Long-term Follow-up and Outcome of Phenylketonuria Patients on Sapropterin: A Retrospective Study

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**KEY WORDS**
hyperphenylalaninemia, tetrahydrobiopterin, BH4, PKU, pharmacological treatment

**ABBREVIATIONS**
AF—allele frequency
BH4—6R-tetrahydrobiopterin
HPA—hyperphenylalaninemia
PAH—phenylalanine hydroxylase
Phe—phenylalanine
PKU—phenylketonuria
QoL—quality of life

(Continued on last page)

**WHAT’S KNOWN ON THIS SUBJECT:** Pharmacologic treatment with sapropterin dihydrochloride (6R-tetrahydrobiopterin; BH4) has been an effective option for some phenylketonuria patients since its approval by the US Food and Drug Administration in 2007 and the European Medicines Agency in 2008.

**WHAT THIS STUDY ADDS:** This retrospective multicenter study revealed the long-term effects of sapropterin on metabolic control, dietary tolerance, and the outcome of BH4-responsive phenylketonuria patients harboring specific phenotypes and genotypes. It also confirmed that the minor adverse events disappeared by lowering the dose.

**OBJECTIVE:** Sapropterin dihydrochloride, the synthetic form of 6R-tetrahydrobiopterin (BH4), is an approved drug for the treatment of patients with BH4-responsive phenylketonuria (PKU). The purpose of this study was to assess genotypes and data on the long-term effects of BH4/sapropterin on metabolic control and patient-related outcomes in 6 large European countries.

**METHODS:** A questionnaire was developed to assess phenotype, genotype, blood phenylalanine (Phe) levels, Phe tolerance, quality of life, mood changes, and adherence to diet in PKU patients from 16 medical centers.

**RESULTS:** One hundred forty-seven patients, of whom 41.9% had mild hyperphenylalaninemia, 50.7% mild PKU, and 7.4% classic PKU, were followed up over ≥12 years. A total of 85 different genotypes were reported. With the exception of two splice variants, all of the most common mutations were reported to be associated with substantial residual Phe hydroxylase activity. Median Phe tolerance increased 3.9 times with BH4/sapropterin therapy, compared with dietary treatment, and median Phe blood concentrations were within the therapeutic range in all patients. Compared with diet alone, improvement in quality of life was reported in 49.6% of patients, improvement in adherence to diet was reported in 47% of patients, and improvement in adherence to treatment was reported in 63.3% of patients. No severe adverse events were reported.

**CONCLUSIONS:** Our data document a long-term beneficial effect of orally administered BH4/sapropterin in responsive PKU patients by improving the metabolic control, increasing daily tolerance for dietary Phe intake, and for some, by improving dietary adherence and quality of life. Patient genotypes help in predicting BH4 responsiveness. *Pediatrics* 2013;131:e1881–e1888
Phenylketonuria (PKU) is the most common autosomal-recessive inherited disorder of amino acid metabolism and is caused by phenylalanine (Phe) hydroxylase (PAH) deficiency in the liver. This reaction is dependent on the PAH cofactor 6R-tetrahydrobiopterin (BH4; sapropterin dihydrochloride).

In PKU patients, neurotoxic Phe accumulates in the blood (hyperphenylalaninemia; HPA) and brain, and patients, if untreated, can suffer from severe mental retardation. Several mutations within the PAH gene. More than 830 variations in the PAH gene and almost 4200 patients with full genotypes, about 50% of them associated with results from BH4 challenge tests, are tabulated in the BIOPKU database (http://www.biopku.org; accessed April 8, 2013). It has been shown that genotypes are useful in predicting BH4 responsiveness in PKU patients.

The aim of PKU treatment is to maintain Phe blood concentrations within the therapeutic range, which is mainly achieved by a natural protein–restricted diet and synthetic amino acid supplementation without Phe. However, the recommended low-Phe diet potentially impairs quality of life by decreasing patients’ flexibility and autonomy. Therefore, compliance is often poor, especially in adolescence.

An alternative option to the low-Phe diet is to add pharmacologic treatment with BH4. It has been previously shown that, depending on the country, ~20% to 50% of all PKU patients (predominantly mild to moderate PKU) respond to oral administration of BH4, which lowers their blood Phe concentrations significantly.

