

Vaccinal effect of monoclonal antibodies

A Global HIV Vaccine Enterprise Timely Topics roundtable

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Introduction

Several investigational studies of monoclonal antibodies (mAbs) for the prevention of infectious diseases and the treatment of cancer have shown that they are able to enhance the adaptive immune response, in addition to providing protective immunity or anti-tumour activity.

Various mechanisms of action have been identified, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular viral inhibition (ADCVI).

In addition, immune complexes (ICs) formed with different viral elements can be recognized by both activating and inhibitory Fc γ Rs on various cell types, including dendritic cells. Activating these receptors can stimulate dendritic cells to generate effector T-cells, leading to longer and stronger antiviral immune responses, known as the "vaccinal effect".

This vaccinal effect has been observed in a range of conditions, including cancer, influenza, SARS-CoV-2 and hepatitis. However, the Fc-mediated vaccinal effect of monoclonal antibodies as a component of the immune response to HIV is poorly studied and a contentious matter.

With the increased role of bnAbs for the prevention and treatment of HIV, understanding the immunological mechanisms driving the induction of the vaccinal effect by mAbs could contribute to the design of effective preventive and therapeutic interventions.

PRESENTATIONS
An introduction to Fc-Dependent Immunomodulation induced by antiviral antibodies Mireia Pelegrin, IRMB, University of Montpellier, INSERM, CNRS, France (Timestamp: 2:40-26:01)
Vaccine-induced antibody-mediated protection against infection by SARS-COV-2 Dan Barouch, Beth Israel Deaconess Medical Center, USA (Timestamp: 26:56-45:49)
Vaccinal effect of HIV-1 antibody Ole Søgaard, Aarhus University Hospital, Denmark

(Timestamp: 47:05-1:10)

ROUNDTABLE DISCUSSION

Moderators:

Elise Landais, IAVI Neutralizing Antibody Center (NAC), USA

Colin Havenar Daughton, Vir Biotechnology, USA

(Timestamp: 1:11-2:00)

Roundtable discussion

Summary

The reality and definition of the vaccinal effect is a critical aspect of ongoing debates within the HIV vaccine and cure research field. It is imperative to agree on a clear definition given the potential controversies surrounding the data supporting or refuting the vaccinal effect. Such a definition should not exclude the possibility of other mechanisms to explain clinical observations.

The role of Fc γ Rs polymorphisms, the adaptive response induced by antibodies, the nature of the immune complex and the unique repertoire of infected cells are all factors that could be involved in the existence of a vaccinal effect and its mechanisms of action.

Clinical strategies involving smart use and modification of bnAbs, optimal timing and suitable combinations with other immune effectors were suggested. Experiments would be necessary to bridge human and animal models.

Acknowledging the interplay between bnAbs and non-neutralizing antibodies, it was also proposed that Fc-mediated effects of non-neutralizing antibodies be examined to gain additional insights; these have been correlated with some level of protection in HIV prevention clinical trials.

The complex landscape of defining and understanding the vaccinal effect requires further exploration from various perspectives and with various strategies, and could contribute to future research and clinical approaches in the field of HIV prevention and cure.

Definition of vaccinal effect

Considering the potential for debate surrounding the data supporting or challenging the vaccinal effect in the HIV field, it becomes crucial to establish a clear definition of the vaccinal effect.

Mireia Pelegrin (MP) commented that it was important to distinguish between the induction of host immune responses and a protective immune response. In some cases, a boosted immune response, either antibody or CD8 response, has been observed but did not lead to long-term protective immunity. Furthermore, there is no formal demonstration that the binding of immune complexes to Fc γ Rs was responsible for a boosted immune response. Viral control and virus/host interactions may be important in the mechanism leading to the long-term control of viral immunity.

Dan Barouch (DB) emphasized that a clear definition is important when there are strong feelings in the field. It is very clear that administration of broadly neutralizing antibodies (bnAbs) to people living with HIV, on or off therapy, does lead in a fraction of cases to long-term viral control. This

definition may be less controversial: "the induction of long-term host control in the absence of ARVs induced by bnAb administration". A more stringent definition proposing that the binding of bnAbs to the virus, and forming of immune complexes that act as antigens, is the specific mechanism that triggers humoral or cellular autologous immune responses, would need more careful consideration. This observation may or may not be attributable to the vaccine's efficacy.

This stricter definition may lead to missing other potential mechanisms of virologic control. For example, in both NHPs and humans, Ab-mediated viral suppression, either acutely or later, or a delayed rebound could be sufficient in some cases to trigger autologous induction of T-cell responses or alteration of host/virus balance. These responses may not be due to the vaccinal effect but still suggest that a long-term outcome of bnAbs is long-term viral control. A broad definition would avoid missing some of the mechanisms explaining the clinical observations.

Elise Landais (EL) commented that in her and Colin Havenar Daughton's work on the development of bnAbs during natural infection, some observations were consistent with the mechanisms described here. For example, elevated levels of IgG were correlated with the development of bnAbs, as well as higher levels of cellular activity.

Ole Sogaard (OS) commented that having a better definition would be helpful to avert the controversy. The question is how to demonstrate the vaccinal effect in humans, as CD4/CD8 depletion is not possible. From a practical perspective, the question is how to take advantage of the vaccinal effect in the HIV cure field if it exists. Signals have been observed in clinical trials, and attempts to boost antibody responses through the combination of bnAbs and immunoregulators have been conducted, but without success. Reaching a consensus on how to define the observation of the vaccinal effect in humans is also necessary.

