Journal of Clinical Virology 65 (2015) 32–37

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

A single chimpanzee-human neutralizing monoclonal antibody provides post-exposure protection against type 1 and type 2 polioviruses

Diana Kouiavskaia[a], Zhaochun Chen[b], Eugenia Dragunsky[a], Olga Mirochnitchenko[a], Robert Purcell[b], Konstantin Chumakov[a,*]

[a] Center for Biologics Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Building 52, Room 1126, Silver Spring, MD 20993-0002, USA
[b] National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 15 October 2014
Received in revised form 20 January 2015
Accepted 31 January 2015

Keywords:
Polio eradication
Antiviral therapy
Drug-resistance
Chronic virus excretors
Emergency prophylaxis

ABSTRACT

Background: Development of anti-poliovirus therapies to complement vaccination is an urgent priority. A number of antiviral drugs are in development. Recently we have developed human monoclonal antibodies that could be used for treatment of chronically infected individuals and emergency response to potential reappearance of polioviruses after eradication.
Objective: The aim of this study was to characterize neutralizing activity of anti-poliovirus monoclonal antibody A12 against wild type, vaccine-derived, and drug-resistant poliovirus strains, evaluate *in vivo* pre- and post-exposure protective properties of the antibody against polioviruses of serotypes 1 and 2, and to determine whether it interferes with response to immunization with poliovirus vaccine.
Study design: Immunogenicity studies were performed in CD1 mice. Poliovirus neutralizing titers were determined in poliovirus microneutralization assay. Poliovirus immunization-challenge experiments were performed in poliovirus-susceptible TgPVR21 mice.
Results: We show that monoclonal antibody A12 effectively neutralizes *in vitro* a broad range of type 1 and type 2 wild and vaccine-derived polioviruses, provides effective pre- and post-exposure protection of TgPVR21 mice from challenge with a lethal dose of poliovirus. Treatment of animals with the antibody concurrent with IPV immunization does not prevent immune response to the vaccine.
Conclusions: Anti-poliovirus antibody A12 effectively neutralizes a range of wild and VDPV strains and protectstransgenic mice susceptible to poliovirus against lethal challenge upon pre- and post-exposure administration. This suggests that the antibodies could be used in combination with drugs and/or vaccine to improve their efficacy and prevent emergence of resistant variants, and provides a justification for initiating their clinical evaluation.

1. Introduction

1.1. Background

The worldwide polio eradication campaign depends on extensive use of oral poliovirus vaccine (OPV) [1,2] that is highly effective and safe. However, in rare cases it may lead to emergence of vaccine-derived polioviruses (VDPV) that cause paralytic poliomyelitis and establish chronic infection in subjects with primary immunodeficiencies [3–5]. These patients can develop paralysis and persistently excrete virulent poliovirus capable of restarting circulation in poliovirus-free populations. Efforts are underway to develop new tools that could be used along with vaccines to stop circulation of all polioviruses [6] and for emergency response if poliovirus reappears. At least one antiviral drug is now in clinical development, and several other candidates are undergoing preclinical evaluation.

Recently we have isolated hybrid human/chimpanzee monoclonal antibodies (mAb) that are highly active against polioviruses

* Corresponding author at: CBER/FDA, 10903 New Hampshire Avenue, Building 52, Room 1128, Silver Spring, MD 20993-0002, USA. Tel.: +240 402 9440; fax: +301 595 1440.
E-mail address: konstantin.chumakov@fda.hhs.gov (K. Chumakov).

