

Valacyclovir in the Treatment of Idiopathic Pulmonary Fibrosis: IRB Protocol

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1. Study Purpose and Rationale

a. Hypothesis

Herpesviridae, and specifically Epstein Barr Virus (EBV), may play a role in the pathogenesis of idiopathic pulmonary fibrosis (IPF), and therefore antiviral therapy with the drug valacyclovir could affect the clinical course of this disease.

b. Background and literature review

IPF is an interstitial lung disease of unknown etiology characterized by a progressive course, a poor prognosis with a median survival of approximately three years,¹ and a lack of evidence that any treatment prolongs survival.² While the pathogenesis of IPF is still unclear, increasing evidence points to an unidentified stimulus resulting in repetitive focal injury of alveolar epithelial cells and an aberrant wound repair response characterized by fibroblastic proliferation.³ This fibroproliferative response, in turn, results in a progressively restrictive lung physiology which produces the symptoms of the disease.

However, the initial instigating insult that produces this cascade is as of yet unknown. Although a variety of potential environmental insults have been studied, a body of evidence has raised the intriguing possibility of a role for a virus, most strongly for Epstein-Barr Virus (EBV). EBV is a widely disseminated member of the herpesviridae family with a worldwide; it is notably capable of resulting in a lifelong asymptomatic latent phase in humans. It is most well known for causing infectious mononucleosis, but may also play a role in a number of lymphoproliferative disorders.⁴

Data supporting a correlation between EBV and IPF include serological correlations, immunohistochemical localization of EBV antigens in IPF lung tissue, identification of EBV DNA in IPF tissue by PCR, and a mouse model linking a herpesvirus with pulmonary fibrosis. The serological studies were the first studies which suggested a link; two such studies demonstrated that IPF patients are more likely to have anti-EBV antibodies compared to controls and patients with other lung disease,^{5 6} although another one demonstrated elevated titers of several herpesviridae in IPF patients.⁷ More suggestive, however, are the several immunohistochemical studies which identified EBV antigens of IPF lung tissue within alveolar epithelial cells,^{8 9 10} one of which localized the virus to the type II pneumocyte,⁸ thought to play an important role in the pathogenesis of IPF. Although PCR studies have not been entirely consistent,^{11 12} a predominance of them have in fact correlated the presence of EBV DNA in lung tissue with the disease state of IPF.^{6,7,8,13,14} Finally, some additional studies have attempted to more causally link herpesvirus infection with the production of pulmonary fibrosis in mouse

models. Using a Th2-skewed mouse, instillation of a herpesvirus endemic to mice and very similar to EBV resulted in pulmonary fibrosis and restrictive lung disease.¹⁵ Even more interesting was the fact that use of an antiviral drug effective at clearing lytic virus resulted in reduction in the severity of the fibrosis and greatly improved survival in these animals.¹⁶

While these data are far from conclusive, taken in aggregate, they are nonetheless sufficient to proceed with a clinical trial in humans with IPF with an antiviral drug effective against EBV. This is warranted given that no effective treatment exists for IPF, given the dismal prognosis of patients with IPF, and given that the proposed study drug, valacyclovir, is relatively quite safe and well tolerated. Our hypothesis is that drug treatment with this agent may ameliorate progression of the disease.

2. Study Design and Statistical Procedures

This will be a randomized, double-blinded, placebo-controlled clinical trial comparing valacyclovir against placebo in patients with IPF with respect to a primary outcome of lung function. Lung function will be measured as a decline in DLCO and FVC at 18 months compared to baseline. Secondary outcomes that will be examined will include degree of pulmonary fibrosis as manifested on Chest CT; symptomatic change as determined by the St. George Respiratory Questionnaire; survival and hospitalizations; gas exchange as measured by the A-a gradient; and exercise tolerance as measured by the six-minute walk test. Patients will be randomized through a computerized phone system to either receive study drug or placebo. Patients and clinicians will be blinded to subjects' assignments. Following their initial study visit and enrollment, patients will be seen at 6, 12, and 18 months after enrollment. Blood work (including blood count and blood chemistry), PFTs, arterial blood gas analysis, and a respiratory questionnaire will be completed at these intervals; a six-minute walk test and HRCT will be performed only at the initial and 18 month visits.

