Perspective Piece

When Potentially Lifesaving Drugs are Both Experimental and in Very Short Supply: A Clinician's Story from the Front Lines of the Battle against Ebola

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On the night of July 31, 2014, Kent Brantly, a physician working with Samaritan's Purse (Monrovia, Liberia), received a dose of ZMapp (Mapp Pharmaceuticals, San Diego, CA), an experimental cocktail of three Ebola virus glycoprotein-specific monoclonal antibodies, thus becoming the first patient in the west African Ebola virus disease (EVD) outbreak to receive an experimental therapy. He contracted EVD while working in Liberia and became a patient under the direct care of his SIM (Monrovia, Liberia) and Samaritan's Purse colleagues. Nancy Writebol, a missionary who was also Ebola virus-infected and worked with Brantly at the Eternal Love Winning Africa (ELWA, Monrovia, Liberia) Ebola Treatment Center, was designated to be the sole recipient of ZMapp that night. Brantly had graciously offered to give Writebol the only course of treatment (a full course of treatment is administered in three doses). As one of the physicians overseeing the clinical care of these two patients in Liberia, I examined Brantly and noted his persistent fever, tachypnea, tachycardia, worsening rash, and headache. He was already receiving supportive care including intravenous fluids, antimalarial prophylaxis, and antibiotics per *Médecins Sans Frontières*, Geneva, Switzerland, guidelines. Despite these efforts, over several hours, before the scheduled administration of ZMapp to Writebol, Brantly's condition continued to deteriorate. He was critically ill, and worsening.

My colleagues and I had read the original research articles in which ZMapp conferred a survival benefit in animal models when administered early the course of EVD.¹ However, administering an experimental drug whose safety had not been tested in a human clinical trial was daunting and potentially dangerous. As a vial of ZMapp thawed under Writebol's arm, Lance Plyler, the medical director of the Samaritan's Purse Disaster Response Unit, who was responsible for obtaining ZMapp from Mapp Pharmaceuticals, was preparing to administer the drug to Writebol. We discussed Brantly's condition and, given his rapid deterioration, decided to administer a dose of ZMapp. I drew up a dose of dexamethasone to be used in the event he developed an allergic reaction and set it at his bedside. Informed consent was given, and I started the ZMapp infusion.

I anxiously waited with physician assistant Allison Rolston, watching for an adverse reaction. Rolston had worked tirelessly for days providing care to dozens of EVD patients. I had been wearing heavy personal protective equipment (PPE) for almost 3 hours, and had to step outside. Tim Mosher, a nurse practitioner, donned PPE and moved to the

bedside to monitor Brantly's condition. During Mosher's watch, Brantly developed rigors, which could have been a side effect from ZMapp.

Though both patients survived, infusing an experimental drug that had never been administered to a human being before was not a decision that was made lightly. Knowing the results of trials in animal models, we decided to administer this untested experimental drug with unknown side effects. We were keenly aware of the maxim "do not harm," and knew that our patients could have experienced an adverse reaction, or even died because of the treatment. According to the Federal Drug Administration, the use of an experimental drug under compassionate use is justified when there is "no other comparable or satisfactory alternative therapy to treat the disease or condition" in a seriously ill patient.² As those reading this know, both Writebol and Brantly have made a full recovery. Brantly had treated multiple EVD patients and recognized that his condition was worsening. He later shared that he did not expect to live, especially since at the time, the case fatality rate at ELWA was 79% (unpublished data, Samaritan's Purse).

Though both Brantly and Writebol improved after administration of ZMapp, in the absence of a clinical trial establishing its efficacy, we cannot state that ZMapp was responsible for their recovery. In addition to ZMapp, they received multiple interventions including aggressive fluid replacement, electrolyte repletion, as well as transfusions of blood products.³

In the aftermath of the events described above, multiple media and scientific articles have been published discussing the ethical implications of utilizing a drug that had never been tested in a clinical trial. Still others have expressed concern that Americans received preferential treatment over west Africans stricken by the same disease.

The World Health Organization convened a panel of experts on August 11, 2014, which concluded: "it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention. Ethical criteria must guide the provision of such interventions. These include transparency about all aspects of care, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community."⁴

Sheik Humarr Khan, a physician from Sierra Leone, was one of the world's leading experts in the clinical care of viral hemorrhagic fevers. He had selflessly provided care to Ebola patients, and in the end he succumbed to the disease. After agonizing over whether to provide an experimental drug, the team caring for him ultimately opted not to do so.⁵ It is impossible to know whether this would have altered the course of his illness.

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It is difficult to determine who should be prioritized when a potentially lifesaving therapy exists in limited quantity, especially for an illness with such a high case fatality rate. When investigational agents are scarce, thoughtful selection of participants is essential, especially in an emergency setting. I think all health-care workers who put their lives at risk should be prioritized to receive experimental therapies when in limited quantity because they have put themselves in harm's way for others. Further, they are more likely than others to have an understanding of potential risks and are therefore more able to provide informed consent. Providing an untested treatment has its risks, but I am confident that we are in this case better able than with the average patient to "do no harm" because we trust the consent of the health-care worker. In persons with low health literacy and language barriers, we cannot be assured that a patient understands risks, and so for this group using untested therapies is more difficult. If different decisions were made in the management of Kahn, Brantly, and Writebol, would the outcomes have changed? It is impossible to know. Once heavy clinical management decisions are made, however, the weight of the decision does not necessarily lighten. These life-and-death moments stay with us, and we carry them. We do so on behalf of the Ebola fighters of the world. And we move forward, so as to continue their heroic work in advocating for those facing a most deadly disease.

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