

Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema

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Objective: To estimate health status utility (preference) weights for hereditary angioedema (HAE) during an attack and between attacks using data from the Hereditary Angioedema Burden of Illness Study in Europe (HAE-BOIS-Europe) survey. Utility measures quantitatively describe the net impact of a condition on a patient's life; a score of 0.0 reflects death and 1.0 reflects full health.

Study design and methods: The HAE-BOIS-Europe was a cross-sectional survey conducted in Spain, Germany, and Denmark to assess the real-world experience of HAE from the patient perspective. Survey items that overlapped conceptually with the EuroQol 5-Dimensions (EQ-5D) domains (pain/discomfort, mobility, self-care, usual activities, and anxiety/depression) were manually crosswalked to the corresponding UK population-based EQ-5D utility weights. EQ-5D utilities were computed for each respondent in the HAE-BOIS-Europe survey for acute attacks and between attacks.

Results: Overall, a total of 111 HAE-BOIS-Europe participants completed all selected survey items and thus allowed for computation of EQ-5D-based utilities. The mean utilities for an HAE attack and between attacks were 0.44 and 0.72, respectively. Utilities for an acute attack were dependent on the severity of pain of the last attack (0.61 for no pain or mild pain, 0.47 for moderate pain, and 0.08 for severe pain). There were no significant differences across countries. Mean utilities derived from the study approach compare sensibly with other disease states for both acute attacks and between attacks.

Conclusion: The impacts of HAE translate into substantial health status disutilities associated with acute attacks as well as between attacks, documenting that the detrimental effects of HAE are meaningful from the patient perspective. Results were consistent across countries with regard to pain severity and in comparison to similar disease states. The results can be used to raise awareness of HAE as a serious disease with wide-ranging personal and social impacts.

Keywords: hereditary angioedema, health-related quality of life, burden of illness, EQ-5D

Introduction

Hereditary angioedema (HAE) is a rare genetic disorder caused by C1 inhibitor (C1 INH) deficiency, resulting in recurrent subcutaneous or submucosal edema.¹⁻⁴ HAE is a lifelong disease with symptoms often beginning in early childhood^{1,5} and diagnosis may be delayed for 10 years.^{3,5,6} Patients with HAE may experience disfiguring, functionally disabling, painful, and even life-threatening edema of the face, extremities, upper airway, gastrointestinal tract, and urogenital region.^{2,7,8} Attack frequency may range from rarely to once every 3 days, and the disease presentation may vary throughout a patient's life.^{2,9} Symptoms typically last 1–4 days and patients may be unable to engage in normal social activities for 20–100 days per year.¹⁰ The unpredictable nature and potential seriousness of frequent angioedema attacks may put a strain on the patient and his/her

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family. Recently published data suggest that patients with HAE experience greater interference in their education and careers due to work and school absenteeism and productivity impairment during and between attacks.¹¹ The prevalence of HAE is approximately estimated at 1:50,000.^{10,12}

Disease management strategies include treatment of acute attacks, preprocedure attack prophylaxis, and long-term prophylaxis to minimize the frequency and severity of attacks.^{13,14} Treatment options mostly consist of plasma-derived or recombinant C1 INH concentrates and a B2 bradykinin receptor antagonist for the treatment of acute attacks. Long-term prophylaxis options involve attenuated androgens and a nanofiltered C1 INH (human). Plasma-derived C1 INHs have been recommended for preprocedure prophylaxis.¹⁵

The Hereditary Angioedema Burden of Illness Study in Europe (HAE-BOIS-Europe) survey was undertaken to collect patient-reported European data to address significant gaps in the literature with respect to the humanistic and socioeconomic burden of HAE from the patient perspective, focusing on Spain, Germany, and Denmark, as described by Bygum et al¹⁶ and Caballero et al.¹⁷

Despite the increasing wealth of information about the disease, the broader consequences of HAE on patients' lives are yet to be fully understood. Within this context, the objective of this study was to produce estimates of utility values associated with acute attacks as well as between attacks based on existing patient-reported data. Utility, or preference, measures allow the net impact of the effects of a condition to be captured quantitatively.¹⁸ For such measures, a score of 0.0 reflects death and a score of 1.0 reflects full health; changes of 0.05 are generally considered meaningful to the patient.¹⁹ The utility weights are often used to quality-adjust life expectancy in cost–utility evaluations of medical interventions.^{20,21}

Given the rarity of HAE and the high cost of treatment,^{15,22} utility values could be an important influential factor in policy decision models and cost–utility studies of HAE treatments. Furthermore, due to the rarity and episodic nature of the condition, it may be particularly challenging to accurately estimate the clinical and humanistic impact of HAE in daily practice. Utilities can be used to raise awareness of the seriousness of HAE, provide a basis for comparison with other chronic diseases, and provide evidence of the need for more effective treatments.

