CFID Summer Student Research Project Proposal

Frailty and Immune Response to Influenza Vaccine in Older Adults

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Rationale:

Older adults are at a high risk of complications from influenza including hospitalization and death. Reduced vaccine effectiveness with advanced aging is well described (1--2). Age--related changes in both B cells and T cells impact the response to influenza vaccination (3--4). Many older adults become increasingly frail with age. However, there is sparse data about the impact of frailty on the cellular and antibody response to influenza vaccination in older adults.

Methods:

The CFID Summer Student Research Program project will involve conducting a series of analyses of an existing database of a National Institute of Health funded randomized controlled trial (5). As part of this study, 430 older adults were randomized to either high--dose (HD) or standard dose (SD) influenza vaccination. Frailty was measured using the number of deficits (6) as well as the Frailty Index (7). Hemagglutinin--inhibition (HAI) antibody titres as well as granzyme B (GrB), IFN--gamma, and IL--10 were measured at baseline and at 4, 10, and 20 weeks post vaccination. Three separate sets of analyses will be conducted around three objectives:

Objective 1. To determine the impact of frailty on peak cellular and antibody response

This analysis will consist of the entire cohort of participants in the NIH randomized trial. The dependent variables will be antibody levels at 4 weeks, 10 weeks, and 20 weeks as well as biomarkers of cellular immunity, including GrB, IFN--gamma, and IL--10 at these time points. The main effect will be frailty (as measured by the Fried score and the Frailty index). Other independent variables will be baseline GrB and serological status for cytomegalovirus. Using proportional hazards, time to peak antibody will be modelled by the independent variables. Similarly, time to peak GrB, IFN--gamma, and IL--10 will be measured. Adjustment for multiple testing will be done. It is hypothesized that higher levels of frailty will be independently associated with longer time to peak antibody levels. Moreover, the duration of antibody titres above a threshold level (which will be determined by median level stratified by vaccine type) will be assessed. The hypothesis is that frailty leads to reduced time above the threshold level with the hypothesis being that greater frailty is associated with reduced time above threshold levels.

Objective 2. To assess interactions between frailty and influenza vaccine dose on cellular and antibody response

This set of analyses will build on the structure of the randomized controlled trial. The

question of whether there are interactions with high-dose vaccination will be assessed. Specifically, the interaction of dose of vaccine with a threshold frailty level on antibody level and cellular immune response will be assessed. We hypothesize that a significant interaction between frailty and vaccine dose will exist such that the effect of frailty will affect antibody response to a greater extent with the lower than higher dose.

Objective 3. To develop and validate an immuno-epidemiological predictive model for influenza antibody response

Building predictive scores for antibody response has clinical importance and can serve as a tool for evaluating response to new vaccines. There is sparse data on combining both phenotypic and immunologic variables as predictive markers. We propose to use a derivation cohort to develop such a predictive score using frailty and baseline cellular immune markers. The outcome will be antibody response at 4 weeks, 10 weeks, and 20 weeks. Either chi-square or t-tests will first be performed to assess significant differences between independent variables and outcomes. A logistic regression model will be built to select variables and correlation will be assessed calculating values for tolerance and variance inflation factor. Variables with a $p < 0.10$ will be kept in the model. The bootstrap method will be used for internal validation of the derivation cohort and validation will also be conducted using one tenth of the sample and nine-tenths of the remaining samples for cross-validation. We will create a dichotomous variable for vaccine type and include this in the model.

After building and validating logistic regression models, the sensitivity of the method will be determined using the receiver operating characteristic (ROC) curve. Using the model equation, we will then create a score from the equation by transforming the values assigned to each predictor to integers.

Importance:

The results of these analyses will lead to a better understanding of the relationship between frailty and the cellular and antibody response to influenza vaccination. The research project builds on a rigorously conducted randomized controlled trial and addresses a novel set of questions which were not originally proposed as part of the NIH grant. There are few databases worldwide that can address the questions proposed as part of this program. This research offers a tremendous opportunity for a summer student and will unquestionably result in at least one peer reviewed publication.

References:

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