frontiers in
PUBLIC HEALTH

OPINION ARTICLE
published: 13 November 2013
doi: 10.3389/fpubh.2013.00054

Expanded access for a little boy

John Franklyn Riefler*

ICON Clinical Research, North Wales, PA, USA
**Correspondence: riefler@msn.com*

Edited by:
Evangelos Giamarellos-Bourboulis, University of Athens Medical School, Greece

Keywords: expanded access, compassionate use, pythiosis, orbital cellulitis, lamisil

The following case contains my comments and not those of Sandoz. My team submitted the New Drug Application (NDA) for LAMIISIL®, terbinafine Oral for onychomycosis, fungal infection of toenails and fingernails. We showed efficacy and safety in all six pivotal studies. The FDA granted approval for this indication in adults.

While working on new indications for LAMISIL®, I received a call from Dr. Jerry Shenep at St. Jude's Hospital. A 2-year-old boy was admitted to his hospital with periorbital cellulitis and fever. This child splashed his face with muddy water while playing in a puddle. Physical examination showed swelling, erythema, and tenderness of the left periorbital area. CT of the face revealed left preseptal cellulitis with left maxillary opacification. He received intravenous cefotaxime for a presumed bacterial cellulitis. The infection spread to the nose and throat and compromised the airway. A surgical biopsy specimen grew *Pythium insidiosum*, an invasive water mold, sensitive only to itraconazole and terbinafine. Itraconazole did not slow progression of the disease. *In vitro* testing showed synergy of the two antifungal agents. Consequently, Dr. Shenep pleaded with me to provide terbinafine on compassionate use basis, because it was this child's only hope. Progression of disease may result in cavernous sinus thrombosis, meningitis, and death.

Expanded access, also known as "compassionate use," provides an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options. FDA has a Guidance Document on Expanded Access that explains the requirements (1).

I admired Dr. Shenep's passion and persistence and wanted to help, but we faced several issues. First, we had not conducted pediatric clinical trials with terbinafine. In addition, we did not have an expanded access protocol in place.

At this time, one case of human pythiosis was reported in North America (2), involving a child with a similar presentation to this child. Extensive surgical debridement was required to control the infection.

Pythium species other than *insidiosum* infect plants. In1884, pythiosis was reported in horses by an Indian veterinarian (3). He recognized that inoculation of infected tissue could transmit disease to healthy animals. *P. insidiosum* is the only species that causes infection in horses, dogs, and rarely in humans. Infection spreads through breaks in the skin via contact with water that contains motile zoospores or hyphae. Depending on the entry site, infection can lead to cutaneous, vascular, ocular, gastrointestinal, or rarely systemic infection. A devastating disease, cure of invasive infections in humans usually requires surgical debridement. Successful therapy in animals has not been reported; consequently, horses with this infection usually are destroyed.

As of 1996, 28 cases of human pythiosis had been published. Twenty three patients came from Thailand, almost all had thalassemia (4).

In humans, the few reported cases involving Pythium include arterial infections and cellulitis. Virgile et al. reported the first case of *P. insidiosum* isolated from a human corneal ulcer (5). Since the organism is resistant to standard antifungal drugs, surgical excision is the treatment choice for corneal infection.

Fortunately, my boss, a pediatric infectious diseases specialist agreed with me to help Dr. Shenep's patient. He calculated this child needed a dose of 125 mg twice daily. My Senior CRA called our supply group and we shipped drug overnight. I wrote an expanded access protocol that covered this request to treat this child and informed FDA. At least, I could sleep at night knowing we tried to help this child. I had two young children and would have wanted someone to help them. A month went by. I called Dr. Shenep and inquired about the child's progress? Miraculous to relate, he said "fine." After 1 year of treatment with both antifungals, the child only had a slight left facial droop. Dr. Shenep reported the case (6) and he and I became friends.

Dr. Shenep's request for compassionate use LAMISIL® was important for several reasons: it showed that cure of invasive *P. insidiosum* could be achieved with combination antifungal therapy; in addition, it was a "proof of concept" for expanded access. Sadly, Dr. Shenep passed away, but his good work carries on through the expanded access program. I thank him for his persistence and the lesson he taught me.

ACKNOWLEDGMENTS

I would like to acknowledge my colleagues at Sandoz. There is no funding organization.

REFERENCES

1. FDA DRAFT Guidance for Industry. *Expanded Access to Investigational Drugs for Treatment Use – Qs & As.* Rockville, MD: Food and Drug Administration (2013).
2. Rinaldi MG, Seidenfeld SM, Fotherbell AM, McGough DA. *Pythium insidiosum* causes severe disease in a healthy boy. *Mycol Observ* (1989) **9**:7–8.
3. Smith F. The pathology of bursattee. *Vet J* (1884) **19**:16–7.
4. Thianprasit M, Chaiprasert A, Imwidthaya P. Human pythiosis. *Curr Top Med Mycol* (1996) **7**(1):43–54.
5. Virgile R, Perry HD, Pardanani B, Szabo K, Rahn EK, Stone J, et al. Human infectious corneal ulcer caused by *Pythium insidiosum. Cornea* (1993) **12**(1):81–3. doi: 10.1097/00003226-199301000-00015
6. Shenep JL, English BK, Kaufman L, Pearson TA, Thompson JW, Kaufman RA, et al. Successful medical therapy for deeply invasive facial infection due to *Pythium insidiosum* in a child. *Clin Infect Dis* (1998) **27**(6):1388–93. doi: 10.1086/515042

Received: 02 August 2013; accepted: 11 August 2013; published online: 13 November 2013.
Citation: Riefler JF (2013) Expanded access for a little boy. Front. Public Health ***1****:54. doi: 10.3389/fpubh.2013.00054*
This article was submitted to Infectious Diseases, a section of the journal Frontiers in Public Health.