Sapropterin dihydrochloride (Kuvan; Merck Serono SA, Geneva, Switzerland) has been approved by the Food and Drug Administration in the United States and by the European Medicines Agency in Europe for the treatment of PKU patients in combination with diet. In short- and long-term prospective and retrospective clinical studies, it has resulted in significant and sustained reductions in blood Phe concentrations in patients with PKU, even if administered as monotherapy.

The objective of this multicenter study was to collect data on the long-term metabolic outcomes of PKU patients treated with BH4/sapropterin. We devoted special attention to the influence of genotype.

METHODS

In this study, we retrospectively collected data from PKU patients who had been treated with BH4 (Sichrck’s Laboratories, Jona, Switzerland) or with sapropterin (sapropterin dihydrochloride [Kuvan]) from 16 centers in 6 European countries (France, Germany, Italy, Netherlands, Spain, and Switzerland). The active substance 6R-BH4 was identical in both of the compounds. A total of 147 patients who had previously been diagnosed with PKU and who had been treated with BH4 or sapropterin for at least 6 months were included in the study. The inclusion criteria were as follows: male and female patients without a limit of age, documented diagnosis of PKU, previous response to BH4 with a significant decrease in blood Phe concentrations, current treatment with sapropterin (or with previous BH4 treatment, if applicable), and patient-, parent- and/or guardian-signed informed consent after the nature and content of the questionnaire had been explained. The exclusion criteria were subjects with BH4 deficiency, pregnancy, and severe illness with the use of additional medications. No diagnostic, therapeutic or experimental interventions were involved.

The questionnaire included age at diagnosis, laboratory newborn screening data, BH4/sapropterin loading test, highest blood Phe concentrations before initiation of treatment, and Phe tolerance before and during treatment with BH4/sapropterin. In addition, age at treatment initiation, changes in BH4/sapropterin dosage, number of doses per day, frequency of blood testing, and blood Phe concentrations (minimum, maximum, median) were requested. A simple question (yes/no) about improvement in quality of life (QoL) was used to assess estimated clinical outcomes. Compliance with treatment and mood changes was also assessed; however, these outcomes were not among the primary aims of this study.

The methods used to assess QoL were as follows (open-answered questions): Kidscreen 52, World Health Organization QoL 100, patient and parent interviews, patient letters, pediatric and psychological assessments, and observation by the physician. To assess compliance with diet (open-answered question), index of dietary control, dietary records analyzed by a dietitian, and patient and parent interviews were used. The methods used to assess compliance with treatment in general were as follows (open-answered question): patient and parent interview, pediatric and psychological assessments, and clinical features. To assess changes in mood (open-answered question), patient and parent interviews, pediatric and psychological assessments, and clinical features. To assess changes in mood (open-answered question), patient and parent interviews, pediatric and psychological assessments, and clinical features. To assess changes in mood (open-answered question), patient and parent interviews, pediatric and psychological assessments, and clinical features. To assess changes in mood (open-answered question), patient and parent interviews, pediatric and psychological assessments, and clinical features. The central ethical committee of each country fully approved the protocol valid for all of the clinical centers.

REGISTRAT-MAPI (Lyon, France), a clinical research organization, handled all
of the legal documents and submissions to ethical committees. All of the data were fully anonymized and can no longer be retraced.

**STATISTICAL ANALYSES**

Statistical analysis was performed by using Microsoft Excel with the WinSTAT module (Fitch, Bad Krozingen, Germany). Descriptive data are presented as means ± SD and ranges or as medians and 5th to 95th percentiles.