Patients and methods

The HAE-BOIS-Europe survey was conducted between May and December 2011. The two study components were: 1) a one-time web- or paper-based survey on the humanistic

and socioeconomic burden of HAE, which included questions regarding experience related to the last HAE attack as well as between attacks^{11,16,17} and 2) open-ended patient interviews (N=30 [n=10 per country]).²³ Interview participants were selected from clinical practice centers of excellence, and survey participants were recruited systematically from clinical practice as well as from patient associations. Participants were at least 12 years of age with HAE type I or type II. The study was reviewed and approved by institutional review boards per local requirements. Interview participants provided verbal informed consent before the interview, and survey participants provided written informed consent electronically or on paper before beginning the survey. For participants under the age of 18 years, parental consent was obtained in addition to the child's assent. Means of patient recruitment, population, and attack characteristics, including use of acute attack treatment and long-term prophylaxis, have been previously published.^{11,16,17}

An approach for obtaining utility weights for HAE attacks as well as between attacks was designed by reviewing the HAE-BOIS-Europe survey to identify items that most closely matched the EuroQol 5-Dimensions (EQ-5D) conceptually. Separate items were identified for the most recent HAE attacks and between attacks. The EQ-5D, one of the most common utility measures, is a 5-item instrument measuring current pain/discomfort, mobility, self-care, usual activities, and anxiety/depression.^{24,25} Each domain has three levels of severity (no problems, some or moderate problems, and extreme problems).

Response options for the selected HAE-BOIS-Europe survey items were manually crosswalked to the respective EQ-5D domain severity levels based on the judgment of four clinical expert investigators. For two items, data from the qualitative interviews also provided insight for this. Specifically, the qualitative interviews included obtaining feedback on two HAE-BOIS-Europe survey items. Patients were asked to identify a number on a 0–10 scale reflecting their anxiety about future attacks and the impact of the last attack on their ability to perform daily activities. Patients were then asked why they chose this number. Evaluation of the results determined the ranges within the 0–10 response scales that were assigned to the respective EQ-5D severity levels for anxiety/depression and usual activities for the acute attack. Table 1 shows the patient interpretations of the 0–10 responses to the question inquiring about the impact of the last attack on usual activities, and Table 2 shows the patient interpretations of the 0–10 responses to the item inquiring about anxiety about having an attack in the future. Based

Table 1 HAE-BOIS-Europe interview results: impact of last attack on usual activities and transfer to EQ-5D response levels^a

EQ-5D level as evaluated by clinical experts according to patient-rated level	Level 1: no problems		Level 2: some or moderate problems					Level 3: extreme problems			
	0	1	2	3	4	5	6	7	8	9	10
HAE-BOIS-Europe survey patient-rated level											
Reason given by patient(s) for HAE-BOIS-Europe survey patient-rated level	I was able to do everything I wanted. It was a slight discomfort. I was hardly affected.	There still is some emotional stress in connection with the disease. It only affected me a little bit.	I can resume my activities very soon afterwards. I was still able to get out of bed.	There still is a swelling, so some kind of limitation of my activities but not too much. I was uncomfortable but I just didn't do much.	It is difficult but I still can do most of the things I need to do. In my personal life, if I had to go out to eat with someone, I wouldn't eat. I would prefer to relax to keep the attack down, so that I do not have to delay things.	There indeed are quite a lot of things that I am unable to do. An attack in my hand would impair my activities about 50%. It hampers me in doing a lot of things.	It prevented me from making food, picking up my house, driving, so I couldn't travel where I wanted to. It affected everything. I couldn't eat, drink, or move – I had to lie in bed because I couldn't move. I had to just rest.	It keeps me from going to work. I can only sit down in my chair and just stare. And then my wife has to do all the work at home on her own, because I don't take my share. I was able to stay at home and do a few things, but I had to sit down all day. I was able to read, for example.	I couldn't do anything. I couldn't work. I had to stay in bed [...] I was very afraid. I had to put off doing everything of malaise. I had planned at home and go to bed. I couldn't do the things I had planned for my evening and the next day. I had to stay in bed or just pace around. I am not able to do anything.	I cannot do anything anymore. Dizziness, nausea, diarrhea, general feeling of malaise. It was like I was in a coma, I couldn't do anything. The pain is so bad that I have to stay in bed or just pace around. I am not able to do anything.	

