



## Hereditary angioedema: implications of treating a rare disease

We applaud the recent survey by Riedl et al<sup>1</sup> demonstrating that many allergists are unfamiliar with the new therapeutic agents recently approved for hereditary angioedema (HAE). Today is probably the most fortuitous time to be an HAE patient. Five new therapies either have been approved or are in development for HAE, an orphan disease for which we have had few treatments to offer our patients.

Safe and effective therapy for HAE was not readily available in the United States until recently. One of us introduced androgens for the prophylaxis of attacks in 1976 and noted that the drug was not effective or appropriate in all subjects and that it had no utility as acute therapy.<sup>2</sup> He further reported in 1980 that C1 inhibitor (C1 INH) was effective in terminating attacks<sup>3</sup> and in 1996 demonstrated its efficacy in treating and preventing attacks.<sup>4</sup> Two separate European manufacturers independently developed C1 INH, and it has been available in Europe for over 2 decades. However, in the absence of financial incentives and with FDA's clear requirement that double-blind placebo-controlled studies be performed before approval, these therapies were not introduced in the United States. In fact, before 2009 there were no safe and effective drugs available to treat and prevent HAE attacks in the United States. Patients suffered greatly, and some died.

The new HAE therapies have led to questions regarding therapeutic options and economic considerations.<sup>5</sup> In our experience, decisions regarding prophylaxis or on-demand therapy are patient specific. Quality of life and severity of attack are as clinically meaningful as attack frequency.<sup>6</sup> Each HAE patient is unique; some HAE patients respond more beneficially to certain drugs than others. We have much to learn about the clinical variability and patient-specific factors associated with HAE, and multiple therapies may foster better patient care through the individualization of therapy for each of our patients.

Therapies for orphan diseases are expensive. Currently at least 9 orphan drugs cost more than \$200,000 dollars per year<sup>7</sup>;

among these are treatments for HAE. The 1983 Orphan Drug Act grants time-limited market exclusivity, spurring clinical drug development. Toward that end drug manufacturers make substantial investments and assume significant regulatory and clinical risks in advancing treatments for orphan conditions. Globally, the investment in HAE therapies may exceed \$1.5 billion. The federal government does not have the infrastructure to develop such medications. Without the ability to recoup and profit on their investment, pharmaceutical companies would not develop these drugs, and orphan diseases would go untreated, as was the situation with HAE. To this point, there are 7,000 orphan diseases and only 350 approved therapies. Importantly, ongoing investment in medical education and robust patient assistance programs specifically promote disease awareness and provide access to medications for all patients, regardless of ability to pay. Society, as well as physicians, must recognize the expense associated with drug development if therapeutic advances in HAE and other orphan diseases are to progress and benefit our patients.

The cost dilemma of HAE and other orphan disease therapies is difficult to resolve, and many would assert that such treatment of illness is simply the right thing to do. These are difficult ethical and societal questions, not unlike spending 50 to 60% of a person's total health care dollars during the last 6 to 12 months of life; or providing advanced medical care for children with irreversible neurological damage. No definitive metric can justify the annual spending of hundreds of thousands of dollars to save or normalize a single human life. HAE patients have historically been hospitalized for days to weeks annually at great financial, psychological, and social expense.<sup>8</sup> The new therapeutic agents have changed the lives of thousands of HAE patients, freeing them to pursue educational and professional goals, travel, and vastly improve the quality of their lives. These therapies have been "life altering," in the words of clinicians and patients alike.

We are concerned that cost may limit patient access to these effective medications either because physicians are hesitant to prescribe or payers devise ways to limit coverage. Certainly the health care system can be improved. Evidenced-based medicine, tort reform, and limitations on drug spending are valuable tools in this effort. However, targeting orphan conditions and placing at risk the lives and well-being of the small number of patients who suffer from rare genetic diseases is a particularly unpalatable response.

**Disclosures:** Dr Kalfus is a Consultant to ViroPharma, Thar Pharmaceutical, and RedHill Biopharma. Former VP of Medical Affairs at Lev Pharmaceuticals responsible for the clinical development of Cinryze; Dr Gower has received research grants from ViroPharma, Shire, Pharming, CSL Behring. Speaker bureaus: ViroPharma, Shire, CSL Behring. Advisory boards: ViroPharma, Shire, CSL Behring; Dr Riedl receives support from CSL Behring, Dyax, Shire, Pharming, ViroPharma; Dr Bernstein receives support from ViroPharma, CSL Behring, Dyax, Shire, Pharming; Consulting: ViroPharma, CSL Behring, Dyax, Shire; Speaking: ViroPharma, CSL Behring, Dyax, and Shire. Also co-editor of Joint Task Force Practice Parameter on Angioedema and on Medical Advisory Board of HAEA organization; Dr Lumry is a consultant for Alcon Laboratories, CSL Behring, Dyax, Genentech, Merck, Novartis, Shire, and Viropharma Pharmaceuticals, receives support from Apotex, Alcon Laboratories, Biotest, Boehringer Ingelheim, CSL Behring, Dyax, Genentech, GlaxoSmithKline, Green Cross, Merck, NIH, Novartis, Pharming, Roxanne, Shire, Teva Pharmaceuticals, and Viropharma. He serves on a Speaker's Bureau for Alcon Laboratories, CSL Behring, Dyax, Genentech, Merck, Novartis, and Viropharma. Dr Frank serves on the Consultant or Advisory Board for ViroPharma, Shire, Pharming, CSL Behring, and Dyax.

Ira N. Kalfus, MD\*  
 Richard Glen Gower, MD†  
 Marc Riedl, MD‡  
 Jonathan A. Bernstein, MD§  
 William R. Lumry, MD||¶  
 Michael M. Frank, MD#

\*M2G Consulting  
New York City, New York

†University of Washington  
Seattle, Washington

‡UCLA – David Geffen School of Medicine  
Los Angeles, California

§Department of Medicine  
University of Cincinnati College of Medicine  
Cincinnati, Ohio

||University of Cincinnati College of Medicine  
Cincinnati, Ohio

¶University of Texas Southwestern Medical School  
Dallas, Texas

#Duke University Medical Center  
Durham, North Carolina  
ikalfus@aol.com

## References

- [1] Riedl M, Gower RG, Chrvala CA. Current medical management of hereditary angioedema: results from a large survey of US physicians. *Ann Allergy Asthma Immunol.* 2011;106:316–322.
- [2] Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. *N Engl J Med.* 1976;295:1444–1448.
- [3] Gader JA, Hosea SW, Gelfand JA, et al. Replacement therapy in hereditary angioedema. *N Engl J Med.* 1980;302:542–546.
- [4] Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med.* 1996;334:1630–1634.
- [5] Tilles S, Borish L. A new generation of hereditary angioedema treatments: remarkable advances clash with disturbing economic reality. *Ann Allergy Asthma Immunol.* 2011;106:264–266.
- [6] Craig T, Riedl M, Dykewics MS, et al. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol.* 2009;102:366–372.
- [7] Herper M. The world's most expensive drugs. *Forbes.com.* 02:22:10.
- [8] Wilson DA, Bork K, Shea EP, et al. Economic costs associated with acute attacks and long term management of hereditary angioedema. *Ann Allergy Asthma Immunol.* 2010;104:314–320.