

Pharmacoeconomics of Orphan Disease Treatment with a Focus on Hereditary Angioedema



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KEYWORDS

- Pharmacoeconomics • Orphan disease • Hereditary angioedema • Burden • Treatment

KEY POINTS

- Orphan diseases affect 1 in 10 individuals.
- Legislation has been successful in encouraging development of orphan disease therapies but barriers to their availability exist.
- Expenditures on orphan drugs are less than 10% of pharmaceutical expenditures and 1% of total health care costs.
- Patients with hereditary angioedema have benefited greatly from approval of novel disease-specific therapies.
- Availability of and access to these new therapies is a challenge for patients, families, and health care providers.

OVERVIEW

Hereditary angioedema (HAE) is a rare autosomal dominantly transmitted genetic disease.^{1,2} It occurs in approximately 1 out of 30,000 to 80,000 individuals and affects fewer than 8000 individuals in the United States, 15,000 in North America, and 200,000 worldwide.^{3,4} Although available in other countries since 1979,⁵ disease-specific therapy for HAE only recently became available in the United States and North America. With the US Food and Drug Administration (FDA) approval of a human

Disclosure Statement: Dr W.R. Lumry has received clinical research grants from and serves as a consultant and advisor to BioCryst, CSL Behring, Pharming, and Shire. He provides educational programs for Pharming, CSL Behring, and Shire. He is a member of the Medical Advisory Board for the US Hereditary Angioedema Association.

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Immunol Allergy Clin N Am 37 (2017) 617–628

<http://dx.doi.org/10.1016/j.iac.2017.03.004>

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nanofiltered plasma-derived C1 inhibitor (C1INH) concentrate for routine prophylaxis of HAE attacks on October 10, 2008, a new era in therapy for HAE began.⁶ Since 2008, 4 therapies to treat HAE attacks have received FDA approval, including a pasteurized human plasma-derived C1INH and ecallantide in 2009, icatibant in 2011, and a recombinant C1INH in 2014. These therapies are currently registered in many countries around the world (**Table 1**). (See Meng Chen and Marc Riedl's article, "Emerging Therapies in Hereditary Angioedema", in this issue.)

This burst of development and approvals has greatly benefited individuals with HAE, their families, caregivers, physicians, and health care providers.^{12,13} The burden of HAE has been reduced; quality of life improved; and utilization of urgent care, emergency facilities, and hospitals decreased significantly.^{14,15} Concerns have been raised, however, by health care payers in the United States and health care systems in other countries about the financial impact of these newly approved therapies on health care payment systems.^{16–19} These concerns have led to barriers to and limitation of access to these potentially life-changing and lifesaving therapies.^{16,17,20}

This article discusses the prevalence of orphan diseases, legislative incentives to encourage development of orphan disease therapies, and the impact of orphan disease treatment on health care payment systems. More specifically, the cost burden of HAE on patients, health care systems, and society is reviewed. The impact of availability of and access to novel and specific therapies on morbidity, mortality, and the overall burden of disease is explored. Changes in the treatment paradigms to improve effectiveness and reduce cost of treatment are presented.

ORPHAN DRUG DEVELOPMENT POLICIES AND REIMBURSEMENT ISSUES

Orphan drug policies have been established in the United States, the European Union (EU), and Japan to encourage the development of safe and effective therapies for rare diseases. The US Orphan Drug Act was enacted in 1983.²¹ Under this act, a drug is given orphan designation if the disease it treats affects fewer than 200,000 individuals or if there is no reasonable expectation of profitability for the drug. Some of the incentives provided include tax credits for research costs, grants to aid in clinical research, and a 7-year marketing exclusivity for approved orphan drugs.

In 1999, the EU enacted its orphan drug policy that defines an orphan disease as a disease with 5 patients per 100,000 individuals. Research incentives are available within the EU and its member states and fees are waived for approval of the marketing application. Approved orphan drugs in the EU are given a 10-year marketing exclusivity.²²

These policies have been successful in incentivizing companies to research and develop therapies for a wide variety of rare conditions. Before the passage of the orphan drug policies, orphan disease therapies were often neglected by pharmaceutical companies. In January, 1983, there were 38 drugs approved in the United States for orphan disorders.²³ In December 2016, 588 approved drugs are listed in the Orphan Disease Therapeutic Registry²⁴ and 86 designated orphan drugs approved for marketing in the EU.²⁵