**RESULTS**

Data on 147 patients followed up in these centers between December 2011 and July 2012 were included. The mean age was 14.4 ± 8.8 years (range: 1–46 years). One hundred patients (68%) were minors, with a mean age of 9.5 ± 4.3 years (range: 1–17 years). Forty-seven patients were adults, with a mean age of 24.6 ± 6.7 years (range: 18–46 years). Newborn screening was completed in 130 patients (88.4%). Sixteen patients were diagnosed late: 12 (8.2%) within the first month of life, 2 (1.4%) within the first year of life, and 2 (1.4%) at the ages of 4 and 6 years. For 1 patient, no information regarding the time of diagnosis was available. One hundred forty-five patients (98.9%) underwent a BH4 or sapropterin-loading test: 27 patients were tested in the newborn period, 118 patients were tested after the first month of life. The loading test dosages were 5 mg/kg (n = 4; 3.1%), 10 mg/kg (n = 6; 4.6%), and 20 mg/kg (n = 121; 92.3%). For 14 patients, no information regarding the loading test dosage was available. Sixty-seven patients (45.6%) underwent a Phe challenge before the BH4 or sapropterin test. The maximal reduction in median blood Phe concentration during the test was 62% (range: 28%–89%) and thus significant (P < .001). There were no differences in the outcome of the test between the newborns and older patients.

The median blood Phe concentration (5th–95th percentiles) before the loading test was 604 μmol/L (301–1267 μmol/L); after the test, it was 247 μmol/L (61–720 μmol/L).

Reductions in blood Phe concentration were between 31% and 40% in 20 patients (13.8%), between 41% and 49% in 18 patients (12.5%), and >50% in 99 patients (68.8%). In 7 patients, the reduction in blood Phe was between 20% and 30%, but BH4 administration resulted in an increase of daily Phe tolerance (data not shown). For 1 patient, no information was available regarding the reduction in blood Phe concentration after the test.

The test duration ranged from 8 hours to 3 weeks, with most centers using 24-hour (52.9%) or 48-hour (32.6%) protocols.

**Phenotype**

Phenotype was based on newborn screening Phe concentrations (58 patients; 42.6%), the highest blood Phe concentrations before starting treatment (64 patients; 47.1%), or Phe tolerance between the first and eighth years of life (14 patients; 10.3%). Taking all of the criteria into consideration, 67 patients (41.9%) were classified into the mild HPA group (120–600 μmol/L), 69 patients (50.7%) into the mild PKU group (600–1267 μmol/L), and 11 patients (7.4%) into the classic PKU group (>1200 μmol/L).

**Genotype**

Eighty-five different genotypes were reported in 109 patients. In 8 patients, a mutation was detected on only 1 allele, and in 23 patients (16.4%) the genotype was not available. Of 85 genotypes, 2 genotypes (c.1086-11G>A/p.Y414C and c.1315+1G>A/p.Y414C) occurred in 4 patients (genotype frequency: 3.4%), 17 genotypes occurred in 2 patients, and 66 genotypes were identified in only 1 patient (Supplemental Table 3). A total of 69 different mutations were reported. The most frequent in our patient population were as follows: p.Y414C (allele frequency [AF] = 8.2%), p.R261Q (AF = 7.8%), c.1066-11G>A (AF = 6.9%), p.L48S (AF = 6.5%), p.V388M (AF = 5.7%), p.E390G (AF = 5.3%), c.1315+1G>A (AF = 3.7), and p.A300S (AF = 3.3%) (Table 1). All of these mutations, with the exception of the splice variants c.1066-11G>A and c.1315+1G>A, were reported to be associated with substantially (>30% enzyme activity compared with the wild-type PAH) residual PAH activity (www.biopku.org). Supplemental Table 3 summarizes all of the genotypes and in vitro residual PAH activities.

**Treatment**

A total of 94 patients (63.9%) received treatment with sapropterin alone, and 53 patients (36.1%) were treated with sapropterin in combination with a low-Phe diet. Over the course of treatment, 42 patients (28.6%) were initially treated with the BH4 product, and 19 patients (12.9%) were treated with BH4 plus a low-Phe diet. They all changed treatment from BH4 to sapropterin. The median (5th–95th percentiles) daily Phe tolerance before BH4 or sapropterin treatment in 38 patients with mild to classic PKU was 500 mg/d (200–800 mg/d). During sapropterin therapy, Phe tolerance increased.