Note: 0–10 scale; higher score indicates worse impairment.

Abbreviations: EQ-5D, EuroQol 5-Dimensions; HAE-BOIS-Europe, Hereditary Angioedema Burden of Illness Study in Europe.

on the interpretations, it was determined that for both usual activities and anxiety/depression, the numerical responses 0–1 would be best assigned to the EQ-5D severity level no problems, 2–6 to some or moderate problems, and 7–10 to extreme problems. With respect to the EQ-5D self-care and mobility domains, it was assumed that self-care is not impacted during an attack or between attacks and that mobility is not impacted between attacks; this is a conservative approach and an acknowledged potential limitation. Only patients who had had an attack within the past 6 months were included in the analysis.

Each of the EQ-5D levels has a predetermined utility weight based on the time trade-off exercise; the present research used UK general population weights, as detailed by Dolan.¹⁹ Table 3 shows, for both an attack and between attacks, how each EQ-5D domain severity level and respective UK population disutility weight were linked to the respective HAE-BOIS-Europe survey items and responses. These negative values were added to 1.0 to arrive at an overall EQ-5D index score.²⁶ The formula was applied to the respondents of the HAE-BOIS-Europe survey on the individual patient level. Mean EQ-5D utility scores were calculated for the last attack, overall, and by pain severity (no/mild, moderate, and severe pain), as well as for between attacks. Country-specific utility scores were also computed. As shown in Table 3, to assess pain and discomfort during the latest HAE attack from the HAE-BOIS survey, patients answered the question “what was the worst pain you had during your most recent HAE attack?” Possible responses were “no pain”, “mild or moderate pain”, or “severe pain”, which very closely matches “no pain or discomfort”, “moderate pain or discomfort”, and “extreme pain or discomfort” on the EQ-5D pain/discomfort domain, and so mapping here involved a direct translation of responses. Between attacks, this was interpreted from the HAE-BOIS survey question, “In general, how would you describe your health?” with the answer of “excellent or very good” being translated as “no pain or discomfort” on the EQ-5D pain and discomfort domain, “good and fair” to indicate “moderate pain or discomfort”, and “poor” to be indicative of “extreme pain or discomfort”. An analysis of variance test was used to compare differences in utility scores across countries as well as across pain severity levels of the last attack. SAS® Enterprise Guide® 4.3 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Overall, a total of 111 HAE-BOIS-Europe survey participants completed all of the selected items (41 Spain, 40 Germany,

30 Denmark; 51% female; average [range] age: 40 [16–81] years). The mean EQ-5D utility scores for the last HAE attack and for between attacks were 0.444 and 0.722, respectively and comparable across countries. Utilities worsened as attack pain increased (no/mild pain = 0.613; moderate pain = 0.467; and severe pain = 0.080; $P < 0.001$; Table 4). For both acute attacks and between attacks, the domains with the greatest percentages indicating impairment were pain/discomfort and anxiety/depression. For pain/discomfort, 90% and 81% of patients indicated at least some impairment for acute attacks and between attacks, respectively; for anxiety/depression, 76% and 49% indicated at least some impairment for acute attacks and between attacks, respectively. Results were consistent across countries.

Discussion

This research presents an approach for estimating EQ-5D utility values during an HAE attack as well as between attacks. This approach is sensible based on the reasonable overlap of concepts between the respective HAE-BOIS-Europe survey items and the EQ-5D. The findings suggest that both during and between attacks, HAE causes substantial suffering from the patient perspective. This research fills an unmet need in the HAE literature, providing preference estimates in HAE, based on patient-reported impacts that could be used in future cost–utility analyses of HAE therapies.

