EDITORIALS

Monoclonal Antibody Therapy for Ebola Virus Disease

Myron M. Levine, M.D., D.T.P.H.

Early reports in 1976 and 1995 documented cases in the Democratic Republic of Congo (DRC) of what we now know to be Ebola virus disease (EVD) caused by *Zaire ebolavirus*. The reports showed high case fatality rates and a propensity for transmission to close contacts such as family members caring for ill relatives or health care workers caring for sick patients. The West African *Z. ebolavirus* outbreak of 2013–2016 that resulted in approximately 29,000 cases and about 11,000 deaths showed how extensive transmission can be when the virus is introduced into crowded urban areas. An outbreak of EVD in the DRC that began in 2018 and has continued into 2019 is the second largest EVD outbreak that has been recorded, and once again the case fatality rate is daunting. However, there is some reason for optimism because specific therapeutic tools have been found to reduce the risk of death among persons with EVD.

Mulangu et al. describe a breakthrough in therapy that significantly reduces the high fatality rate of EVD. In the Pamoja Tulinde Maisha (PALM) trial, the results of which are now reported in the *Journal*,[1] patients with confirmed EVD were randomly assigned in 1:1:1:1 ratio to receive the single monoclonal antibody MAb114, the triple monoclonal antibody REGN-EB3, the antiviral drug remdesivir, or the triple monoclonal antibody ZMapp as a control. ZMapp was used as the control because it showed possible efficacy in a clinical trial in West Africa.[2] Randomization was stratified according to baseline viral load, which was determined by reverse-transcriptase–polymerase-chain-reaction assay and expressed as cycle-threshold values (≤22.0 or >22.0, corresponding to higher and lower viral loads, respectively) and according to Ebola treatment center. All patients also received standard supportive care. The primary end point was death at 28 days. After 681 patients had been enrolled in four treatment centers in the provinces of North Kivu and Ituri, the data and safety monitoring board conducted an interim analysis and, on the basis of the results, recommended that no additional patients be assigned to the remdesivir or ZMapp groups because REGN-EB3 and MAb114 showed significantly superior efficacy in preventing death.

There are notable differences between REGN-EB3 and MAb114 in the way they were developed and in their mechanism of action. The three monoclonal antibodies that REGN-EB3 contains (REGN3470, REGN3471, and REGN3479) were obtained by immunizing VelocImmune mice (mice that encode human antibody variable gene segments that generate fully human antibodies).[3,4] The three antibodies in REGN-EB3 bind to distinct nonoverlapping epitopes on the glycoprotein, which potentially increases efficacy and minimizes the occurrence of escape mutants.[4] In contrast, MAb114 was derived from memory B cells from a survivor of the Kikwit EVD epidemic that were obtained 11 years after clinical infection.[5,6] MAb114 binds to a region of conserved amino acids on the receptor-binding domain of the *Z. ebolavirus* glycoprotein and remains bound both in physiologic pH and in low intracellular pH environments, and it averts the glycoprotein from engaging the host cell receptor protein (Niemann–Pick intracellular cholesterol transporter 1 protein [NPC1]) in late endosomes. Targeting of the receptor-binding domain reduces the risk of escape mutants (because the mutants would be less fit), and the neutralizing activity of the monoclonal antibody is high. In the PALM trial, REGN-EB3 was administered as a single intravenous dose of 150 mg per kilogram of body weight, and MAb114 was administered in a single intravenous dose of 50 mg per kilogram. MAb114 and

REGN-EB3 had been shown to reduce mortality among nonhuman primates in controlled challenge studies with *Z. ebolavirus* strains.

The therapeutic effects of these two monoclonal antibody products were sufficiently promising that it is worth exploring the cost, the number of doses that can be manufactured, and the possible target populations for use. The product that would be more suitable for large-scale, economically viable production and the storage requirements and stability over time are unclear. A single monoclonal antibody–based product offers some advantages. It would be desirable to have stockpiles of both products if licensure is obtained for them.

The efficacy of these two agents in reducing the case fatality rate was greater among patients who sought treatment early after symptom onset, who had low viral loads, and who had lower baseline creatinine or alanine aminotransferase levels — that is, these products were more effective in patients who were less severely ill and who were ill for shorter durations. Social engagement with the community can encourage patients to seek care early. But early care of patients also requires the availability of rapid diagnostics and ease of travel to treatment centers.[7] These issues must be addressed in future Ebola outbreaks to enhance the therapeutic effect of the monoclonal antibody products that we hope will be available. How pressing is the need for analogous *Sudan ebolavirus* monoclonal antibody products, and what is in the pipeline?

In total, 74.4% of the patients in the PALM trial were 18 years of age or older, and 55.6% were female; 6.1% of the female patients were pregnant, which provided preliminary safety and efficacy data in this vulnerable population. Moreover, 12.8% of patients were 5 years of age or younger, so the trial yielded some pediatric data.

A laudable feature of this randomized, controlled, clinical trial is that it was performed by investigators from the DRC and international collaborators who worked under difficult conditions in areas of civic disruption and sometimes armed conflict during the second largest Ebola epidemic ever recorded.[8] Dr. Muyembe-Tamfum and colleagues foresaw a potential role for antibodies to treat EVD during the Kikwit outbreak.[9] This latest trial shows unequivocally the role that monoclonal antibodies can play in reducing deaths from EVD. This raises the question of whether monoclonal antibodies could reduce deaths from other viral infections associated with high case fatality and explosive outbreaks, such as severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus.

The year 2019 has been notable for the development of tools to prevent and treat EVD. The European Medicines Agency approved Ervebo, the Ebola vaccine developed by Merck, on the basis of its safety profile and efficacy when used to vaccinate the contacts of persons with EVD in Guinea.[10] The efficacy of MAb114 and REGN-EB3 in the PALM trial in reducing the case fatality rate of EVD opens a potential path toward licensure of these therapeutic agents, once sufficient data are obtained to document their safety and efficacy in target populations, consistency of manufacture, and storage stability.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the University of Maryland School of Medicine, Baltimore.

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