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**Table 1** Most Common Mutations Found in Our BH4-Responsive PKU Patients

<table>
<thead>
<tr>
<th>Variation</th>
<th>Nucleotide Aberration</th>
<th>AF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Y414C</td>
<td>c.1241A&gt;G</td>
<td>8.2</td>
</tr>
<tr>
<td>p.R261Q</td>
<td>c.782G&gt;A</td>
<td>7.8</td>
</tr>
<tr>
<td>p.R261Q</td>
<td>c.782G&gt;A</td>
<td>7.8</td>
</tr>
<tr>
<td>p.IVS12+1G&gt;A</td>
<td>c.1086-11G&gt;A</td>
<td>6.9</td>
</tr>
<tr>
<td>p.L48S</td>
<td>c.143T&gt;C</td>
<td>6.5</td>
</tr>
<tr>
<td>p.V388M</td>
<td>c.1162G&gt;A</td>
<td>5.7</td>
</tr>
<tr>
<td>p.E390G</td>
<td>c.1162G&gt;A</td>
<td>5.7</td>
</tr>
<tr>
<td>p.IVS12+1G&gt;A</td>
<td>c.1315+1G&gt;A</td>
<td>3.7</td>
</tr>
<tr>
<td>p.A300S</td>
<td>c.889G&gt;T</td>
<td>3.3</td>
</tr>
<tr>
<td>p.P281L</td>
<td>c.842G&gt;T</td>
<td>3.3</td>
</tr>
</tbody>
</table>

For details on complementary DNA level, see Supplemental Table 3.
significantly ($P < .001$) to 2500 mg/d (1500–3000 mg/d) (Fig 1).

Within this study, the effects of 4 different treatment protocols on blood Phe concentrations were investigated: (1) BH4, (2) sapropterin, (3) BH4 plus diet, and (4) sapropterin plus diet. Because there was no significant difference in median blood Phe concentrations between BH4 and sapropterin alone (for BH4 and sapropterin, $P = .573$) or BH4 with diet (for BH4 and sapropterin, $P = .024$) (Table 2), we pooled the BH4 and sapropterin data for additional analysis (Table 2).

### Treatment With BH4/Sapropterin Alone

Treatment was initiated at a mean age of 9.4 ± 7.8 years (range: 1 month to 35 years). The mean starting BH4/sapropterin dose was 11.1 ± 5.8 mg/kg per day (5.0–22.7 mg/kg per day), and the dosage was titrated for individual patients to reach a therapeutic range for blood Phe concentrations. The mean lowest BH4/sapropterin dose used was 9.4 ± 4.6 mg/kg per day (4.9–21.0 mg/kg per day), the mean highest dose was 12.1 ± 5.6 mg/kg per day (5.0–22.7 mg/kg per day), and the mean current daily dose of sapropterin (at the time of data collection) was 10.8 ± 5.3 mg/kg per day (4.9–21.0 mg/kg per day). Administration ranged between 1 dose (68%), 2 doses (20%), and 3 doses (12%) per day. Blood Phe concentrations were tested between 4 times per month and 9 times per year, depending on the patient’s age.

In 127 patients (45% mild HPA, 53% mild PKU, 2% classic PKU), the median (5th–95th percentile) blood concentration during treatment was 276 µmol/L (150–590 µmol/L) (Fig 2A). The minimum blood Phe concentration was 148 µmol/L (28–372 µmol/L), and the maximum blood Phe concentration was 476 µmol/L (168–1032 µmol/L) (Fig 2A). The mean treatment duration was 4.2 years (6 months to 8.8 years).

### Treatment With BH4/Sapropterin Plus Low-Phe Diet

Treatment with BH4/sapropterin in combination with a low-Phe diet was started at a mean age of 10.4 ± 9.2 years (range: 1 month to 35 years). The initial mean BH4/sapropterin dose in all patients was 13.7 ± 5.0 mg/kg per day (5.0–22.2 mg/kg per day), the lowest BH4/sapropterin dose was 12.0 ± 4.6 mg/kg per day (2.6–20.0 mg/kg per day), and the highest dose was 14.9 ± 4.5 mg/kg per day (8.0–23.4 mg/kg per day). At the time of survey completion, the current dosage of BH4/sapropterin in all patients was 13.8 ± 4.8 mg/kg per day (2.6–23.4 mg/kg per day). Administration ranged between 1 dose (66%), 2 doses (27%), and 3 doses (5%) per day. Blood Phe was tested between 9 times per month and 4 times per year.