PREVALENCE OF ORPHAN DISEASES

There are 25 to 30 million individuals, 8% to 10% of the population of the United States, affected by 1 of the 7000 diseases designated as orphan diseases who may benefit from provisions of the Orphan Drug Act.^{16,23} Treatments for these rare diseases have provided great benefits to affected individuals and their families. The high cost of many of these therapies has led to the perception by payers and society in general that treatment of orphan diseases places an inordinate burden on the health

care payment systems.^{16,17} This concern about excess costs of this treatment has resulted in barriers being put in place to limit access. Some of these barriers include formulary approval, high coinsurance and copayment rates, prior authorization and multiple reauthorizations, step therapy, and limits on supply and resupply of medication.^{16,17,20}

Drug research and development are time-consuming and expensive propositions. The total average cost of developing and winning market approval for a new prescription drug was recently estimated to be \$2.6 billion, with \$1.4 billion of this amount spent on research and development.^{26,27} Orphan drugs are no exception. With many fewer patients to treat, the cost to recover research and development expenditures may be high per patient treated. In 2014, the average (median) drug costs per patient per year in the United States for treatment of conditions that were not orphan was \$23,331(\$4775) compared with \$111,820 (\$66,057) per the patient treated for an orphan disease.²³

Although the cost per patient to treat an orphan disease is often high, the perception that cost of treatment of rare diseases as a whole has an inordinate impact on total pharmaceutical expenditures and health care costs is inaccurate. Analyses in the United States and the EU have shown this impact is minimal and in line with the 8% to 10% prevalence of these diseases in the population. In 2014, total expenditures for pharmaceuticals in the United States accounted for 9.8% of total health care costs of \$3.0 trillion. Expenditures on orphan drugs for orphan indications was approximately \$33.5 billion, representing less than 10% of pharmaceutical expenditures and 1% of the total health care expenditures.^{23,28}

Despite this discrepancy between the number of drugs approved in the US and the EU, the percentage of pharmaceutical expenditures for orphan drugs in the EU was similar to the United States. Orphan drug expenditures in 17 European countries in 2011 were 3.3% of total pharmaceutical expenditures.²⁹ More specifically, spending was 2.5% in Sweden and 3.1% in France in 2012,³⁰ and 4.2% in the Netherlands in 2014.³¹

Orphan drug expenditures have been increasing over the last decade. In part, this is due to the increasing number of therapies registered and approved. In 2007, \$13.3 billion was spent in the United States, accounting for 4.3% of \$311 billion total expenditures for pharmaceuticals that year. By 2013, this increased to \$25.8 billion, 7.7% of \$337 billion spent. IMS Health's market prognosis has forecasted US total drug expenditures of \$465.0 billion in 2018, with orphan drugs accounting for \$44.10 billion; 9.5% of this amount represents an increase of 0.7% over 4 years.^{28,32}

IMPACT OF NEW THERAPIES FOR HEREDITARY ANGIOEDEMA

Patients with HAE have benefited from approval of novel, disease-specific drugs that treat and prevent swelling attacks. The benefits include improvement in health and quality of life, increased ability to work and pursue educational and career goals, reduced disability, reduction of costly urgent care visits and hospitalizations, and longer survival.^{12–14,33} The development of these drugs was made economically feasible by the orphan drug policies in the United States and the EU.

The cost of these therapies is high. In 2012, the cost of nanofiltered C1INH, Cinryze (Shire, Lexington, MA, USA) indicated for routine prophylaxis of HAE attacks when used at approved dosage and interval was \$487,000 per patient, the most expensive drug for any orphan disease treated in the United States.³⁴ In 2015, sales of Cinryze generated the second highest revenue to a pharmaceutical company, \$210,000 per patient treated, of all orphan drugs in the United States.²³ Current average wholesale

Table 1
Availability of specific treatments for hereditary angioedema across the world in 2017

