The AIDS Vaccine: A Clinical Perspective

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ABSTRACT

The distinctive biology and genetic diversity of the HIV virus has always hindered the development of an effective AIDS vaccine. In the past antibody based vaccines showed some promise in primate models, but these were ineffective in human trials. Currently human vaccine trials are underway which employ vectors to deliver viral genes directly into host cells in order to elicit a potent immune response. Other than establishing vaccine efficacy and safety, these trials also face serious ethical, social and economic hurdles. Although it is unlikely that the vector based vaccines will stop the AIDS pandemic, it may take us a step closer towards developing the ideal vaccine.

INTRODUCTION

Significant efforts are being made worldwide to control the growing HIV/AIDS pandemic. It is estimated that globally more than 40 million people currently live with HIV/AIDS. This includes about 5 million people newly infected with HIV; not to mention the 3 million deaths due to AIDS in 2004 alone.[1] Historically, viral infections like smallpox and polio have been effectively controlled by vaccination programmes, hence, it is hoped that AIDS will be controlled when an effective vaccine against HIV is developed.[2,3] However, two decades since its discovery, the HIV virus continues to evade efforts towards the development of an effective vaccine. This review aims to assess the current status of an AIDS vaccine with particular emphasis on the challenges faced by researchers in developing the vaccine.

THE HIV VIRUS

Despite the high infection rate of HIV, infected individuals almost never exhibit viral clearance by the host immune system or any natural protective immunity against the virus.[2,4] In fact, in most cases, lifelong infection is established and the individuals eventually succumb to fatal infections in absence of antiretroviral therapy.[2] This is partly explained by the virus' unique biological properties which enables it to affect the humoral as well as the cell mediated arms of the normal human immune response. The inherent properties of viral antigens makes them quite impervious to neutralizing antibodies.[2] In the case of the HIV virus, it primarily infects and destroys CD4+ T (Th) cells by attaching its envelope proteins like gp120, gp41 to targets like the CD4 molecule and chemokine receptors (CCR5 or CXCR4) present on T cells.[5] The Th cells are the principal modulators of the adaptive immune system and their depletion results in clinical immunodeficiency. The cell mediated arm of the immune system is based on infected cells incorporating foreign antigens on surface proteins – MHC I molecules, which are recognized by cytotoxic CD8+ T (CTL) cells. Thus, the CTL cells do provide a degree of infection control by terminating the infected cells and neutralizing antibodies do appear eventually, but without the Th cells the mounted response is suboptimal and delayed.[5] To add to this, HIV evades eradication by mechanisms like down regulation of the MHC I molecules on infected cells by the Nef protein or by integrating a provirus within long lived CD4+ T cells, thus establishing a long term reservoir of latent infections.[2]

However, this is only a part of the problem. Due to the inherent inaccuracy of the viral replication mechanism and a high turnover rate,[2] the incidence of mutations in the HIV viral population is quite high. A single infected person may harbour several closely related but unique 'quasi-species' of the virus.[3,6] The variability within the HIV virus species is also responsible for the viral escape phenomena - the immune response directed against specific antigens of a viral strain become obsolete because by the time any response is mounted the original viral strain has mutated with a different sequence at the initially recognized antigen site.[3] The viral variability within an infected individual is mirrored in the global distribution of the HIV virus. HIV is the most variable virus known, with two main types: HIV-1 and HIV-2.[5] HIV-1 is the most common cause of HIV disease throughout the world and is further subdivided into 3 groups, the major M group can be divided into geographical distribution via 9 subtypes (clades), 14 circulating inter-subtype recombinant viruses (CRFs) and other unique recombinants.[3] Each subtype differs by about 20 – 30% at the amino acid level[2,5] and within each viral epitope, 9-15 amino acids will have two or more mutations which adversely affects T cell recognition.[5] This biological hyper-variability of the HIV presents a major challenge to the global AIDS vaccine intiative.[2-6]

IMMUNOLOGICAL CHALLENGES

HIV is transmitted venerally and via contaminated blood products. Hence, an ideal vaccine would need to elicit mucosal as well as systemic immune responses to contain the viral infection.[6] However, this is not the only thing an effective AIDS vaccine will have to do. An infected individual's ability to transmit the HIV virus is directly related to the person's viral 'load' i.e. the concentration of HIV in their blood.[9] When the transmitted HIV virus becomes established in a new host it results in lifelong infection.