The median (5th–95th percentile) blood concentration during the treatment of 66 patients (27% mild HPA, 58% mild PKU, 15% classic PKU) was 308 µmol/L (135–666 µmol/L) (Fig 2B). The minimum blood Phe concentration was 135 µmol/L (38–471 µmol/L), and the maximum blood concentration during treatment was 549 µmol/L (278–1045 µmol/L). The treatment duration was 5.7 ± 2.7 years (range: 2.0–12.0 years). All of the patients except for 5 (no access to Kuvan) terminated BH4 therapy.

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**TABLE 2** Blood Phe Concentrations After Treatment With BH4/Sapropterin With or Without Additional Dietary Supplementation

<table>
<thead>
<tr>
<th></th>
<th>BH4b (n = 42)</th>
<th>Sapropterinb (n = 85)</th>
<th>BH4 + dietc (n = 17)</th>
<th>Sapropterin + dietc (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Blood Phe With Treatment, µmol/L</strong></td>
<td>277</td>
<td>270</td>
<td>241</td>
<td>329</td>
</tr>
<tr>
<td><strong>5th percentile</strong></td>
<td>134</td>
<td>150</td>
<td>110</td>
<td>200</td>
</tr>
<tr>
<td><strong>95th percentile</strong></td>
<td>531</td>
<td>597</td>
<td>482</td>
<td>653</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>46–680</td>
<td>32–96</td>
<td>44–492</td>
<td>63–926</td>
</tr>
</tbody>
</table>

For each patient

b Test for BH4 (Schircks Laboratories) and sapropterin, $P = .573$.

c Test for BH4 (Schircks Laboratories) + diet and sapropterin + diet, $P = .024$ (sample size too small for 5th–95th percentile calculation).
and switched to sapropterin. For the 46 patients, the treatment regimen could be adapted from treatment with BH4/sapropterin plus a low-Phe diet to treatment with BH4/sapropterin alone. Thus, these patients were included in both groups.

**Treatment Termination and Adverse Events**

A total of 5 patients stopped sapropterin treatment for the following reasons: pregnancy, poor compliance of guardians, or poor compliance with treatment regulations regarding obesity. Adverse events, such as gastric pain, frequent urination during the treatment, and dizziness during the loading test, were reported in 3 patients (2%). All adverse events disappeared with lowering the doses of BH4/sapropterin.

**Effect of BH4/Sapropterin Treatment on QoL**

The investigators reported an improvement in QoL for 73 patients (49.6%). For 21 patients (14.3%), no improvement in QoL could be detected, and for 53 patients (36.1%) no information was available or the question was not answered (Fig 3A).

**Effect of BH4/Sapropterin Treatment on Compliance With Diet**

The investigators reported an improvement in compliance with diet in 69 patients (47%). For 39 patients (26.5%), no improvement in compliance with diet could be detected. For 39 patients (26.5%), no information was available or the question was not answered (Fig 3B).

**Effect of Pharmacologic Treatment on Changes in Mood**

The investigators documented positive changes in mood in 18 patients (12.2%). For 57 patients (38.8%), no changes in mood were documented. For 72 patients (49.8%), no information was available or the question was not answered.

**DISCUSSION**

Sapropterin (BH4) is an alternative treatment option for ∼20% to 50% of PKU patients. Primarily patients with mild to moderate PKU phenotypes, but also a few patients with classic PKU, have been shown to respond to oral administration of BH4. BH4 has been used in PKU patients since 1999, when Kure et al demonstrated for the first time that some PKU patients responded to its administration with decreased blood Phe concentrations. At that time, clinical centers used nonregistered BH4 (Schircks Laboratories). In the following years, a number of small local studies documented the effectiveness of BH4 in some PKU patients (for a review of the literature, see ref 24). Since the approval of BH4 as sapropterin dihydrochloride (Kuvan) by the US Food and Drug Administration in 2007 and by the European Medicines Agency in 2008, sapropterin has become a part of the...
standard treatment of PKU patients who respond to its administration. Several placebo-controlled, double-blind studies have revealed that sapropterin administration reduces blood Phe concentrations, increases dietary tolerance for Phe, and is safe in PKU patients, with only few adverse events reported. 

