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Commentary

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Optimal clinical trial designs for immune-based therapies in persistent viral infections

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Abstract

There is now effective therapy for infection by the Human Immunodeficiency Virus (HIV), but there is no cure. Consequently, antiviral drugs must be administered continuously to suppress viral replication. Recently, a large phase III international immune-based therapy trial was discontinued because it is difficult to measure clinical endpoints while antivirals are administered. Since the immune system has evolved under the selective force of microbial infections, the immune reaction is antiviral. This commentary explores the rationale of using "Diagnostic Treatment Interruptions" of antiviral therapies to determine efficacies of immune-based therapies.

Introduction

Recently, the Chiron Corporation announced the discontinuation of an international phase III trial, which was designed to determine whether high dose intermittent interleukin-2 (IL2) therapy could improve on the clinical outcome of standard antiviral therapy for individuals infected with the Human Immunodeficiency Virus (HIV). After several years and the enrollment of almost 2000 volunteers in 18 countries, the company yielded to reality. The primary endpoint of the study, i.e. the rate of progression to an AIDS-defining illness while receiving Highly Active Anti-Retroviral Therapy (HAART), is only ~2%/year [1]. Therefore, to improve upon such an already successful outcome by the addition of an immune-based therapy (or any kind of therapy for that matter) would require five more years. It proved to be too expensive for the company to pursue. How then will it be possible to determine efficacy when testing immune-based therapies combined with antiviral therapies, especially efficacy that is acceptable to the Food and Drug Administration (FDA)?

Discussion

The FDA will approve an agent for the treatment of any disease if it can be shown to meet one of three fundamental clinical outcome criteria: 1) It is curative in a disease or curative for a fraction of those afflicted. 2) It can prolong disease-free survival. 3) It can improve the quality of life while the therapy is administered. In some diseases the FDA will accept a "surrogate outcome" if it has been shown that the surrogate measurement correlates with the clinical outcome, which usually requires more time, and/or the clinical outcome is associated with significant morbidity or mortality. For example, in the treatment of persistent infection with Hepatitis C Virus (HCV), it has been shown that a disappearance of detectable plasma HCV levels 6 months after the cessation of therapy correlates with a lack of progression to decompensated liver disease [2]. Since the progression to decompensated liver disease generally takes years and even decades, and results in a fatal prognostic outcome without a liver transplant, the FDA has accepted the clearance of plasma HCV as a "surrogate" for a clinical outcome.

Similarly, in the treatment of HIV infection, the FDA has accepted agents that can be shown to reduce the concentration of circulating HIV, even for as short a time interval as 6 months. Actually, all of the antiviral agents now on the market have been approved by the FDA on the basis of these criteria. It follows that these same criteria may be useful to determine whether immune-based therapies are effective in this and other chronic viral infections.

In this regard, it is important to note and to emphasize that *the immune response is antiviral*. In fact, viral infections have been largely responsible for the selection of the host defenses that have evolved to protect us against pathogens that invade and replicate within our cells. Thus, the exquisite efficiency of the host reaction to viral infections is attributable to the innate and acquired immune systems and the capacity of virus-reactive NK cells and T cells to proliferate massively and to differentiate into killer cells and cells capable of producing antiviral cytokines and chemokines.

Moreover, it is also important to note and to emphasize that the immune response to HIV infection is the same as it is in other viral infections, such as HCV, or poliovirus, measles virus, mumps virus, EB-virus etc. In addition, the fundamental ways in which the immune system has of recognizing and responding to the introduction of foreign molecules is identical, whether the source of the foreign molecules is a microbial infection, an allograft, an allergen, an autoantigen, or a tumor antigen. It follows that immune-based therapies that focus on promoting the *quantity and quality* of the immune response should be beneficial in the treatment of a range of diseases, especially persistent viral infections and cancer. Moreover, treatments that diminish the quantity and quality of the immune reaction should be beneficial in the treatment of allergies, allograft recipients and autoimmune disorders.

Given these principles, what is the best way to determine the efficacy of IBTs? In cancer therapy the paradigm of treating for a finite interval followed by discontinuation of therapy and monitoring for the relapse rate over time has been a tried-and-true clinical trial design for decades. As well, the same clinical trial design has been used successfully in persistent infections by HCV. In this instance, the standard approach is to administer the therapy for 48 weeks, then to discontinue therapy and monitor for detectable plasma HCV concentrations 24 weeks after the cessation of therapy. Studies have shown that the absence of detectable plasma HCV that persists 6 months after the cessation of therapy, which is termed a "sustained viral response", indicates that the individual will remain virus-free for an extended interval, i.e. years. Consequently, these individuals are considered "cured".

With regard to persistent HCV infection, the sustained viral response rate to standard antiviral therapy, which consists of pegylated interferon-alpha (PEG-IFN-α) and Ribavirin is ~56% [3,4]. However, if the data are analyzed according to the genotype type of HCV, those infected by Genotype I, which accounts for ~75% of all of those individuals in the U.S., the response rates are lower. Moreover, if one examines the results of standard therapy for those individuals who are infected with Genotype I who present initially with a high plasma virus concentration, i.e. > 2 million mol/mL or > 800,000 IU/mL, then the sustained viral response rate is only ~40%. Since ~75% of those individuals infected by Genotype I also have a high plasma virus concentration, more than 50% of individuals in the U.S. have only a 1 in 2.5 chance for a cure.

