Study Protocol and Statistical Analysis Plan

A Study of Cytomegalovirus Disease Epidemiology in Pediatric and Adult Liver Transplant Recipients in China

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1 Study Protocol

1.1 Background and Rationale

Cytomegalovirus (CMV) remains one of the most common and clinically significant infections following solid organ transplantation, particularly liver transplantation. In China, the epidemiology of CMV disease in liver transplant recipients is not well characterized, especially in pediatric populations. This study aims to fill this knowledge gap by providing comprehensive data on CMV disease incidence, risk factors, and outcomes in both pediatric and adult liver transplant recipients across multiple Chinese transplant centers.

1.2 Study Objectives

1.2.1 Primary Objective

To determine the incidence of CMV disease within the first year post-transplantation in pediatric and adult liver transplant recipients.

1.2.2 Secondary Objectives

1. To identify risk factors for CMV disease development
2. To compare outcomes between patients who develop CMV disease and those who do not
3. To evaluate the impact of different CMV prevention strategies on CMV disease incidence
4. To assess economic burden associated with CMV disease management

1.3 Study Design

Prospective, multicenter, observational cohort study with 12-month follow-up period.

1.4 Study Population

1.4.1 Inclusion Criteria

- Pediatric (ages 0-17 years) or adult (ages 18 years) patients
- Recipients of primary liver transplantation
- Willing and able to provide informed consent (or parental consent for minors)
- Planned follow-up at participating center for at least 12 months

1.4.2 Exclusion Criteria

- Multi-organ transplant recipients
- HIV-positive patients
- Re-transplantation cases
- Expected survival less than 72 hours post-transplantation

1.5 Study Procedures

1. Baseline data collection: Demographic information, transplant characteristics, CMV serostatus of donor and recipient
2. Regular follow-up visits at months 1, 3, 6, 9, and 12 post-transplantation
3. CMV DNA monitoring by PCR at each visit and when clinically indicated
4. Documentation of CMV disease episodes, treatment, and outcomes of data on immunosuppression regimens and other infections

1.6 Outcome Measures

1.6.1 Primary Endpoint

Incidence of CMV disease (syndrome or end-organ disease) within 12 months post-transplantation.

1.6.2 Secondary Endpoints

- Time to first CMV disease episode
- CMV disease recurrence rate
- Graft function and rejection episodes
- Patient survival
- Healthcare resource utilization

1.7 Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol has been approved by the institutional review boards of all participating centers. Written informed consent will be obtained from all participants or their legal representatives.

2 Statistical Analysis Plan

2.1 Analysis Populations

2.1.1 Full Analysis Set

All enrolled patients who meet eligibility criteria and have at least one post-baseline assessment.

2.1.2 Per-Protocol Set

Patients who complete the study without major protocol deviations.

2.2 Sample Size Calculation

Assuming a CMV disease incidence of 25% in the overall population, with 80% power and 5% significance level, a sample size of 800 patients (600 adults and 200 children) will allow detection of a 10% difference in CMV incidence between key subgroups.

2.3 Statistical Methods

2.3.1 Primary Analysis

The incidence of CMV disease will be calculated as the proportion of patients developing CMV disease within 12 months post-transplantation, with 95% confidence intervals. Kaplan-Meier analysis will be used to estimate time-to-event curves.

2.3.2 Secondary Analyses

- Risk factor analysis using multivariable Cox proportional hazards regression
- Comparison of outcomes between groups using chi-square tests, t-tests, or non-parametric tests as appropriate
- Subgroup analyses by age group (pediatric vs. adult), CMV serostatus, and immunosuppression regimen
- Economic analysis using generalized linear models for cost data

2.3.3 Handling of Missing Data

Multiple imputation will be used for handling missing data for key variables. Sensitivity analyses will be performed to assess the impact of missing data.

2.4 Interim Analysis

No formal interim analysis for efficacy is planned. A safety interim analysis will be conducted after enrollment of 400 patients to assess serious adverse events.

2.5 Software

All statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 4.0 or higher.

2.6 Significance Level

A two-sided alpha level of 0.05 will be used for all statistical tests, with adjustments for multiple comparisons where appropriate.