In HAE, utility values have previously been measured in the following ways: clinician report reflecting the clinician’s perception of the patient’s experience of a moderate or severe attack;²⁷ using the standard gamble approach for HAE health states in a general population sample (comparing the health states of HAE without any effective emergency medication, HAE with effective emergency medication available in a hospital, and HAE with effective emergency medication available for self-administration);²⁸ and retrospectively in a survey in which HAE patients estimated EQ-5D responses for the attack-free and acute attack states but did not include disease-specific considerations.²⁹ This study has taken a different approach by estimating utilities based on HAE disease-specific items characterizing the patient’s reported disease experience.

Our results show that patients with HAE experience low utilities during acute attacks, and this is dependent upon the pain severity of the attack. Indeed, we observed statistically significant differences between the utility values of different attack severities, suggesting that utilities could discriminate between mild/moderate and severe attacks. The utility for a severe attack was very low, 0.08, indicating substantial

Table 3 Mapping of EQ-5D responses to HAE-BOIS-Europe survey items

EQ-5D domain ²⁶	EQ-5D description ²⁶	EQ-5D disutility (UK) ²⁶		Rating of HAE-BOIS-Europe survey items for EQ-5D utility	
				During the latest attack	Between attacks
Pain/discomfort			Question on survey	What was the worst pain you had during your most recent HAE attack?	In general, how would you describe your health?
Level 1	No pain or discomfort	−0.0		No pain	Excellent or very good
Level 2	Moderate pain or discomfort	−0.123		Mild or moderate pain	Good or fair
Level 3	Extreme pain or discomfort	−0.386		Severe pain	Poor
Mobility			Question on survey	How long did the attack stop you from performing daily activities?	N/A
Level 1	No problems in walking about	−0.0		2 h or 2–4 h	Assume HAE does not impact mobility between attacks (ie, EQ-5D disutility = −0.0)
Level 2	Some problems in walking about	−0.069		4–12 h, 12–24 h, or 2 d	
Level 3	Confined to bed	−0.314		3 d, 4 d, or >4 d	
Self-care			Question on survey	N/A	N/A
Level 1	No problems with self-care	−0.0		Assume HAE attack does not impact self-care (ie, EQ-5D disutility = −0.0)	Assume HAE does not impact self-care between attacks (ie, EQ-5D disutility = −0.0)
Level 2	Some problems washing or dressing myself	−0.104			
Level 3	Unable to wash or dress myself	−0.214			
Usual activities			Question on survey	During your most recent attack, how much did the HAE attack affect your ability to do your regular daily activities, other than work at a job/be a student?	In the past 6 months, please think how much HAE affected your ability to do your regular daily activities, other than work at a job/be a student, between attacks
Level 1	No problems with performing my usual activities	−0.0		No problems (ie, HAE-BOIS-Europe survey patient-rated level = 0.0–1.0)	No problems (ie, HAE-BOIS-Europe survey patient-rated level = 0.0–1.0)
Level 2	Some problems with performing my usual activities	−0.036		Some or moderate levels (ie, HAE-BOIS-Europe survey patient-rated level = 2.0–6.0)	Some or moderate levels (ie, HAE-BOIS-Europe survey patient-rated level = 2.0–6.0)
Level 3	Unable to perform my usual activities	−0.094		Extreme problems (ie, HAE-BOIS-Europe survey patient-rated level = 7.0–10.0)	Extreme problems (ie, HAE-BOIS-Europe survey patient-rated level = 7.0–10.0)
Anxiety/depression			Question on survey	How anxious are you about having an HAE attack in the future?	Average of How often did you get sudden feelings of panic about HAE symptoms/attacks during the past 6 months? and How distressed are you about your HAE attacks/symptoms now? (1–5 scale each)
Level 1	Not anxious or depressed	−0.0		No problems (ie, HAE-BOIS-Europe survey patient-rated level = 0.0–1.0)	HAE-BOIS-Europe survey patient-rated level <2.5 (1–5 scale)
Level 2	Moderately anxious or depressed	−0.071		Some or moderate levels (ie, HAE-BOIS-Europe survey patient-rated level = 2.0–6.0)	HAE-BOIS-Europe survey patient-rated level = 2.5–4.0
Level 3	Extremely anxious or depressed	−0.236		Extreme problems (ie, HAE-BOIS-Europe survey patient-rated level = 7.0–10.0)	HAE-BOIS-Europe survey patient-rated level >4.0 (1–5 scale)

