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EDITORIAL

View from inside: Rare diseases in the times of COVID19

Over 10 million infected and nearly 250 000 dead. In the context of a pandemic, life and death in rare disease patients may seem like a small matter. But it is not. Matthew (I have his parents' permission to share his story) was born with mitochondrial beta-oxidation trifunctional protein (TFP) deficiency over 24 years ago. This defect impairs the body's ability to generate cellular energy with devastating consequences. Still a relatively new disorder, its newborn and early infancy implications would have portended an early death for Matthew prior to newborn screening. But it did not. The family, aware of an experimental medication in development for TFP and other long chain fatty oxidation disorders, fought for their son. Traveling halfway across the country to enroll in a study, he was treated with the medication and survived.[1] But it was more than survival. He thrived.

I first met Matthew nearly 10 years ago when I took over leadership of the development program for triheptanoin.[2] (That is a polite euphemism for "I was suddenly responsible for caring for over two dozen patients on an experimental drug with no financial resources and an uncertain supply; not to mention no experience in moving a drug to FDA approval!"). His family rolled into the exam room not so much participating in a study visit, but enveloping the study team with the vibrant life that they had willed for Matthew. It was a roiling circus of a meeting that immediately made it clear that there was no room to feel sorry for him or talk about limitations related to his disease. Rather, we had no choice but to revel in their adventures and rejoice in the energy that a mother, father, brother, and sister could bring to assure that Matthew would not feel the limitations of his disease, but the possibilities that come with a second chance. Baseball games, vacation cruises, and yes, even road trips to Pittsburgh for twice a year study visits. It was patients such as Matthew and their families that ultimately led me to overcome whatever hesitation I had to take on the challenge of drug development; just sort out the means to an end to bring a drug to approval. On 30 June 2020, the dream of Matthew and many other patients with long chain fatty acid oxidation disorders was realized as triheptanoin, newly christened as Doljovi®, was approved by the FDA as the first medication to treat long chain fatty acid oxidation disorders.[3,4] A celebration was in order! Patients, families, their long-time care providers, and even our study team saw it as a time to bask in the glow of a job accomplished and turn to the future of a new beginning. Except it was not.

Shortly after the approval, Matthew took ill. There was nothing to distinguish it from the countless other minor illnesses that he had beaten over the years. However, his respiratory symptoms worsened, and he ended up needing ventilator support due to a pneumonia of undetermined origin. The obvious specter of COVID-19 loomed over him, then was dispelled as his testing was negative. Serologic titers for Lyme disease returned positive and he was treated for it. He even improved for a while, though a tracheostomy was necessary to help him better manage his airway and allow continued respiratory support. Then his heart started to fail, and, in the end, just gave out. Why? Why after a battle of 24 years and a future bolstered by a medication that he very much helped develop did this illness end differently from all of his others? How could the miracle of modern medicine fail him, not provide sufficient support for his body to heal itself the way it had so many times before? How could I have failed his family? They brought an endless supply of emotional energy to supplant the ATP that Matthew's body could not make; and all of the understanding gained by studying him and others like him was not enough to allow me to give him the long life he deserved. A dose of reality amid the celebration of a nominal success; a splash of cold water in the face; an unnecessary reminder to me that much work remains to be done; another name added to a list that includes too many other patients with rare diseases.

I do not know how to process 6 million patients affected in a pandemic, or to console >260 000 souls taken by a disease that is as indiscriminate as it is deadly. I do know that every patient with a rare disease very much has his or her own story, and it is as compelling to them and their family as a pandemic is to a nation. Paradoxically, many such patients have done better than usual due to reduced exposures resulting from COVID precautions. Matthew was not one of the lucky ones. While his life is over, his life story will never end. It will be carried on by friends and families who will remember

him not as a patient with TFP deficiency, but a vibrant young man who beat the odds and accomplished much in the years that were given to him. It will live on in every patient whose care is improved by the determination he creates in those looking for more tools to fight rare disease. It will be with me in every patient for whom I care, in every experiment I perform, no matter how seemingly small, to bring new therapies for rare diseases to light. I owe Matthew this much. We owe all patients with rare diseases as much as we can give, even in a pandemic.

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