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ARTICLE

Erythropoietic protoporphyria: time to prodrome, the warning signal to exit sun exposure without pain—a patient-reported outcome efficacy measure

D. Wensink[1,5], J. G. Langendonk[1,5], J. R. Overbey[2], M. Balwani[3], E. J. E. Van Broekhoven[1], M. A. E. M. Wagenmakers[1], J. H. P. Wilson[3], K. Wheeden[4], H. Naik[3] and R. J. Desnick[3]✉

PURPOSE: Patients with erythropoietic protoporphyria (EPP), a severe painful photodermatosis, experience prodromal sensations when exposed to sunlight, which are the "warning signals" to exit the sun, as prolonged exposure causes an excruciatingly painful phototoxic attack. The unique prodromal cutaneous sensations are reversible and differ from the severe burning pain attack lasting 2–7 days. Previously, afamelanotide treatment was studied using time to pain or time outside as primary outcome measures. Since patients have an ingrained fear of sunlight, these measures did not capture the full treatment effect. We retrospectively characterized and evaluated time to prodrome (TTP) as a safer, patient-reported outcome (PRO) measure in afamelanotide-treated patients.

METHODS: Structured interviews recorded TTP before and during afamelanotide treatment in retrospective US and Dutch cohort studies.

RESULTS: Thirty-one US and 58 Dutch EPP patients participated. Before afamelanotide treatment, 54.8% US and 39.7% Dutch patients reported TTP onset <10 minutes in direct sunlight. In both studies, patients' TTP's were significantly longer during afamelanotide treatment ($p < 0.0001$). All US patients' TTP increased; no TTP was <10 minutes. Among Dutch patients 81% improved; only 10.3% reported TTPs < 10 minutes.

CONCLUSION: EPP patients reported substantial improvements in TTP during afamelanotide treatment. TTP could provide a safer, PRO-based efficacy endpoint for assessing future EPP treatments.

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INTRODUCTION

Erythropoietic protoporphyria (EPP, OMIM 177000), an autosomal recessive photodermatosis, is a rare disorder that affects children and adults. This disorder typically manifests in early childhood with severe, excruciating pain on sun exposure. The disease results from the deficient activity of the heme biosynthetic enzyme, ferrochelatase, and the resultant accumulation of protoporphyrin IX (PPIX) in erythroid cells. The accumulated PPIX is released from erythroid cells into the circulation, gains access to the vascular endothelium, and adjacent tissues including the skin, is excreted by the hepatobiliary system, and may cause acute cholestasis and liver failure (1–4%).[1] When the skin is exposed to sun or visible light, the PPIX accumulated in the superficial dermal vascular endothelium is activated primarily by visible light in the Soret band (400 to 410 nm), and to a lesser extent at higher wavelengths, triggering singlet oxygen free-radical reactions that lead to inflammation and severe excruciating and incapacitating neuropathic pain.[2–4] The phototoxic pain typically lasts several days and does not respond to pain medications, including narcotic analgesics.[5,6] EPP is panethnic, and its prevalence in various populations may depend in part on the frequency of the ferrochelatase low expression allele (c.315–48T>C) which ranges from ~2% in Africans, ~9% in Caucasians including Finlanders, and estimated 32–43% in the East Asian/Japanese population.[5,7–11]

Previously, large UK and US cohort studies of EPP patients described the first photosensitivity symptoms as tingling, itching, stinging, pins and needles, or heat/burning sensations on exposed skin that occurred in <10 minutes to an hour in most patients,[7] while the severe, incapacitating, and untreatable burning pain occurred with continued sun exposure, typically in 30 minutes to several hours, and lasted 2–7 days.[7,12] The severe burning pain on prolonged light-exposed areas (e.g., hands and face) is followed by edema and erythema.[13]

We define the prodrome as having two components that distinguish it from an excruciating pain attack: (1) the characteristic early warning symptoms on sun exposure and (2) the reversibility of the prodromal symptoms when patients immediately exit further sun exposure. The reversibility or disappearance of these symptoms on rapidly exiting the sun can be measured as "time to recovery." Notably, neither the large US or UK patient studies, nor previous reviews,[12,14] fully recognized that the prodromal sensations were unique and reversible, rather than the early symptoms of an excruciatingly painful full-blown phototoxic attack. The tolerance for light exposure is dependent on several factors, including location, season, and weather conditions,[15] PPIX levels,[7] the intensity of the light, and the amount of light the day before (i.e., photopriming).[13] Patients suffer from sun-induced pain from early childhood, which leads to an early and ingrained fear of sunlight and deliberate efforts to