Notes: For EQ-5D disutility (UK), the constant term accounted for any dysfunctional state = −0.081, the constant term N3 accounted for if level 3 occurs within at least one dimension: −0.269, and full health = 1. The summation of EQ-5D disutility (UK) values, including these three terms and EQ-5D disutility values for each EQ-5D domain at one of three levels in each domain, gives rise to the estimated value of EQ-5D utility.²⁶

Abbreviations: EQ-5D, EuroQol 5-Dimensions; HAE, hereditary angioedema; HAE-BOIS-Europe, Hereditary Angioedema Burden of Illness Study in Europe; h, hours, d, days; N/A, not applicable.

Table 4 Estimated EQ-5D utilities during and between attacks by country

HAE-related health state	All		Spain		Germany		Denmark		P-value ^a
	n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD	
Acute HAE state									
Overall	111	0.444 \pm 0.30	41	0.412 \pm 0.30	40	0.514 \pm 0.29	30	0.396 \pm 0.32	0.184
By pain severity of last attack: [*]									
No pain or mild	41	0.613 \pm 0.26	22	0.538 \pm 0.28	12	0.672 \pm 0.22	7	0.745 \pm 0.22	
Moderate	48	0.467 \pm 0.27	14	0.358 \pm 0.25	19	0.606 \pm 0.20	15	0.394 \pm 0.27	
Severe	22	0.080 \pm 0.08	5	0.006 \pm 0.01	9	0.110 \pm 0.08	8	0.093 \pm 0.09	
Between HAE attacks	111	0.722 \pm 0.23	41	0.705 \pm 0.26	40	0.737 \pm 0.19	30	0.728 \pm 0.24	0.816

Notes: ^aAnalysis of variance test. * $P < 0.001$ for comparison of differences in utility values by pain severity levels among overall sample.

Abbreviations: EQ-5D, EuroQol 5-Dimensions; HAE, hereditary angioedema; SD, standard deviation.

patient burden. In addition, between attacks, utilities do not reach UK general population norms (0.72 compared with 0.86; $P < 0.001$).³⁰ In contrast, utilities for the chronic state appear to be similar to UK population norms for other episodic diseases (migraine, epilepsy), suggesting that HAE as a condition has further long-term impacts on patients' lives even when they are not having an attack.^{31,32}

In comparison with the published literature reporting utilities for other disease areas, between attacks the mean utility is similar (ie, < 0.05 difference) to that of partially controlled or uncontrolled asthma (0.72)³³ and ankylosing spondylitis (0.69; Table 5).³⁴ The mean utility of an acute HAE attack (0.44) is comparable to that of ischemic heart disease with moderate/severe angina (0.45)³⁵ or renal failure on hemodialysis (0.44).³⁶ Furthermore, an EQ-5D value of 0.44 indicates that the general population would be willing to trade off 56% of their remaining life to avoid living in that health state.

Study limitations include the use of an indirect non-validated approach for obtaining EQ-5D-based utilities. Nevertheless, the use of mapping to predict utility values has been broadly used previously³⁷ and the HAE-BOIS-Europe survey items selected for the manual crosswalking to the EQ-5D appear to be sufficiently comparable conceptually. A comparison with utilities derived from the EQ-5D instrument would be a useful area for future study. In addition, it was assumed that attacks do not impact self-care and that between attacks, there is no impact on self-care or mobility; while the results appear sensible and compare realistically to other disease states, this approach may underestimate patient burden. Nonetheless, utilities were derived based on patient-reported responses to disease-specific items; this should result in more disease-specific results. Also, the results are consistent on several levels: overall mean utilities derived from the study approach compare sensibly