Colin Havenar Daughton said that the key question for the field is why people living with HIV do not experience a rebound after receiving bnAbs. The vaccinal effect could be a possible explanation, considering a broad definition, that could be rethought as immune engagement between antibodies and the virus leading to a state where the host can control the virus. This may not be possible in all individuals for various reasons, such as different states of the immune response and viral fitness or the Ab portion of the immune complex. There is much to unravel. However, it is important to understand the mechanisms of control after bnAbs therapy; vaccinal effect and engagement of the host immune response may be one explanation among others.

Exploring the ability of the host to control viruses after bnAb therapy

Colin Havenar Daughton suggested two types of studies to help prove or define the vaccinal effect: one involving people living with HIV receiving bnAbs and bnAbs knocked out for effector functions; and one involving people living with HIV receiving bnAbs or non-neutralizing Ab, both with preserved effector functions.

Ole Sogaard noted that conducting studies was required, but studies were limited by the availability of GMP-grade material for clinical trials in humans. Studies could also include bnAbs with enhanced functions (such as GAALIE, the acronym for the amino acid mutations in the Fc region, specifically G236A, A330L and I332E).

Mireia Pelegrin commented that polyfunctional antibodies with all their functions were required and that using Ab missing some functions would present some ethical challenges. The immunological profile of the healthcare clients could also be important to characterize and

understand for conducting stratified studies that could provide better insight into the correlates of protection.

Dan Barouch added that an NHP would be a go-to model to conduct studies.

Role of Fc γ Rs polymorphism in the vaccinal effect

Fc γ RIII polymorphism is common, as well as polymorphism of the Fc γ RIIa. Mireia Pelegrin stated that there was no study specifically investing the role of Fc γ Rs polymorphism on the vaccinal effect, but several studies investigated its impact on HIV progression. Colin Havenar Daughton noted that work has been done in the cancer field, showing dramatic differences in outcomes.

Role of Ab in the adaptive response

Colin Havenar Daughton asked whether Ab can induce an adaptive response in a strict sense, whether or not they are responsible for viral control, and what the significance of antigens, immune complex and immune cells is for the response.

Mireia Pelegrin said that the nature of the immune complex matters because the repertoire of antigens expressed in infected cells is not the same as the one on virions. Notably, the uptake of cellular ICs might allow the presentation of a broader viral antigenic repertoire. In addition, HIV-infected cells are stronger inducers of innate immunity than cell-free virions. Thus, cellular ICs can trigger different immunologic outcomes. Antigen matters, as well as the property of the Ab. It is possible to modulate the response using mutated Fc or glycosylated Fc, for example.

Ole Søgaard commented that a series of experiments could be done with newly diagnosed individuals that could be randomized to early bnAbs with or without ARV therapy to measure cellular immune responses and when antibodies have washed out, measuring humoral responses. Three trials are due to start soon and could provide more information. One challenge is that different strains are involved, which need to be accounted for when performing assays.

Bridging animal and human studies

Colin Havenar Daughton noted that it was more challenging to tease out mechanisms in humans than in animal models although it was important to keep in mind that human studies are conducted during chronic infection with existing Ab and T-cell responses. In contrast, animal studies involve administering antibodies early after infection, reflecting a different state of the immune system, which may account for potential differences.

Mireia Pelegrin said that questions could be addressed in various contexts, such as early infection or childhood. Clearly, during chronic infections, there were huge differences in cell functions (for example, NK cells).

Future clinical strategies for inducing the vaccinal effect or viral suppression

Ole Søgaard added that bnAbs are the only tools that have provided long-term control so far after dosing. How can bnAbs be used smartly and modified to enhance immune functions or other functions? Essential questions to address include determining the best timing for the effective use of antibodies, such as their potency during ART re-initiation, and identifying suitable combinations with other agents.

Mireia Pelegrin noted that combinatory approaches were an important and growing area of research, particularly in cancer.

Colin Havenar Daughton stated that one of the areas to probe with bnAbs was a larger group of clients with different attributes, for example, in viral load, host immune responses and non-progressors.

Role of non-neutralizing antibodies

Susan Zolla Pazner (SZP) observed the lack of success in eliciting bnAbs in both animals and humans. Concurrently, she highlighted the demonstrated Fc-mediated effects of non-neutralizing antibodies and pondered whether it might be beneficial to examine non-neutralizing antibodies more closely as potential effectors for use in passive immunization and vaccines.

Colin Havenar Daughton, pointed out that the mechanisms to prevent infection might be different from those to achieve long-term viral suppression, with the possibility of overlapping or entirely distinct processes. While he favoured bnAbs, he acknowledged the merit of conducting experiments with non-neutralizing antibodies to gain additional insights.

Ole Søgaard noted that a reason for using bnAbs was that the virus had not yet escaped from bnAbs and that the strength of neutralization correlated with the T-cell responses. It would be interesting to look at the strength of binding and immune responses.

Susan Zolla Pazner stressed that research should include both nAb and non-neutralizing Ab. Two studies presented by HVTN (702-705) showed a correlate of protection through V2 antibodies, as was shown in the RV144 clinical trials.

Colin Havenar Daughton, also emphasized that, within the cure space, non-neutralizing antibodies proved valuable in conjunction with bnAbs to further limit the escape mechanisms the virus might employ against bnAbs. There is an undeniable interplay between bnAbs and non-neutralizing antibodies, and both, along with T-cell responses, should be induced in an optimal scenario.

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