Drug	Registration	Indication				Age Groups		Route
		Acute Treatment	Prophylaxis		Home-Therapy	Children <12 y	Adolescence 12–18 y	
pdC1NH (Berinert) ⁷	EU	✓	✓	—	✓	✓	✓	IV
	US	✓	—	—	✓	✓	✓	
	Latin America (Brazil, Argentina, Mexico, Colombia, Chile, Puerto Rico)	✓	✓	—	✓	✓	✓	IV
	Australia, Canada	✓	✓	—	✓	—	✓	IV
	Israel	✓	✓	—	✓	✓	✓	IV
	Japan	✓	✓	—	✓	—	✓	IV
	South Korea	✓	✓	—	✓	✓	✓	IV
rhC1INH (Ruconest) ⁸	EU	✓	—	—	—	—	—	IV
	US	✓	—	—	✓	—	✓	
pdC1INH (Cinryze) ⁹	EU	✓	✓	✓	✓	—	✓	IV
	US	—	—	✓	✓	—	✓	
	Australia, Canada, Israel	✓	✓	✓	✓	—	—	IV
Icatibant (Firazyr) ¹⁰	EU	✓	—	—	✓	—	—	SC
	US	✓	—	—	✓	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	✓	—	—	✓	—	—	SC
	Australia, Canada	✓	—	—	✓	—	—	SC
	Israel, Kuwait, South Africa	✓	—	—	✓	—	—	SC
Ecallantide (Kalbitor) ¹¹	EU	—	—	—	—	—	—	SC
	US	✓	—	—	—	—	✓	
Attenuated Androgens	EU	—	✓	✓	✓	—	✓	Oral
	US	—	—	✓	✓	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	✓	—	—	✓	—	—	Oral

Transexamic Acid	EU	—	✓	✓	—	✓	✓	Oral
	US	—	—	—	—	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	✓	—	—	✓	—	—	Oral
Epsilon Amino Caproic Acid	EU	—	—	—	—	—	—	Oral
	US	—	—	—	—	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	—	—	—	—	—	—	Oral
Icatibant (Firazyr) ¹⁰	EU	✓	—	—	✓	—	—	SC
	US	✓	—	—	✓	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	✓	—	—	✓	—	—	SC
	Australia	✓	—	—	✓	—	—	SC
	Canada	✓	—	—	✓	—	—	SC
	Israel	✓	—	—	✓	—	—	SC
	Kuwait	✓	—	—	✓	—	—	SC
	South Africa	✓	—	—	✓	—	—	SC
Ecallantide (Kalbitor) ¹¹	EU	—	—	—	—	—	—	SC
	US	✓	—	—	—	—	✓	
	Latin America (Brazil, Argentina, Mexico, Colombia)	—	—	—	—	—	—	IV
Attenuated Androgens	EU	—	✓	✓	✓	—	✓	Oral
	US	—	—	✓	✓	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	✓	—	—	✓	—	—	Oral
Transexamic Acid	EU	—	✓	✓	—	✓	✓	Oral
	US	—	—	—	—	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	✓	—	—	✓	—	—	Oral
Epsilon Amino Caproic Acid	EU	—	—	—	—	✓	✓	Oral
	US	—	—	—	—	—	—	
	Latin America (Brazil, Argentina, Mexico, Colombia)	—	—	—	—	—	—	Oral

Abbreviations: IV, intravenous; LTP, Long term (routine) prophylaxis; SC, subcutaneous; STP, Short term prophylaxis.

prices for treatments of acute attacks range from \$5000 to more than \$10,000 per attack treated. The cost of these therapies is generally lower outside of the United States, with some national health systems able to acquire them at a significant discount to United States prices.

The cost of not adequately treating HAE is also high. These costs include not only the direct cost of providing medical care to these patients but also the indirect cost of the disease on patients, their family, and on society. Patients with HAE consume more health care and are more costly to the health care system, even if the costs of the newer medications are not included. In a United Kingdom (UK) study, the cost of care for a patient was 160% for primary care and 447% for secondary care, even if the costs of specialist care and medications were excluded.³⁵ Patients with HAE and their caregivers miss a significant amount of time from work and school, are often less productive at work, and may be unable to achieve their educational and career goals, or even maintain employment, as a result of their attacks.^{33,36}

COST OF HEREDITARY ANGIOEDEMA CARE BEFORE 2008 IN THE UNITED STATES

Disease-specific therapies for HAE were not available in the United States before 2008. This provides an opportunity to review costs and impact of the disease before current therapies became available. An Internet survey completed by members of the US Hereditary Angioedema Association (HAEA) in 2007 found that patients experienced an average of 26.9 swelling attacks per year, lasting 61.3 hours each. More than 80% were considered moderate to severe in intensity.³⁶ Total annual cost of having and treating HAE was also assessed in this survey.³⁷ The average annual cost per patient was \$44,597. Cost varied depending on the severity of the disease, ranging from \$11,587 for mildly affected patients to \$28,764 and \$104,857, respectively, for those moderately or severely affected. The total mean annual expenditure per HAE patient of \$44,597 included direct medical costs of \$29,177, which comprised \$17,381 for hospital admissions, \$2827 for emergency department (ED) visits, \$3777 for outpatient care, and \$5194 for medications; and indirect costs of \$15,420, including \$5157 for reduced productivity, \$6417 for reduced income, \$3402 for missed work, and \$4444 for travel and childcare.³⁷ Accounting for inflation, the average annual cost per patient in 2016 dollars would be \$62,440.