Studies of individuals who have responded to standard antiviral therapy for HCV have revealed that they have readily detectable immune responses that are specific for HCV [5]. For example, these individuals can be identified by detectable antigen-specific lymphocyte proliferation assays (LPA) or cytolytic T lymphocyte (CTL) assays, while those who do not respond to standard antiviral therapy do not have easily detectable immune reactivity specific for HCV. Accordingly, this information leads to the hypothesis that IBTs should synergize with standard antiviral therapy and lead to higher sustained viral response rates.

In this regard, because only ~40% of individuals with Genotype I and a high plasma HCV concentration respond to standard therapy, the determination of the efficacy of the addition of an IBT to the standard antiviral therapy should not require thousands of volunteers. As well, because the clinical trial design of a "Diagnostic Treatment Interruption" (DTI) is standard in this disease, the determination of the efficacy of IBTs should not require many years. Instead, a trial should be accomplished within a relatively short interval, i.e. 2–3 years.

The same logic can also be applied to clinical trial designs in the treatment of HIV infection. At this time there is effective antiviral therapy for HIV, but still the disease cannot be cured. Even though continuous antiviral therapy for several years can lead to undetectable plasma HIV concentrations, as soon as the therapy is discontinued, plasma HIV once again becomes detectable within just a few weeks [6]. Therefore, this infectious disease is unusual, in that most microbial infections for which we have effective antimicrobial therapy can be cured. In many respects, chronic infection with HIV resembles cancer. Often effective cancer chemotherapy, radiotherapy or surgery can result in the complete disappearance of detectable tumor cells, yet upon cessation of therapy the cancer once again recurs.

Accordingly, since antiviral therapy of HIV infection cannot result in any "cures", now the primary question confronting the field is how can one achieve a "cure", and how can one determine whether a "cure" has been achieved. In this regard, it is important to define what we mean by "cure". Webster's Dictionary defines cure as "*to rectify an abnormal or undesirable condition, usually by means of medicines*". Therefore, we are not seeking to eradicate or eliminate the offending organism. Rather, the goal would be to prevent replication of any residual virus that persists after antiviral therapy. Given the understanding that viral infections are naturally combated by cell-mediated immunity (CMI), it follows that stimulation of the virus-specific CMI while suppressing viral replication with antiviral drugs should be more effective than the antiviral drugs alone.

A clinical trial design to rapidly and quantitatively measure the efficacy of an IBT is most important, given the capacity of the antiviral drugs to very effectively suppress viral replication. The Chiron Corporation eventually realized that it is difficult to assess efficacy using clinical endpoints while individuals continue to receive antiviral drugs. Accordingly, given the knowledge that the immune response is antiviral, the most logical measurement of the efficacy of HIV immunity is the measurement of the virus itself, in other words the "surrogate" endpoint. However, it is difficult to quantify residual virus while individuals continue to receive antiviral drugs. Several groups thought that they had achieved elimination of all residual viral particles as evidenced by the inability to detect viral RNA or DNA in biopsies, only to observe rapid viral relapse when the antivirals were discontinued [7,8].

We have found that using a clinical trial design that includes a DTI provides for a very rapid and quantitative endpoint for testing IBTs [9,10]. As well, if the IBTs are administered while antivirals suppress endogenous viral replication maximally, then the immune system should not be laboring under the influence of an ongoing ineffectual immune response to a persistent viral infection. The idea is to improve both the quantity and quality of the immunity to HIV before the antiviral drugs are withdrawn, so that the immune system is better equipped to combat viral replication when the antiviral drugs are no longer present.

Because HIV resumes replication very rapidly upon interruption of antiviral therapy, it is not even necessary to wait 6 months to determine whether there are any sustained viral responders. The mean time to detectable plasma HIV is ~2 1/2 weeks, and our experience is that all individuals relapse within 6 weeks [9]. Therefore, by monitoring plasma HIV concentration weekly, it is possible to very accurate determine the characteristics of the viral relapse just 12 weeks after the cessation of antiviral therapy. In addition, because the determination of plasma HIV concentration is very quantitative and sensitive (LLD = 50 molecules/mL), measurement of the "surrogate endpoint" is more *accurate* than measurement of a clinical endpoint. Accordingly, this clinical trial design does not require large numbers of subjects to identify promising therapies. Instead, studies designed to involve < 100 subjects can be powered sufficiently to determine efficacy.

These considerations are important when large phase III HIV vaccine trials are contemplated, testing the efficacy of potential prophylactic vaccines in areas of the world where the incidence of infection is high. Such large placebo controlled trials will require thousands of volunteers and many years to await natural infection. The costs and complexities of conducting such large trials, especially in third world countries that lack sufficient medical infrastructure, are enormous. All of these considerations lead to the proposal to first conduct therapeutic trials of immune-based therapies and vaccines in the first world where there are readily available clinical and research facilities, only moving to large phase III prophylactic trials in the third world when a given vaccine and IBT is proved therapeutically efficacious.

Conclusions

Several pharmaceutical firms, including Chiron, are developing HIV vaccines with the intention to test them as a means of prophylaxis against this dread infection. In addition, some are proceeding to test their best vaccine candidates as therapeutics. It is important that these trials move forward as rapidly as possible. For this to occur, the community of scientists, physicians and HIV-infected individuals need to promote the concept that we all must work together to participate in clinical trials designed to work towards a cure for this viral infection. Without a concerted effort, it really will take decades to achieve a cure, and even more decades to achieve prevention.

Competing interests

None declared

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