Now for Something Completely Different

Interspersed with my average of 25 daily communications with patients regarding COVID-19, which ballooned to more than 300 emails over the weekend after the CDC recommended additional vaccines to immunosuppressed patients, are the occasional patients I see with something different. Two of the interesting patients I saw this past week made me wonder about ways to intervene that might be preferable to our current standard of care. The first patient had red cell aplasia due to parvovirus, and the second patient had progressive multifocal leukoencephalopathy (PML). The commonality of these two cases is that both diseases are rare, and both are caused by very common viruses. Regarding outcomes, they represent the two ends of the spectrum.

Whereas antibodies to parvovirus B19 are found in approximately 90% of blood donors older than 61 years (Tsujimura M. *Vox Sang*. 1995), the incidence of hydrops fetalis due to parvovirus is quite low, estimated at 0.003% (Gratacos E. *J Infect Dis*. 1995). Similarly, the incidence of aplastic crisis due to parvovirus in patients who are immunocompromised or dependent on increased red cell turnover is small. Thus, parvovirus infection is a common infection with extremely rare consequences.

Similarly, antibodies to the JC virus are found in approximately 50% to 80% of adults (Khalili K. *Neurology*. 2007). The JC virus typically establishes a latent infection in the kidneys, with immunosuppression allowing reactivation and viral replication that results in brain infection and PML. Before the HIV epidemic, more than 60% of cases of PML were seen in patients with lymphoproliferative disorders. The risk for PML in patients with a hematologic malignancy is estimated to be 0.07%; the highest incidence is in patients with CLL (0.5%).

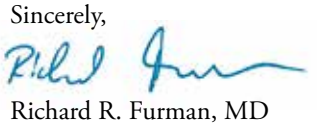
Currently established treatments for my two patients include IVIG for the one with aplastic anemia and nothing for the one with PML. The first patient will recover, resume her chemotherapy, and do well. The second patient will progressively worsen and succumb to her disease. Both of these diseases are caused by a virus whose structures and biology are well-known. The necessary components of a humoral immune response (such as epitopes to target) to control these diseases are also well known. The tour de force that Eli Lilly and Regeneron achieved in developing effective monoclonal antibodies to SARS-CoV-2 in such a short time made me wonder why we could not do the same for parvovirus and JC infections.

One could argue that we already have an effective therapy for parvovirus in the form of IVIG. But IVIG is becoming increasingly scarce and is extremely expensive, with one treatment costing approximately $15,000. Wouldn't it be great just to take a lyophilized vial from the shelf, reconstitute it, and treat the patient successfully? In the case of the JC virus, for which no effective therapy is currently available but several extremely costly therapies are under investigation, including virus-specific T-cell therapies, the need for anti-JC monoclonal antibodies is more obvious.

So what are the obstacles? The rarity of these conditions limits the profitability of any commercial venture. The development of SARS-CoV-2 monoclonal antibodies sheds some light on this situation. The global reach of COVID-19 and its effect on society made the rapid development of therapeutics a must. Cooperation between governments and pharmaceutical companies provided resources and funding. We now have two monoclonal preparations to treat SARS-CoV-2 infections. With the US Government underwriting 80% of the costs for the development of the antibody cocktail REGN-CoV2, Doctors Without Borders states on its website that Regeneron should be allowed to charge no more than the production cost, which is $240 for one course of the treatment.

Could this be a model for parvovirus and JC virus therapeutics? Unlike in the case of SARS-CoV-2, we already have much of the research completed. We know the epitopes to target and have ample ability to generate monoclonal antibodies. Most of the costs associated with drug development are related to running clinical trials, regulatory oversight, and FDA filings. The FDA and the US Department of Health and Human Services could partner with the goal of lessening the regulatory hurdles and helping the development of treatments for these rare diseases. Trials could be conducted through NIH-sponsored groups (which already work for free). Subcontracting, often a four-letter word, could be undertaken to produce and distribute these materials. It actually sounds a lot like the current military-industrial complex, doesn't it? I bet we could do this inexpensively and successfully, and so provide a tremendous number of new therapeutics that could markedly improve patient care. How is that for something different?

Sincerely,



Richard R. Furman, MD