ED usage and hospitalization before 2008 was high because only supportive treatment was available, including intravenous fluids, antiemetics, analgesics, and airway support. In 2007, there were 2705 ED visits with HAE as the primary diagnosis, with 40.9% resulting in hospitalization. At a mean cost of \$1479 per ED visit, \$3,727,080 was spent in the United States for urgent care.³⁸ Between 2004 and 2007, there were 10,125 hospitalizations in which HAE was the primary or secondary diagnosis. The average length of stay was 5.1 days and the average cost per hospitalization was \$8383, resulting in \$21,220,000 annual expenditure for hospital services.³⁹

BURDEN OF DISEASE

In addition to the direct cost of care, indirect costs must be considered. Missed time from work or school, decreased productivity at work, and loss of opportunity are significant costs to the patient and society. Patients report a decrease of productivity at the job due to HAE.³⁷ A national audit in the UK of patients with HAE and acquired angioedema revealed that patients lost on average 9 days of work per year, ranging from 0 to 43 days.⁴⁰ An EU study of the socioeconomic burden of HAE revealed both patients and caregivers were affected, with each losing an average of 20 days from work or school per year.^{33,41}

Loss of educational and career opportunity is commonly reported. In the HAEA survey conducted in 2007, 57% of HAE patients reported having career advancement hindered, 69% thought that they could not consider certain types of jobs because of their disease, 100% thought that educational advancement had been hindered, 55% had to limit their educational choices, and 48% had not achieved the level of education that they desired.³⁶ Even after disease-specific therapies became available, decreased opportunity is still a problem. In the EU socioeconomic burden of disease report published in 2014 after current therapies became available, 42% patients reported their educational advancement was hindered, 40% were prevented from applying for certain jobs, 36% thought that their career advancement was diminished, 9% switched positions within their company, and 10% left their position permanently because of this disabling disease.³³ HAE patients also suffer from anxiety and depression at much higher rates than the normal population. Results from 2 independent studies suggest that between 14% and 43% of patients of HAE experience clinically significant depression, further adding to their disability.^{36,42}

A fatal HAE attack with loss of an individual from both the work force and society is the ultimate burden of this disease, and results in significant hardship both socially and economically to the patient's family and society. Unfortunately, patients with HAE continue to succumb to this treatable disease. In a review of all US death certificates from 1999 to 2010, HAE was considered a contributing factor or the underlying cause of death in 600 people, with 270 of these deaths directly attributed to HAE.⁴³ In a German study that included 728 subjects from 182 families with HAE type I and type II, 214 deaths were recorded. The mean age of death from an HAE attack was 40.6 years.⁴⁴

INNOVATIVE TREATMENT PARADIGMS

Although disease-specific treatments for HAE are expensive, appropriate and timely treatment decreases ED visits, hospitalizations, lost time from school and work, and prevents death, lowering the overall cost of the disease to the health care system and to society. ED visits and hospitalization for supportive treatment were the norm before availability of home and self-administration of treatment.³⁶ Self-administration of treatment and prevention of attacks is safe, effective, and encouraged. Patients can accurately recognize and safely self-treat HAE attacks, leading to earlier treatment, earlier resolution of symptoms, decreased ED and hospital visits, improved quality of life, and cost savings.^{15,41,45–49}

Innovative treatment paradigms may further lower the cost and the burden of disease. Italian HAE subjects who self-administered C1INH concentrate decreased their mean annual number of hospitalizations from 16.8 to 2.1, time to administration of treatment from 3.2 to 1.9 hours, time to symptom improvement from 84 to 54 minutes, time to symptom resolution from 12.8 to 10.8 hours, and number of missed days of work or school from 23.3 to 7.1 compared with therapy administered in a hospital or ED. The total cost of therapy, including direct and indirect cost, was approximately 30,010 Euros (\$40,500) per subjects when the therapy was administered in a hospital or clinic setting, and 26,621 Euros (\$36,000) when treatment was administered at home. This represented a savings of 11% or 57,619 Euros (\$78,000) for the 17 subjects reported in the study.⁵⁰

