HIV Neutralizing Antibodies: Clinical Correlates and Implications for Vaccines

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(See the article by Euler et al, on pages 1045–1053.)

Neutralizing humoral immunity has been the subject of intense investigation since early human immunodeficiency virus (HIV) research. Although virtually all HIV-positive patients have antibodies capable of binding to HIV envelope protein, only a subset of these antibodies, termed neutralizing antibodies, are able to block viral entry into target cells. Neutralizing antibodies develop later than other immune responses, 12 weeks after infection [1, 2], and initially target only the infecting strain. Over time, in many patients this response broadens to allow recognition of heterologous strains [3, 4]. It is generally thought that neutralizing antibodies will be a critical component of a successful vaccine-elicited immune response.

Given the immense diversity of HIV strains worldwide, vaccine-elicited neutralizing antibodies would ideally be broadly cross-reactive. To date, the antibodies elicited by candidate vaccines have had no or weak neutralizing activity, mainly against laboratory-adapted strains and with very limited breadth [5–7]. However, many HIV-infected individuals produce neutralizing antibodies, and a small fraction produce extremely potent neutralizing antibodies with activity against diverse clinical (primary) isolates [3, 4, 8–11]. Understanding how broad neutralizing antibodies develop naturally in some HIV-1–infected patients should provide guidance for vaccine design. The prevalence of broadly reactive neutralizing antibodies in serum and the associated clinical parameters have been the subject of several recent studies [10–14]. Euler and colleagues, in an article appearing in this issue of Journal [15], examined these findings in a European cohort.

Euler et al [15] evaluated samples from 82 patients participating in the Amsterdam Cohort Studies. Because this cohort has been followed from seroconversion onward, the authors were able to look for associations between neutralizing antibodies and clinical outcomes, as well as immunological parameters. They chose samples from 3 years after infection, allowing time for broad neutralizing antibodies to have developed. Neutralizing activity in serum was measured using the well-accepted TZM-bl assay and pseudo-viruses derived from primary isolates [2, 16]. They found that neutralizing antibody breadth varies widely among chronically infected patients. Consistent with findings in studies of other cohorts in multiple geographic areas [10–14], the authors observed that 33% of their patients with chronic HIV infection had broad neutralizing antibodies. An important finding was the lack of association between breadth of neutralizing antibodies and the time from seroconversion to diagnosis with AIDS, AIDS-related death, or the survival time after AIDS diagnosis. This agrees with findings in a Kenyan cohort [13]. The authors also noted a positive association of neutralizing antibody breadth with viral load, although the association did not reach statistical significance, as it did in other cohorts [10, 13, 14].

Unexpectedly, Euler et al [15] observed that broad neutralizing antibodies were associated with lower CD4+ T cell counts before and 1 year after seroconversion. This finding seems counterintuitive, because one would expect broad neutralizing antibodies to be produced by highly functional B cells that have undergone class switching and multiple rounds of somatic hypermutation [17], events that require intact T cell help. The authors speculate that lower levels of CD4+ T cells result in less HIV-induced polyclonal B cell activation, with a concomitant boost to virus-specific antibody, as seen in the lymphocytic choriomeningitis virus mouse model [18]. However, in HIV infection, polyclonal activation and other B cell abnormal...
ities are more pronounced in patients with depleted CD4+ T cells and can be partially reversed by antiretroviral treatment [19]. A second possibility is that lower initial CD4+ T cell counts lead to less effective control of viremia; because higher levels of viremia and extended exposure to antigen are associated with the development of broad neutralizing antibodies [10, 14], the relationship between low CD4+ T cell counts and broad neutralizing antibodies could be a side effect of viremia rather than causal. Nonetheless, the observation by Euler and colleagues is intriguing and needs to be validated and explored in larger cohorts.

Why are neutralizing antibodies the focus of such interest for vaccine research? On the basis of the data from patients with chronic infection, neutralizing antibodies may not seem advantageous. Broad neutralizing antibodies are not associated with better clinical outcomes among chronically infected patients, as shown by Euler et al [15] and Piantadosi et al [13], and they correlate with higher viral load [10, 13, 14]. Patients whose virus load is controlled to <50 copies/mL without antiretroviral treatment have very low levels of autologous [20] and heterologous [9, 14, 21, 22] neutralizing antibodies. Furthermore, a study of superinfection in women did not find a protective effect of broad neutralizing antibodies [23]. Thus, neutralizing antibodies may not be of value when present in chronic infection.