[1]Porphyria Center Rotterdam, Center for Lysosomal and Metabolic Disease, Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Erasmus, MC, The Netherlands. [2]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [4]American Porphyria Foundation, Bethesda, MD, USA. [5]These authors contributed equally: D. Wensink, J. G. Langendonk. ✉email: Robert.desnick@mssm.edu

avoid sun exposure. Therefore, patients rapidly learn to recognize the discomfort of the prodromal "early warning" signal, the sensations of tingling, itching, stinging, or heat/burning on their sun-exposed skin.

Recently, the time to prodrome (TTP) for 226 EPP patients was reported in an observational non-interventional study.[7] Most patients (76%) reported that their TTP occurred within one hour of sun exposure, with 25% and 37% of the patients experiencing prodromes in less than 10 or within 10–30 minutes, respectively. Following the first prodromal warning symptom, patients learn to leave direct sunlight immediately to avoid an incapacitating pain attack.[16] This behavior protects them from the onset of the excruciating pain that will occur if they continue sunlight exposure. Thus, patients prevent the painful phototoxic reactions by limiting outdoor activities or minimizing sun exposure by wearing wide-brim hats, gloves, and other protective clothing. Such adaptive behavior begins in early childhood and markedly affects patients' social relationships, lifestyle choices, work opportunities, ability to perform daily activities, and overall, impacts their quality of life.[12,17,18]

Until recently, there was no effective treatment for EPP. In December 2014, afamelanotide (Scenesse®, Clinuvel Pharmaceuticals), a potent α-melanocyte–stimulating hormone (α-MSH) analogue administered as a biodegradable implant every 60 days, was approved by the European Medicines Agency (EMA), under the "exceptional circumstances" provision.[19,20] Afamelanotide increases the production of eumelanin, independent of ultraviolet radiation, by binding to the melanocortin 1 receptor (MC1R).[21,22] In phase 3 clinical trials, the primary efficacy endpoint was "time in the sun without pain." Afamelanotide implants proved safe, but the primary efficacy endpoint did not provide robust results in the US or EU trials.[18,19] Moreover, patients' lifelong behavior of light avoidance limited their sun exposure such that the incremental time in the sun was only ~8 minutes per day.[23] Notably, afamelanotide does not correct the basic metabolic defect of EPP and patients on treatment continue to accumulate PPIX, which can lead to severe liver damage in 1–5% of patients, with some requiring liver and bone marrow transplantation.[1] In addition, afamelanotide has not been tested in children, where there is a significant medical need and impact on quality of life.

Clinical trials for EPP are limited by the lack of objective, disease-specific biomarkers and, therefore, have relied instead on patient reports. In addition, seasonal and geographical variability can significantly affect sun tolerance making interpatient variance challenging to quantitate. Given the rarity of EPP, it is important to identify reliable and reproducible endpoints for clinical trials.[24] Since new therapies are being developed by several companies and academic laboratories,[25–28] it is important to evaluate new potential primary efficacy endpoints to allow assessment of a drug's safety and effectiveness, without risking prolonged sun exposure and incapacitating pain attacks. Therefore, we hypothesized that average daily TTP may be a more patient-compatible primary outcome measure to investigate the clinical efficacy of treatments for EPP. The first prodromal symptom endpoint is the "warning signal" for the patient to avoid further sun exposure, thereby markedly minimizing the risk of a painful phototoxic attack.

Moreover, the FDA and EMA increasingly request or require that clinical trials for new treatments for rare diseases include patient-reported outcome (PRO) measures for approval.[29] PROs are designed to assess the effect of the treatment on meaningful improvements in specific quality of life problems from the patients' perspective, that existing questionnaires typically do not access. TTP is disease-specific and addresses the core problem of EPP patients in daily life. To investigate this potential efficacy endpoint, we developed a structured questionnaire to interview patients concerning their time in sunlight until the onset of their first prodromal symptom, the nature of the sensation, and the time for the sensation to disappear. Here, we present two retrospective studies to characterize these features of the "prodrome" before and during afamelanotide treatment. We hypothesized that the TTP increases with afamelanotide treatment.