Spanish investigators estimated patients who self-treated their HAE attacks with icatibant compared with health care setting administration would save an average of 121 Euros (\$170) per attack in direct and indirect costs, a 9.2% decrease in costs. Reduction in direct costs accounted for 74% of the savings. This would achieve an annual health system savings of 551,371 Euros (\$772,000).⁵¹ A US study reported a

\$650,000 savings when 249 HAE attacks over 5 months were treated with ecallantide given at home by an infusion nurse compared with the cost of treating these attacks in the ED or hospital.⁵² In the UK, home administration of icatibant compared with hospital administration of C1INH saved \$861 to \$1167 per attack.⁵³

In Denmark, 80 HAE subjects were followed prospectively for 10 years. By 2012, 49% were self-administering C1NH or icatibant, with 84% reduction in ED visits. In the self-treated subjects, there was no need for tracheotomy, no deaths reported, and an improved quality of life in all physical and psychological domains. Despite a 300% increase in use of newer so-called high-cost treatments, the cost to treat an average of 36 attacks per subject per year was manageable at \$16,766.⁴⁹

Unfortunately, in many countries, implementation of a home or self-administration policy is not possible. In Japan, Greece, and most of Eastern Europe, acute therapies are only available at the hospital or specialty clinics, if available at all. In Brazil and Mexico, home therapy is available but is not reimbursed (personal communication).

Specific treatments for HAE attacks are available in many countries (see [Table 1](#)). Treatments to prevent attacks are less widely available. What is not obvious from this [Table 1](#) is that, although these treatments may be registered and approved for marketing in a particular country, they may not be accessible to the patients that need them. Barriers to access include requirement for health care system or judicial approval, availability only in specialized treatment centers or hospitals, limits on reimbursement, and limits on number of treatments allowed or resupply of medication to providers or patients.

An example of this problem is found in Argentina. Members of the Argentine Hereditary Angioedema Patient Association completed questionnaires about the availability and their access to HAE treatments in 2009, 2013, and 2016. Despite C1INH being registered and approved for treatment of HAE attacks before 2009, C1INH was available to only 26% of those responding to the survey in 2009. This increased to 55% by 2016. Only 10% had access to icatibant in 2016. Reimbursement for these medications in 2016 was also a challenge, with only 64% reimbursed at 100% and 19% having no reimbursement available at all. Most patients received treatment from health personnel or at the hospital and more than 50% reported not receiving treatment until their attack was severely painful. Reordering and resupply of medication was difficult for 66% of patients, with only 20% reporting a fast replacement and 53% able to obtain replacement within 10 days.⁵⁴

Despite the advances in the treatment of HAE, with availability of new, effective, on-demand, and prophylactic treatments, many of these medications are not approved in many countries around the world. Even if approved, they are not accessible by the patients who need them. Despite improvement of treatment outcomes and cost savings when the treatment is self-administered or given in the home setting, on-demand therapies are only accessible in hospital and clinic settings in many countries.

SUMMARY

Orphan drug policies are in place to encourage development of safe and effective therapies for orphan diseases. With a limited number of patients to treat, the cost per patient of orphan drugs to recover research and development costs is high. Orphan diseases affect approximately 8% to 10% of the population. Overall, expenditures for drugs to treat orphan diseases remain proportionately less than the incidence of these diseases in the population. Expenditures for orphan drugs are currently less than 10% of pharmaceutical expenditures and 1% of the total health care costs in the United States. Despite these facts, payers in the United States

and health care authorities around the world perceive that care for orphan diseases places an inordinate burden on their payment systems and have put barriers in place to limit their use.

Orphan drugs benefit many people with previously underserved orphan diseases. These drugs offer significant value to patients and society in terms of improvements in health; reduced disability; increased productivity, including the ability to continue working; reduced health care utilization; improved quality of life; and survival. Patients with HAE are not an exception and have benefited greatly. Availability of new and novel therapies to treat and prevent swelling attacks have dramatically decreased the burden of disease in this heretofore underserved population. Prudent therapeutic choices, utilization of new treatment paradigms, and improvement in availability and accessibility of these new therapies will continue to improve the lives of patients with HAE. Continued coverage of these life-altering and lifesaving therapies should continue and barriers to access should be addressed.

The conversation about the high cost for the benefit obtained of orphan drugs with payers, society, and patients needs to change to recognition of the benefits of timely and appropriate care. Clinicians need to solve the access problem by working with health systems, patients, and their advocates on the most cost-effective and efficient ways to deliver this care. Clinicians must continue to disseminate knowledge regarding benefits to patients and to society of effective and safe treatments for HAE and all rare diseases.

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