Hence, unlike other vaccines which do not prevent infection but do prevent microbial replication to a level associated with disease, an AIDS vaccine would need to completely block infection and replication and provide what is referred to as "sterilising immunity".[3] By blocking viral replication, transmission rates will be reduced, thereby slowing the spread of the AIDS pandemic.[6]

In order to achieve the above, both humoral and cellular immune responses need to be mounted. Several nonhuman primate models have been useful in testing this hypothesis. The simian HIV virus (SHIV), has been shown to cause the human equivalent of AIDS in monkeys.[8] Passive administration of monoclonal antibodies that bind to diverse HIV envelope proteins, have been shown to prevent SHIV infection in monkeys.[9] Also, topical administration of antibodies to the vaginal mucosa protects macaques from intravaginal SHIV challenges.[10] The SHIV strains used in these trials were altered to express human HIV-1 envelope proteins,[8] hence it was hoped that a vaccine strategy based on a similar principle would be effective in humans. However, human vaccine trials that used the HIV-1 envelope protein – gp120 as an immunogen, have not yielded favourable results. The first two phase III HIV-1 vaccine trials (VAX004 and VAX003), showed that when compared to a placebo the vaccine did not protect against HIV-1 infection.[11,12] These results were expected as research that was published after initiation of the above trials showed that antibodies against gp120 protein were not broadly effective against different viral strains.[13] This demonstrates how the development of broadly cross-neutralising antibodies to counteract the diversity of the HIV remains one of the biggest hurdles to the AIDS vaccine initiative. The passive high-dose antibody immunisation strategies used in the animal models show promise, but these approaches in human trials may have practical limitations due to the high doses and the associated high manufacturing costs.[2]

HIV viral diversity clearly hinders the development of vaccines that induce humoral immune responses. Hence, researches are pursuing alternative vaccine strategies that stimulate CD8+ cytotoxic T lymphocyte (CTL) immune responses.[2-6] Currently, there is substantial evidence emerging in favour of the CTL based vaccines. Prior CTL cell depletion in SHIV infected macaques resulted in an accelerated disease course when compared to controls.[14] In humans, good clinical status of infected individuals has been shown to be proportional to the presence of virus specific CTLs in their blood.[15] Cohort studies of recently infected humans and long term non-progressors have shown that in acute infections, control of virus replication was associated with a strong rise in CTL response.[16,17] Interestingly, a similar study of highly exposed and HIV-resistant sex-workers from Nairobi; showed that as the frequency of high risk exposures decreased the rates of HIV infection increased.[18] This highlights the fact that even though CTL responses may be effective at controlling viral replication it is not consistent with conventional vaccines which tend to induce and maintain CD8+ T-cell memory responses.[2] Virus specific CD8+ T cells can only recognize and destroy infected CD4+ Th cells, hence, they block replication and secondary spread of the HIV virus. However, they do not prevent primary infection of the CD4+ T cells and hence, it is unlikely that a CD8+ T cell AIDS vaccine could achieve sterilising immunity.[19]