MATERIALS AND METHODS

Study populations

The study populations included adult EPP patients who received afamelanotide treatment. In the initial US pilot study, there were 31 US EPP patients who participated in the proof-of-concept survey, which was conducted by a coordinator from the American Porphyria Foundation (APF) who contacted the patients by telephone. Of these, 27 had received three doses of afamelanotide in the FDA-approved phase 3 trial (NCT01605136, completed July 2013), and four were patients that traveled to Switzerland for afamelanotide treatment from 2015 to 2018 prior to the survey. The US patients were interviewed between January 2018 and April 2018. A subsequent larger study of afamelanotide-treated patients was performed in the Netherlands, where the drug has been approved and reimbursed for several years. All Dutch patients received one to four doses of afamelanotide annually for up to two years, and they were interviewed between June 2018 and August 2018 at the Erasmus Medical Center in Rotterdam.

Study conduct, measures, and ethics statement

In the US study, patients were interviewed over the phone by a single study coordinator from the American Porphyria Foundation (APF). The principles of the Declaration of Helsinki were followed, and patients provided oral consent at the time of interview. In the Dutch study, patients were interviewed in-person by a specialized nurse during clinic visits. Patients provided written informed consent at the time of interview or earlier. The study adhered to the principles of the Declaration of Helsinki. Institutional review board approval was not required for the preliminary interviews as the APF receives no federal funds. The follow-up study was approved by the Medical Ethics Review Board of the Erasmus MC Rotterdam.

In both studies, patients were asked the same questions by the study coordinators, using the same questionnaire (see Supplementary Table 1). The prodrome was explained to the participants as the characteristic early warning symptoms, or sensations, that they experience on their skin when exposed to direct sunlight. These sensations or discomforts are the warning signals to avoid further sun exposure that can lead to the excruciating and incapacitating phototoxic pain that can last for 2–7 days. Time to recovery is measured as the reversibility or disappearance of these symptoms on rapidly exiting the sun. The primary outcome of interest was each patient's time to his/her first prodromal symptom in direct sunlight during the summer. Patients were asked to recall their time to prodrome before they started taking afamelanotide and during treatment. In addition, they were asked their time to recover from the prodromal symptoms once they left the sun, intensity of the prodromal symptoms, and whether their prodrome led to a pain attack if they immediately removed themselves from the sun, before and during treatment. Additional collected measures include the patients' age and gender.

Statistical analysis

In both studies, the TTP was categorized as <10 minutes, 11–30 minutes, 31–60 minutes, and then 30-minute increments up to 360+ minutes. Change was determined as shifting to another time category, if the time increased to one category higher, it was noted as value 1, or if it shifted one category lower it was noted as value −1, and no change in the time category was given a 0. Change in the TTP before and after treatment was evaluated using a Wilcoxon signed-rank test. If a patient did not experience a prodrome during treatment, the longest period of time they reported staying out in the sun was used in the analyses. Changes in time to recovery and intensity of the prodrome were also evaluated using Wilcoxon signed-rank tests. If patients answered the same response for intensity, it was given a value 0, less was given a value −1 and more was 1. Changes in whether prodromal symptoms led to pain, despite stopping sun exposure, during and before treatment were assessed using McNemar's tests. Missing values were excluded from the analyses. All

Table 1. Patient characteristics and time to prodrome before and during treatment: US cohort.