http://dx.doi.org/10.1016/j.jcv.2015.01.023
1386-6532/

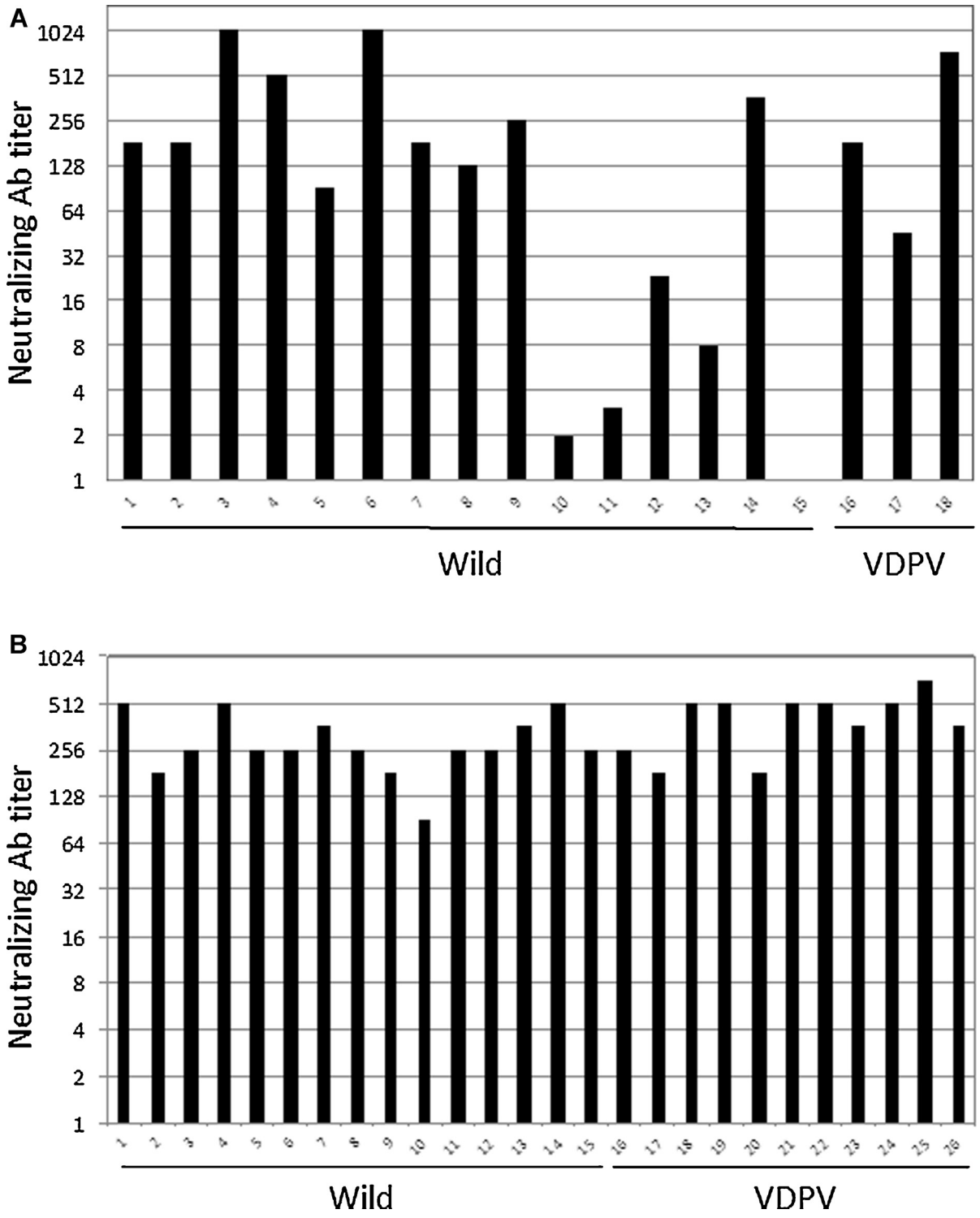

Fig. 1. Neutralization of wild type (WT) and vaccine-derived poliovirus (VDPV) strains by A 12 monoclonal antibody.
A12 (5 μg/ml) was tested in microneutralization assay with either type 1 (A) or type 2 (B) WT and VDPV strains as challenge viruses. Results are expressed as reciprocal neutralization titers against the indicated strains.

of all three serotypes; some of these antibodies neutralize more than one serotype [7]. We have also demonstrated that these antibodies protect TgPVR21 transgenic mice susceptible to poliovirus [8] from a lethal challenge, including post-exposure administration [7]. This suggested that monoclonal antibodies could be used for emergency protection from poliovirus or to treat chronically infected immunodeficient patients.

Treatment with antiviral drugs or monoclonal antibodies can trigger emergence of resistant poliovirus variants [9–11]. Using a combination of drugs and antibodies could prevent the development of resistance. The synergistic effect depends on the mechanism of action of drugs and antibodies. Therefore, several questions need to be answered before such combinations could be evaluated in clinical studies. How broad is the spectrum of