Table 5 EQ-5D utilities reported for selected conditions

Reference/country	Condition	Utility
Stafford et al (2012)/UK ³¹	Migraine: chronic state	0.87
Kind et al (1999)/UK ³⁰	UK general population norm	0.86
Westerhuis et al (2011)/the Netherlands ³²	Epilepsy	0.80
Dyer et al (2010)/worldwide ³⁵	Ischemic heart disease with mild angina	0.80
Ismail et al (2010)/England ³⁸	Type I diabetes mellitus	0.79
Terzano et al (2012)/Italy ³³	Asthma, partially controlled or uncontrolled	0.72
HAE-BOIS-Europe ^a	HAE: chronic (between attacks)	0.72
Mustur et al (2009)/Montenegro ³⁴	Ankylosing spondylitis	0.69
Marra et al (2004)/Canada ³⁹	Rheumatoid arthritis	0.66
Pickard et al (2004)/Canada ⁴⁰	6 months after stroke	0.62
HAE-BOIS-Europe ^a	HAE: attack with no pain or mild pain	0.61
Stafford et al (2012)/UK ³¹	Migraine: moderate severity	0.53
HAE-BOIS-Europe ^a	HAE: attack with moderate pain	0.47
Dyer et al (2010)/worldwide ³⁵	Ischemic heart disease with moderate/severe angina	0.45
Lee et al (2005)/Wales ³⁶	Renal failure on hemodialysis	0.44
HAE-BOIS-Europe ^a	HAE: acute attack (overall)	0.44
Pickard et al (2004)/Canada ⁴⁰	Acute stroke	0.31
HAE-BOIS-Europe ^a	HAE: attack with severe pain	0.08

Note: ^aRefers to current study with data shown in bold.

Abbreviations: EQ-5D, EuroQol 5-Dimensions; HAE, hereditary angioedema; HAE-BOIS-Europe, Hereditary Angioedema Burden of Illness Study in Europe.

with other disease states for both acute attacks and between attacks (Table 5). As expected, as pain severity increased, attack utilities declined and were comparable with conditions generally considered more severe; these values were consistent across countries. Future research might incorporate this methodology, providing additional data that may substantiate the validity of our approach.

Conclusion

In summary, acute attacks as well as the chronic experience of HAE impair patients' quality of life to a degree similar to that of other serious chronic diseases. This suggests that the detrimental effects of HAE as a lifelong disease characterized by acute attacks are meaningful and may cause long-lasting lifestyle impairment. This may translate into long-term reductions in quality of life. Our findings suggest that despite the availability of various treatment options, more comprehensive disease management strategies need to be considered to minimize the severity, frequency, and overall impact of HAE attacks. Utility values can be used to help advocate for and raise awareness among policymakers, the global community, and the clinical community of the burden of HAE and the substantial unmet need for effective treatments.

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Author contributions

EAP, AB, and TC contributed to the study design, participated in the acquisition and analysis of patient data, and provided substantive input to the manuscript. KB and EH contributed to the study design and provided input on survey

design, analysis, and medical writing support on behalf of the HAE-BOIS-Europe Steering Committee. ZS coordinated the work of the Steering Committee, performed literature searches, and provided substantive input to the manuscript. HBB contributed to the study design, participated in the acquisition of patient data, and provided substantive input to the manuscript. All authors contributed to the study design, acquisition of data, analysis, or interpretation of data, and contributed to drafting or revising the manuscript. All authors read and approved the final manuscript and agree to be accountable for the data reported herein.

Disclosure

EAP has received sponsorship for educational purposes and has provided consultancy services or has participated in clinical trials sponsored by CSL Behring, Jerini AG/Shire, Sobi, ViroPharma Incorporated (now part of the Shire Group of Companies), and Biocryst. AB has been involved in clinical research or educational events involving CSL Behring, Jerini AG/Shire, Sobi, and ViroPharma Incorporated. At the time of the study KB and EH were employees of Oxford Outcomes Inc., an ICON plc company, which consults for ViroPharma Incorporated. ZS was an employee of ViroPharma Incorporated at the time of this study. HBB is the Executive Director of HAEi–International Patient Organization for C1 Inhibitor Deficiencies, which receives funding from most pharmaceutical companies, including ViroPharma Incorporated. TC has received sponsorship for educational purposes, has been paid for providing consultancy services, or has participated in clinical trials sponsored by CSL Behring, Jerini AG/Shire, Pharming NV, Sobi, and ViroPharma Incorporated. The authors report no other conflicts of interest in this work.

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