A sample size of 70 patients will be enrolled in each arm of the study. This number was determined based on an expected decline in mean predicted FVC over 18 months of approximately 15%, as based on the placebo arm of a prior large randomized clinical trial involving IPF patients¹⁷; with 70 patients in each arm, we would expect to have 80% power to detect a 50% reduction in degree of decline of FVC between the two groups, i.e. from 15% to 7.5%.

An unpaired t-test will be used to compare the decline in percent predicted FVC and percent predicted DLCO between the two groups.

3. Study Procedures

Pulmonary function testing (PFTs) including carbon monoxide diffusing capacity and blood gas analysis will be conducted at baseline and at 6, 12, and 18 months. PFTs involve the patient performing various breathing maneuvers and therefore involves some inconvenience but minimal

discomfort and essentially no risk. Blood gas analysis involves puncture of the radial artery and therefore involves greater discomfort. However, performing PFTs at these intervals is mostly consistent with common clinical care for these patients. A six-minute walk test will also be performed at baseline and at 18 months; this test involves minimal risk and inconvenience for the patient. Finally, a high-resolution CT of the Chest will be performed at baseline and at 18 months, perhaps exposing the patients to a greater degree of radiation than they might expect to receive in common clinical care.

4. Study Drugs

The only study drug in this study is valacyclovir, a drug FDA approved for treatment and prophylaxis of oral and genital herpes infections. It is a prodrug of the antiviral drug acyclovir, to which it is converted *in vivo*. The rationale for the choice of valacyclovir is its documented capacity for preventing EBV replication by blocking EBV DNA polymerase.¹⁸ Valacyclovir has been demonstrated to be efficacious in treating and preventing genital herpes simplex virus outbreaks.^{19 20} When used at approved dosages, it has been very well tolerated.²¹ Common adverse reactions include headache (13-38%), nausea (5-15%), abdominal pain (1-11%), increases in transaminases (2-16%), and nasopharyngitis (<16%); neutropenia (<18%) and thrombocytopenia (<3%) have also been reported; complete blood counts will therefore be followed in these patients every six months.²² It also requires dose reduction with impaired renal function; renal function will be followed every six months with basic metabolic panels. The drug will be administered in its standard method of administration (PO) and at the standard dose for the treatment of herpes zoster, 1 gram thrice daily.

5. Study Questionnaires:

The St. George's Respiratory Questionnaire will be completed by study subjects at baseline and at 18 months. It is a 76-item questionnaire which has been validated in chronic lung diseases.²³

Additionally a general medical questionnaire will be completed by participants to determine eligibility for enrollment and to determine baseline demographic information.

6. Study Subjects

a. Inclusion Criteria

These include patients aged 30-80 who had received a diagnosis of IPF within the past 2 years, had a FVC of 55-90% of the predicted value and a DLCO of 35-90%. The diagnosis of IPF had to be made either on the basis of histopathology, or a definite read of IPF on a High Resolution CT. There is no restriction on the basis of sex or race.

b. Exclusion Criteria

These include evidence of obstructive lung disease on PFTs (FEV1/FVC ratio of < 0.60); a diagnosis of congestive heart failure; a diagnosis of cancer within the preceding five years excluding resected skin cancer; a diagnosis of a connective tissue disease; another possible etiology for interstitial lung disease. Patients with a CrCl < 30 will also be excluded, as will patients with dementia or an inability to consent with the study or participate in study procedures. The patient cannot be enrolled in another experimental drug trial or have received another experimental study drug within the past 28 days.

7. Confidentiality of Study Data:

All study data will be coded to remove identifying data, and will be kept in a secure location accessible only to study investigators.

8. Potential Risks:

The potential risks relate almost entirely to the use of the study drug, valacyclovir. However, at the dosages that will be used in this study, the study drug has been well tolerated, with mostly mildly symptoms as adverse events (see section 4 above). Hematologic side effects have been seen, and therefore blood counts will have to be followed and study drug discontinued if marked or persistent abnormalities emerge. Given that valacyclovir is not known to be effective, and given that no other drugs have been clearly shown to be effective in changing the disease course of IPF, study participants in both arms are not missing out on important alternatives.

9. Potential Benefits:

If the study drug is effective, it could markedly affect the quality and potentially quantity of life of study participants. However, it is quite possible that study participants will not benefit from participation in the study.

10. Alternatives:

Given the lack of clearly beneficial alternative treatments, the primary alternative for study participants with IPF would be participation in other clinical trials.

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