However, several lines of evidence strongly suggest that vaccine-elicited neutralizing antibodies could be useful in preventing infection. The most convincing data come from the nonhuman primate model of HIV using simian-human immunodeficiency viruses (SHIVs)—chimeric viruses bearing an HIV env gene on a simian immunodeficiency virus backbone. In a large number of studies, macaques were administered HIV-neutralizing antibodies intravenously and subsequently challenged with SHIV. Neutralizing antibodies could completely prevent SHIV infection by intravenous, intravaginal, or oral routes. In some cases, animals became infected but had delayed disease kinetics and controlled viremia [24]. These findings demonstrate the potential for antibodies to prevent infection or disease if they are present at the time of exposure, as they would be if elicited by a vaccine.

Data from other areas of research speak to the prophylactic potential of neutralizing antibodies. Vertical transmission of HIV may be influenced by neutralizing antibodies; some (although not all) studies find less frequent HIV transmission to infants by mothers with higher neutralizing antibody titers. Antibodies can be passively transferred from mother to child transplacentally or in breast milk. When transmission does occur, the transmitted variants are often those that are resistant to the mother’s neutralizing antibodies [25]. In addition, many licensed vaccines for other pathogens protect via neutralizing antibodies [26]. Finally, it is likely that vaccine-induced T cells would be unable to prevent infection in the absence of antibodies; in clinical trials of an adenovirus serotype 5–based HIV vaccine [27] and experimental adoptive transfer of CD8+ T cells in the macaque model [28], preexisting virus-specific T cells showed no efficacy in preventing infection or lowering viral load. Thus, despite the ineffectiveness of neutralizing antibodies at mitigating chronic infection, the in vivo production of broad neutralizing antibodies is still a major goal for prophylactic vaccines.

The recent announcement of results from a phase III vaccine trial in Thailand has focused much attention on vaccine-induced humoral responses. The RV144 trial tested a canarypox prime, recombinant gp120 boost regimen (compared with placebo) in 16,000 volunteers. The modified-intent-to-treat analysis showed a vaccine efficacy of 31.2% (P = .04) [29]. This modest, but positive, result surprised many in the field [30, 31]. Immunogenicity studies showed a lack of CD8+ T cell responses and very low CD4+ T cell responses to the vaccine; thus, cellular immunity was unlikely to have contributed to efficacy. In contrast, humoral immunity in the form of gp120-binding antibodies was noted in nearly all vaccinees. Furthermore, 71% of serum samples had neutralizing antibodies against the laboratory-adapted HIV-MN strain. MN neutralization was also measured in the VAX004 phase III trial of recombinant gp120 (AIDSVAX), but the effect of MN neutralizing antibodies on HIV acquisition was unclear [32, 33]. Neutralization of primary isolates is widely assumed to be a more relevant antibody function [34]. Primary isolate neutralization was not measured, and indeed was not expected, in RV144 samples based on more than a decade of experience with gp120 vaccines [6]. However, the vaccine regimen tested in RV144 was shown elsewhere in a phase I/II trial to elicit a different antibody function, antibody-dependent cell mediated cytotoxicity (ADCC), in most vaccinees [35]. ADCC is the destruction of antibody-coated HIV-infected cells by natural killer cells. Measurement of ADCC responses in serum from RV144 may allow determination of their contributions to vaccine efficacy. The vaccine development field can build on the results of this trial, and future trials of vaccines that elicit additional responses expected to be useful—including neutralizing antibodies—may have better outcomes.

In the absence of vaccine-elicited neutralizing antibodies in clinical trials, the potential importance of neutralizing antibodies in protection from incident HIV infection remains speculative. Euler et al have added to the growing number of reports showing that broadly cross-reactive neutralizing antibodies provide no benefit to chronically infected patients. Further dissection of the mechanisms by which such antibodies are generated, however, may yield valuable clues for designing vaccines that can elicit antibodies that are protective when present before virus exposure. As shown by Euler et al and in similar studies, broad neutralizing anti-
bodies are produced by a substantial proportion of HIV-infected patients, at titers in the range shown to be protective in some passive-transfer SHIV experiments [36]. Thus, the human immune system can achieve neutralizing antibody responses at levels that could be protective. Now the challenge to the field is to achieve a prophylactic vaccine that elicits them.

References


