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Review

Use of predictive markers of HIV disease progression in vaccine trials

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ABSTRACT

Generating broadly neutralizing antibodies with candidate vaccines has remained an elusive goal. Consequently, vaccine candidates developed have aimed at eliciting cell-mediated immune effector activities (CMI) that could delay disease progression, and maybe also limit secondary transmission, by controlling virus replication. There is considerable discussion about what types of endpoints would constitute definable standardized clinical benefit to the individual that would result in licensure of these candidate vaccines. Identifying biomarkers that can be used as surrogates for clinical endpoints in randomized clinical trials would be useful, because it would shorten studies and reduce costs. Biological markers associated with disease progression and secondary transmission and that may be used as prognosis markers and surrogate endpoints in HIV vaccine trials have emerged from analyses of data from studies on natural history of HIV infection. Extensive literature is cited to support the use of plasma viral load as a primary endpoint for supporting licensure decisions. Overall, a significant result on viral load in a vaccine trial should be considered as a significant breakthrough for vaccines and be aggressively pursued with the caveat that such a result should rapidly be followed by well-defined studies to verify durable virological and immunological vaccine benefit, as well as ultimate clinical benefit. The review also provides perspectives on magnitude of viral load reduction, durability of viral load reduction for reduced progression of HIV disease.

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1. Introduction

Complete protection against HIV-1 infection would likely require induction of broadly neutralizing antibodies against HIV-1 in addition to the induction of effective cellular T cell responses to eradicate infecting virions that escaped neutralization, a task which has proven very difficult. The first efficacy trials using an HIV subunit vaccine did not elicit broadly neutralizing antibodies and failed to show protection [1]. Vaccine candidates developed consequently aimed at eliciting solely cell-mediated immune effector activities (CMI) that could delay disease progression, and maybe also limit secondary transmission, by controlling virus replication.

There is considerable discussion about what types of endpoints would constitute definable standardized clinical benefit to the individual that would result in licensure of a T-cell based vaccine. Identifying biomarkers that can be used as surrogates for clinical endpoints in randomized clinical trials would be useful, because it would shorten studies and reduce costs. In addition, some data on the potential indirect benefits of the vaccine, especially at a population level, regarding reducing transmission may be needed. While such data may not be a requirement for licensure, they may well be an important factor in worldwide uptake and utilization of a T-cell based vaccine and hence some consideration of these issues will need to be addressed. It should be recognized that none of the current standard efficacy clinical trial designs evaluate such benefits and there is, at present, no consensus on how to best measure the effects of a vaccine on virus transmission in a community.

Biological markers associated with disease progression and secondary transmission and that may be used as prognosis markers and surrogate endpoints in HIV vaccine trials have emerged from analyses of data from studies on natural history of HIV infection.

2. Natural history of HIV infection

AIDS is a clinical syndrome caused by a retrovirus, the Human Immunodeficiency Virus (HIV), characterized by the progressive depletion of the CD4+ T-lymphocyte population, which represents a major target of viral infection *in vivo*, leading to a progressive deterioration of the immune system leaving the infected person vulnerable to a variety of infections.

Large cohorts of HIV-infected subjects (Table 1) followed up since seroconversion have produced information regarding the natural course of the disease.

The clinical evolution of HIV infection can be divided into three phases: an acute phase that lasts for weeks to months, followed by a chronic/clinically latent phase that lasts for years, and ultimately, in the absence of treatment, the immune collapse characteristic of AIDS [2–14].

2.1. The acute phase

2.1.1. Clinical data

Primary infection with HIV ranges from asymptomatic seroconversion to severe illness that can result in hospitalization. Symptoms are typical of viral infections like influenza or mononucleosis. Within days or weeks of HIV infection, most patients experience fever, disseminated lymphadenopathy, often associated with headache, myalgias, anorexia, rash, and/or diarrhea.

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