed. Derived from Ad5, INGN 007 mediates the over-expression of ADP (Adenovirus Death Protein), an adenovirus-coded protein that functions in the normal adenovirus life cycle to cause infected cells to lyse and release infectious progeny adenovirus. The over-expression of ADP causes a more efficient lysis of infected cells, and a more rapid overall life cycle. As a result, INGN 007 spreads from cell to cell more quickly than vectors that express normal levels of ADP (including Ad5) or no ADP at all, thereby causing a more rapid lysis of cancer cells.

Efficacy

Preclinical efficacy studies in various in vitro and animal tumor models have demonstrated potent anti-tumor activity correlated with INGN 007 replication. INGN 007 appears more potent than other adenoviral vectors we have studied, including several conditionally replicating vectors.

INGN 007 replicates well in all 18 human cancer cell lines (derived from nine different human cancer types) and 4 rodent cells lines tested. In vitro, INGN 007 is efficiently released from cells, and infects adjacent uninfected cells to induce widespread cell lysis. In vivo, studies in three different types of animal models show that INGN 007 suppresses tumor growth. INGN 007 delivered intratumorally or intravenously (IV) inhibited the growth of four different subcutaneous human tumors in nude mice (lung, colon, prostate, liver), and in a lung metastasis model in nude mice when delivered IV. INGN 007 also slowed tumor growth in three different aggressive syngeneic subcutaneous tumor models in immunocompetent Syrian hamsters and cotton rats; intratumoral INGN 007 inhibited the growth of both the local tumor and of spontaneous metastatic lesions.

Safety

Because INGN 007 is a fully replication-competent vector, safety data from several sources may be relevant. First, the replication-competent Ad5 virus, from which INGN 007 is derived, is largely benign ((Fox, Brandt et al. 1969), (Fox, Hall et al. 1977)). Ad5 infections are common in humans, resulting in a self-limiting cold or flu-like syndrome which is often not observed even in immunocompromised patients (Hierholzer 1992).
Second, wild-type adenoviruses were administered to cancer patients in the 1950's without significant toxicities. These studies included inoculation of cervical carcinoma patients with non-attenuated strains of adenovirus from subgroup C (which contains Ad5) by four different routes, including intratumoral and IV (Smith, Huebner et al. 1956), or with adenovirus serotypes 1-7 and 9 by intratumoral and/or IV routes (Georgiades, Zielinski et al. 1959). Our preclinical data (below, and Appendix M) demonstrate that the distribution and toxicity of INGN 007 are very similar to that of Ad5, suggesting that INGN 007 may also be well tolerated.

Third, while INGN 007 has no genetic features specifically designed to restrict replication to cancer cells, INGN 007 appears to have less effect on normal cells than on cancer cells. Ad5 and INGN 007 replication and cell killing is greatly attenuated in quiescent normal cells (the usual state of most cells in the adult human body) compared to proliferating normal cells ((Vaillancourt, Atencio et al. 2005), Appendix M). Even in proliferating normal cells, INGN 007 replication produces a lower virus yield per cell than in cancer cells (up to 100-fold less). This poor replication in normal cells correlates well with the good safety profile of INGN 007 in the Syrian hamster, which is permissive for Ad5 and INGN 007 replication. The No-Observed-Adverse-Effect-Level in this model was the maximum human dose in the Phase I study (Appendix M).

In addition, the adenoviral immune evasion genes encoded by the deleted E3 region (Lichtenstein, Toth et al. 2004)) are missing in INGN 007. The absence of these genes should make INGN 007 more susceptible to the immune system than Ad5 (e.g., (Morin, Lubeck et al. 1987)).

Five studies have been conducted with INGN 007 to explore biodistribution and potential toxicities in two animal models, the Syrian hamster (permissive for Ad5 and INGN 007 replication) and the mouse (not permissive for Ad5 replication). Four studies used an IV route of administration as a worst-case scenario for INGN 007 dissemination, as biodistribution following intratumoral injection is expected to be less systemic than that seen following IV administration. The liver is the primary target organ for both INGN 007 biodistribution and toxicity. Little or no toxicity was observed at doses to be used in this clinical trial. Significant toxicity was observed only at high doses of INGN 007; these toxicities were qualitatively similar to those observed with a replication-defective adenoviral vector, and quantitatively similar to those observed with Ad5 (a benign virus).

Clinical trial

This Phase I/IIA clinical trial is designed to determine the safety, maximum tolerated dose (MTD) and therapeutic efficacy of intratumoral administration of INGN 007, a replication-competent oncolytic adenovirus vector with augmented expression of the adenoviral ADP protein, in subjects with accessible advanced solid tumors.

The biological activity of INGN 007 will be evaluated based on evidence of transduction and replication of INGN 007 in human solid tumors. Replication of INGN 007 in the tumor and in other samples from subjects will be assessed using immunohistochemical methods, and by measuring the levels of INGN 007. The levels of INGN 007 DNA in tumor tissue will be detected via PCR, and levels of infectious INGN 007 particles in subject samples (blood, urine, tumor tissue) will be detected using the Cytopathic Effect
bio-assay. The pharmacokinetics of INGN 007 replication, ADP protein expression, and the immune response to INGN 007 will be evaluated. Immune response will be measured by following changes of blood antibody and cytokine levels before and after treatment.

Each eligible subject will be enrolled into one of the dose escalation cohorts, and the clinically relevant lesion will be identified and treated (no more than two lesions treated per subject). Five subjects will be enrolled at each dose level: 2 x 10^8 vp, 2 x 10^9 vp, 2 x 10^10 vp, 2 x 10^11 vp, or 2 x 10^12 vp. Each subject will receive a single dose of INGN 007 intratumorally on Day 1 of the study. Subjects are to complete the study at Day 28, unless they experience an ongoing adverse event which will be followed until resolution.

INGN 007 is fully replication-competent. While the safety data in animal studies suggests that INGN 007 will be well tolerated in humans, a number of precautions have been taken in the design of the clinical trial:

1. The only humans known to be at risk from replicating adenoviruses are massively immunosuppressed transplant patients. Patient inclusion and exclusion criteria are designed to ensure that subjects are not immunosuppressed.

2. The proposed clinical trial will employ a conservative dose-escalation regimen. The starting dose is 1,000-fold lower (on a vp/kg basis) than that which caused little or no toxicity in animal studies; the MHD caused no significant toxicity in animal studies.

3. Intratumoral injection should result in the majority of the INGN 007 dose concentrated in the tumor itself, minimizing systemic exposure and exposure of potential target organs (lung and liver), compared to an IV route.

4. Subjects will be monitored for possible symptomatic viremia, which will be treated with appropriate anti-viral therapy (intravenous ribavirin or cidofovir) if necessary.

5. Lesions selected for injection will be accessible and superficial, to allow for surgical removal of the tumor should replication within the tumor become problematic for the subjects.

Conclusions

INGN 007, a replication-competent adenoviral vector, is effective both in vitro and in animal models of cancer, even in demanding animal models (subcutaneous tumors with an IV route of administration, aggressive syngeneic tumors). Little or no toxicity was observed in safety studies at doses to be used in this clinical trial. Significant toxicity was observed only at high doses of INGN 007; these toxicities were qualitatively similar to those observed with a replication-defective adenoviral vector, and quantitatively similar to those observed with Ad5 (a benign virus). The clinical trial has been designed to maximize subject safety, and uses a low starting dose with a large margin of safety relative to doses that have an effect in animal toxicology studies.
References


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Last Revised: October 2005