CURRENT VACCINES

Since 2000, there has been a shift in the vaccine strategies towards using safe modified DNA, viral or bacterial vectors to deliver HIV genes into cells for protein expression and the induction of a more potent CTL response.[3] Although this approach may seem extreme, the vectors are proven to be safe in animal trials[6] and the risk of adverse events in humans is very low in the long term.[4] More importantly, these are live replicating viruses and will induce both humoral and cell medicated immunity towards the vector and the gene product.[6] The most promising results to date, come from recombinant adenovirus[5] which have stimulated strong and sustained T cell responses but have limited applicability owing to the high frequency of antibodies to this virus in many human populations.[5] Currently, a number of small phase I trials,[2] three large phase II trials[20, 21] and a recently initiated phase III trial[22] are underway to test the safety, immunogenicity and efficacy of vector based vaccines. However, initial results of human clinical trials of plasmid DNA vectors suggest that their immunogenicity in human beings may be less than that observed in preclinical animal models.[2] Despite that, a phase I double blind placebo-controlled trial published recently in Vaccine[22], showed a reduction in the frequency of transient viremia (viral blips) in HIV positive patients on anti-retroviral therapy who were given HIV DNA plasmid vaccination.

The current hype surrounding CTL based vector vaccines is perhaps the same as that surrounding viral envelope protein vaccines in the early 90's. In view of past failures, it has become imperative to prove soon whether vaccines based on the CTL hypotheses are efficacious in large human trials.[2]

STRATEGIC AND ETHICAL CHALLENGES

Many of the upcoming HIV vaccine trials are being carried out in developing countries where the impact of the AIDS pandemic is the worst.[20, 21] Recruitment of volunteers in less-educated populations is more difficult owing to the stigma, discrimination, rumours, misunderstandings, and media opinion associated with AIDS in these countries.[24] As far as barriers to participation in HIV vaccine trials are concerned, fear of social discrimination is on par with vaccine safety concerns.[25] A major ethical issue in resource poor settings is that of providing antiretroviral therapy and general medical care to people who do become infected with HIV while participating in the study.[2] Conversely, individuals in socio-economically deprived conditions may view participation in the trial as the only way to get access to any medical care. Hence, care will need to be taken to avoid compromising the participants' autonomy and provide appropriate consent procedures.[2]

Besides the above considerations, there are the obvious costs and resource barriers. Efforts in implementing clinical trials in developing countries are plagued by poor approval processes, ethics committees and regulatory authorities unprepared and inadequately staffed for reviewing complex dossiers of 'high tech' genetically engineered products and dealing with constant changes that characterize research and development.[24] Unlike traditional vaccines, efficacy trials of CTL based vaccines will include quantification of endpoints such as plasma viral RNA levels and peripheral blood CD4+ T cell counts which will prove a challenge in multiple developing world sites.[4] The implementation of any co-ordinated national programme in developing countries requires a stable political, social and economical environment, which unfortunately, is not the luxury of many countries.

FUTURE PROSPECTS

The ideal AIDS vaccine will i) need to stimulate humoral and cellular immunity; mucosal and circulating immunity ii) be able to stimulate strong immune responses which are broadly effective against diverse viral strains; iii) cheap enough to manufacture and efficacious enough to stop infection and spread of the HIV virus. Thus, it is not hard to see why an AIDS vaccine still remains elusive. However, the future of the AIDS vaccine is not bleak

Despite the discussed obstacles, the HIV-1 envelope (Env) glycoprotein still has potential for developing neutralizing antibodies that react with diverse strains of the virus. A recent article in Science lists four such sites on the two subunits (gp120 and gp41) of the Env. The most important of these is the MPR region which is highly conserved among viral strains.[4] Although the antibodies to this MPR region (2F5 and 4E10) have been shown to neutralize viruses from multiple HIV-1 clades,[4] they are normally selectively deleted from the immune system due to their reactivity with self-antigens.[4, 26]

The CTL based vaccines have shown broad immunogenicity potential in animal trials and the results of the phase III trials are awaited. However, the CTL hypothesis has spawned a whole new generation of vaccination vector systems. Recently, a topical immunisation technology called Derma Vir, which targets Langerhans cells, has been shown to suppress viral load rebound after interruption of antiretroviral therapy in chronically infected macaques.[27] However, further randomized trials are needed to assess the efficacy and safety of this technique.