Our retrospective study with 147 PKU patients adds to the available knowledge and documents the long-term efficiency (up to 12 years) of BH4/sapropterin. In patients who were receiving sapropterin >3 years, BH4 was used during the first years. Ninety-four patients (63.9%) received treatment with sapropterin only, and 54 patients (36.7%) were treated with sapropterin in combination with diet. The 48-hour loading test with 20 mg/kg per day of sapropterin is recommended by the European working group for PKU and has been adopted by most clinical centers. In our study, most of the centers used the 24-hour (52.9%) or 48-hour (32.6%) protocols. The test dose ranged from 5 to 20 mg/kg, with most of the centers (92.3%) using 20 mg/kg.

The most widely accepted cutoff value to consider the test positive is a reduction in blood Phe of 30%. In our study, the median reduction in blood Phe concentration was 62%, and all of the tested patients proved to be responders over longer periods of time. One should, however, bear in mind that the BH4/sapropterin challenge is only a screening test to detect potential responders and that long-term supplementation can confirm initial results indicating real responsiveness.

In addition to blood Phe reduction, an increase in tolerance for dietary Phe intake is another factor that determines true BH4 responsiveness. As previously shown and as documented in our survey, a significant increase in daily Phe tolerance was recorded with sapropterin treatment (Fig 1). In addition to reduction in blood Phe, an increase in Phe tolerance by at least a factor of 2 is now required by several protocols. Moreover, blood Phe concentrations were stable and within the therapeutic range in all patients (Fig 2), no severe adverse events were reported, and all of the side effects disappeared with reduced therapeutic sapropterin doses. However, treatment recommendations (blood Phe cutoff for starting treatment) are different in different countries, as recently documented by Blau et al. Today, it is generally accepted that only the full genotype determines both phenotype and BH4 responsiveness. A number of mutations are more frequently found in BH4 responders, whereas BH4 non-responders harbor more severe mutations, with less or little residual PAH activity. All of the 85 genotypes identified within our survey and the 8 mutations detected on only 1 allele were reported to be associated with substantial (>30%) residual PAH activity (www.biopku.org). With the exception of the splice site mutations in introns 10 and 11, p.Y414C, p.R261Q, p.L48S, p.V388M, and p.E390G presented with substantial (>25%) residual PAH activity when expressed in recombinant eukaryotic cell systems. The same mutations were also found in the most common genotype among our patients (Supplemental Table 3), p.Y414C, with c.1066-11G>A and c.1315+1G>A being the 2 most common. Therefore, patient genotype is an important option for predicting BH4 responsiveness, although it should always be confirmed by the loading test.

For 49.6% of patients, an improvement in QoL with therapy with sapropterin was reported. Hennermann et al reported similar results in patients with PKU. Ziesch et al did not detect an improvement in health-related QoL in their study, at least not during the first 3 months of BH4/sapropterin treatment. In our survey, this question was not answered in 36% of patients, and the assessment to evaluate QoL was rather heterogeneous (ie, subjective observation by the physician, patient and parent interviews, and questionnaires). Thus, our data are an estimate rather than fully quantitative, and a more topic-focused study is needed to document the real value and the cost-benefit effects of BH4/sapropterin on QoL in PKU patients.

A high percentage of investigators (63.3%) have reported improvements in compliance with general treatment. It is not clear whether it is a problem for patients to continue a relaxed Phe-free diet, and it has been suggested that specialized questionnaires (for patients and physicians) should be developed to answer this question.

CONCLUSIONS

Our survey emphasizes that sapropterin is a safe and effective alternative to conventional dietary treatment of PKU patients who respond to long-term treatment by stabilizing their blood Phe concentrations in the therapeutic range, thus possibly lowering the burden of the strict low-Phe diet. A sapropterin loading test should be performed under standardized conditions and, if possible, in combination with genotyping, but this requirement could change, depending on the patient’s current blood Phe concentrations. 

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Dr Keil designed the data collection instruments, coordinated data collection at all sites, and drafted the initial manuscript; Drs Anjema, van Spronsen, Lambruschini, Burlina, Bélanger-Quintana, Couce, Feillet, Lotz-Havla, Muntau, Bosch, Meli, Billette de Villemeur, Kern, Riva, Giovannini, Damaj, and Leuzzi and Mr Cerone carried out the initial analyses and interviews with patients, and reviewed and revised the manuscript; Dr Blau conceptualized and designed the study and coordinated and supervised data collection at all sites, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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