Therapeutic potential of neutralizing antibodies in the treatment of HIV-1 infection

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In 1981 unusual cases of severe immune deficiency were reported. Two years later the cause of the acquired immuno-deficiency syndrome (AIDS) was identified: a retrovirus, designated the human immunodeficiency virus (HIV), that caused a loss of important immune functions leading to a dramatic vulnerability to a variety of bacterial, viral and fungal infections. The finding that the presence of neutralizing antibodies correlated with the disease status suggested that infusion with hyperimmune plasma and human HIV-specific immunoglobulin (HIVIG) obtained from chronically HIV-1-infected asymptomatic donors may be of benefit to patients. However, early clinical studies were disappointing. No clear benefits were found for the majority of patients treated.1

The introduction of highly active antiretroviral therapy (HAART) in 1996 caused great excitement. HAART drugs inhibit viral replication within infected cells by interfering with two crucial viral enzymes: reverse transcriptase and protease. The initial hope that HIV could be eradicated in patients undergoing several years of HAART was not fulfilled and it became clear that HAART had major drawbacks. The high degree of severe side effects, short drug half-life, persistent viral reservoirs and the increasing prevalence of drug-resistant viruses underscored the need for additional therapeutic approaches against HIV-1. Drugs that prevent viral replication at earlier steps such as virus entry into target cells and integration of the viral genome into the host genome are the focus of current drug development. Fusion inhibitors such as the T20 peptide, which prevents conformational changes in the viral membrane necessary for virus entry, are currently in clinical development.2 However, T20 has to be injected daily owing to its short half-life, and induces adverse reactions at the site of administration.

During the last decade several human monoclonal antibodies (hmAbs) were established to have an unusually high antiviral potential against HIV-1. The hmAbs neutralize the virus by binding to conserved epitopes of the proteins gp120 (antibodies 2G12,3,4 IgG1b125) or gp41 (2F5,6 4E107) representing ‘natural’ entry inhibitors with half-lives 50–100 times longer than fusion inhibitor peptides. These antibodies inhibit replication of the majority of primary isolates with high potency.8 Moreover, there is evidence that these antibodies are capable of lysing virus particles and infected cells by antibody-dependent cellular cytotoxicity (ADCC) and complement activation.4,9 Although the high antiviral potential of these antibodies has been demonstrated in vitro, their usefulness for in vivo application was doubted by many. The unsatisfying results in HIVIG studies and the difficulties in hmAb large-scale technology were major hurdles for the development of antibody therapy.

The concept of passive immune therapy came back into the focus of general interest when several animal studies using the macaque model showed that neutralizing antibodies could potently prevent infection with chimeric simian–human immunodeficiency virus (SHIV). Infusion of 2F5, 2G12 and HIVIG alone or in combination protected macaques against a highly pathogenic intravenous10 or vaginal11 virus challenge. In contrast, all control animals that had received non-HIV-specific human polyclonal IgG rapidly progressed to AIDS. In other studies the concept of prevention of mother-to-infant HIV-1 transmission by passive immunization was evaluated. Different antibody combinations of F105,12 directed against gp120, 2F5, 2G12, 4E10 and IgG1b12, given pre- and post-exposure protected neonate macaques against oral challenge.13,14 These animal studies strongly support the hypothesis that neutralizing antibodies may also be able to prevent HIV-1 infection in humans when present in sufficient amounts before or shortly after exposure. Administration of hmAbs may be a feasible approach to preventing infection of infants by their HIV-1-positive mothers during birth or the breastfeeding period, or as prophylaxis after exposure to HIV-1-contaminated matter. However, although animal studies

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suggest a role for preventive application in humans, conclusive evidence that hmAb therapy may be useful in established infection is still lacking. Primate studies using antibodies as therapeutic approach during established infection have not yet been carried out.

Nevertheless, there are some observations from HIV-1-infected humans that support the concept of passive immune therapy with hmAbs during chronic infection. Subsequent to infection with HIV-1 patients develop antibody responses that are initially capable of neutralizing autologous plasma virus. However, in the majority of patients rapid virus escape is found. The quality of the antibody response changes significantly and the majority of HIV-specific antibodies are not able to neutralize plasma virus; there is even evidence of the presence of infection enhancing antibodies. There are indications that the development of a broad neutralizing immune response, as found in patients that do not progress to AIDS despite being HIV-1 infected for a long time, delays disease progression, in contrast to rapid disease progressors where neutralizing antibody titres are often low. A general correlation between the decline in HIV-specific antibody responses and a poor prognosis was found.

The first clinical study performed with an hmAb (F105) did not show beneficial effects for patients following a single dose infusion. However, this antibody has only modest neutralizing activity in vitro. In contrast, a single dose of 10 mg/kg recombinant tetrameric antibody-like fusion protein composed of IgG2 and the virus binding domains of CD4 of anti-2F5 and anti-2G12 immune response were found. The antibodies within 4 weeks), no adverse events or development of anti-2F5 and anti-2G12 immune response were found. The half-lives were 8 and 16 days for 2F5 and 2G12, respectively. Significant transient reduction in viral loads was observed in five of seven patients. Vigorous complement activation was observed directly after HIV-specific antibody infusions for all patients. The number of infective peripheral blood mono-nuclear cells was reduced in some patients, whereas CD4+ T lymphocyte counts and CD4+/CD8+ ratios were transiently increased in all patients. However, in vitro experiments with isolates obtained from these patients were rather disappointing. Only one virus was neutralized by both hmAbs, five by 2F5 and one by 2G12 alone, showing that de facto an hmAb monotherapy was administered in six out of seven patients. In the two patients whose isolates were susceptible to 2G12 before the first infusion, neutralization escape against 2G12 was found. However, 1 year later, when 2G12 was no longer detectable, reversion of circulating virus to a 2G12-susceptible type was observed. This, on the one hand, demonstrates activity of the hmAb against susceptible strains, but, on the other hand, argues for hmAbs to be administered in combination, similar to HAART. The combination of several antibodies may improve the antiviral efficacy, decrease the required dose and reduce the occurrence of neutralization escape. Antibodies such as 4E10 and IgG1b12 are possible candidates for combination with 2F5 and 2G12. The combination of these four antibodies has been shown to result in synergic activity in vitro. Moreover, 4E10 neutralized all seven and IgG1b12 five of six tested isolates of the 2F5/2G12 Phase I trial.

Over recent years large-scale technologies have been developed and optimized for the production of high amounts of antibodies at reasonable cost. Meanwhile antibodies have become major products in the pipeline of many pharmaceutical and biotech companies. In our pilot plant >1 kg of 2F5, 2G12 and 4E10 has been produced. Studies in larger patient cohorts can now be performed and the final conclusion of whether or not treatment with neutralizing antibodies is beneficial for HIV-1-infected individuals will be drawn within the next 2 years. If passive immune therapy proves to be successful it may be of major benefit for patients. Easy treatment regimens would be possible requiring 1–2 monthly intramuscular or subcutaneous self-administrations only. Treatment of acute and chronic infection with hmAbs alone or in combination with other anti-HIV drugs, and therapy during HAART interruption and in prophylactic settings, such as perinatal and occupational transmission, may then be realistic options.

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