Characteristics	$n = 31$		
Male (*n*, %)	18 (58.1%)		
Age (years, mean ± SD)	46.8 ± 12.3		
	Before treatment	During treatment	*p* value
Time to prodrome[a] (minutes)	*n* (%)	*n* (%)	**<0.0001**
<10	17 (54.8)	0	
10–29	6 (19.4)	1 (3.2)	
30–59	5 (16.1)	1 (3.2)	
60–89	2 (6.5)	1 (3.2)	
90–119	1 (3.2)	5 (16.1)	
120–149	0	2 (6.5)	
150–179	0	2 (6.5)	
180–209	0	4 (12.9)	
210–239	0	2 (6.5)	
240–269	0	1 (3.2)	
270–299	0	0	
300–329	0	1 (3.2)	
330–359	0	1 (3.2)	
360+	0	10 (32.3)	
Time to recovery			**<0.0001**
None	0	16 (51.6)	
<1 day	4 (12.9)	10 (32.3)	
1 day	10 (32.3)	2 (6.5)	
>1 to 2 days	11 (35.5)	2 (6.5)	
>2 to 3 days	3 (9.7)	1 (3.2)	
>3 to 4 days	1 (3.2)		
>4 to 5 days	2 (6.5)		
Intensity compared to before treatment			**0.04**
Less	NA	10 (32.3)	
Same	NA	19 (61.3)	
More	NA	2 (6.5)	
Prodrome progresses to pain despite eliminating sun exposure (yes)	17/29 (58.6)	2/29 (6.9)	**0.0001**

[a]Censored patients who did not experience a prodrome are categorized by the longest time they spent in the sun.

Table 2. Patient characteristics and time to prodrome before and during treatment: Dutch cohort.

Characteristics	$n = 58$		
Male (*n*, %)	26 (44.8%)		
Age (years, mean ± SD)	43.6 ± 14.9		
	Before treatment	During treatment	*p* value
Time to prodrome[a] *(minutes)*	*n* (%)	*n* (%)	**<0.0001**
<10	23 (39.7)	6 (10.3)	
10–29	21 (36.2)	8 (13.8)	
30–59	8 (13.8)	12 (20.7)	
60–89	3 (5.2)	10 (17.2)	
90–119	1 (1.7)	4 (6.9)	
120–149	0	6 (10.3)	
150–179	0	0	
180–209	1 (1.7)	3 (5.2)	
210–239	0	0	
240–269	0	1 (1.7)	
270–299	0	0	
300–329	0	0	
330–359	0	0	
360+	1 (1.7)	8 (13.8)	
Time to recovery		$n = 53$	**<0.0001**
None	5 (8.6)	10 (18.9)	
<1 day	16 (27.6)	25 (47.2)	
1 day	18 (31)	13 (24.5)	
>1 to 2 days	11 (19)	3 (5.7)	
>2 to 3 days	5 (8.6)	2 (3.8)	
>3 to 4 days	0	0	
>4 to 5 days	3 (5.2)	0	
Intensity compared to before treatment		$n = 57$	**<0.001**
Less	NA	33 (57.9)	
Same	NA	23 (40.4)	
More	NA	1 (1.8)	
Prodrome progresses to pain despite eliminating sun exposure (yes)	19/58 (32.8)	6/58 (10.3)	**0.0008**

[a]Censored patients who did not experience a prodrome are categorized by the longest time they spent in the sun.

analyses were conducted at the 0.05 significance level using SAS version 9.4 (Cary, NC).

RESULTS

A total of 31 US patients were interviewed in the preliminary study and 58 patients in the Dutch study. Patient demographics and prodrome characteristics are shown in Tables 1 and 2 for each cohort. The prodromal symptoms most commonly described by the patients include tingling, itching, stinging, and pins and needles (Supplementary Table 2).

Time to prodrome

All patients recognized their prodromal symptoms, and were able to provide a time of exposure in direct sunlight until the onset of their first prodromal symptom. Prior to treatment with afamelanotide, 54.8% (17/31) of US patients and 39.7% (23/58) of Dutch patients reported a TTP less than 10 minutes (Tables 1 and 2). In both cohorts, patients' time to first prodromal symptom significantly improved during afamelanotide treatment ($p < 0.0001$ and $p < 0.0001$ in US and Dutch cohorts, respectively [Fig. 1a, b]). During treatment in the United States, 100% (31/31) indicated that the TTP onset was increased and no patients reported a TTP < 10 minutes (Table 1). In the Dutch cohort, the TTP increased during treatment in 81% of the patients (47/58), and only 10.3% (6/58) reported a TTP < 10 minutes (Table 2). Of note, 12 US patients did not challenge their limits and restricted their sun exposure despite experiencing no prodrome during treatment. Most of these patients (8/12, 66.7%) reported a TTP < 10 minutes prior to treatment, and the maximum time of exposure after treatment for most patients was greater than 2 hours (7/12, 58.3%). In both

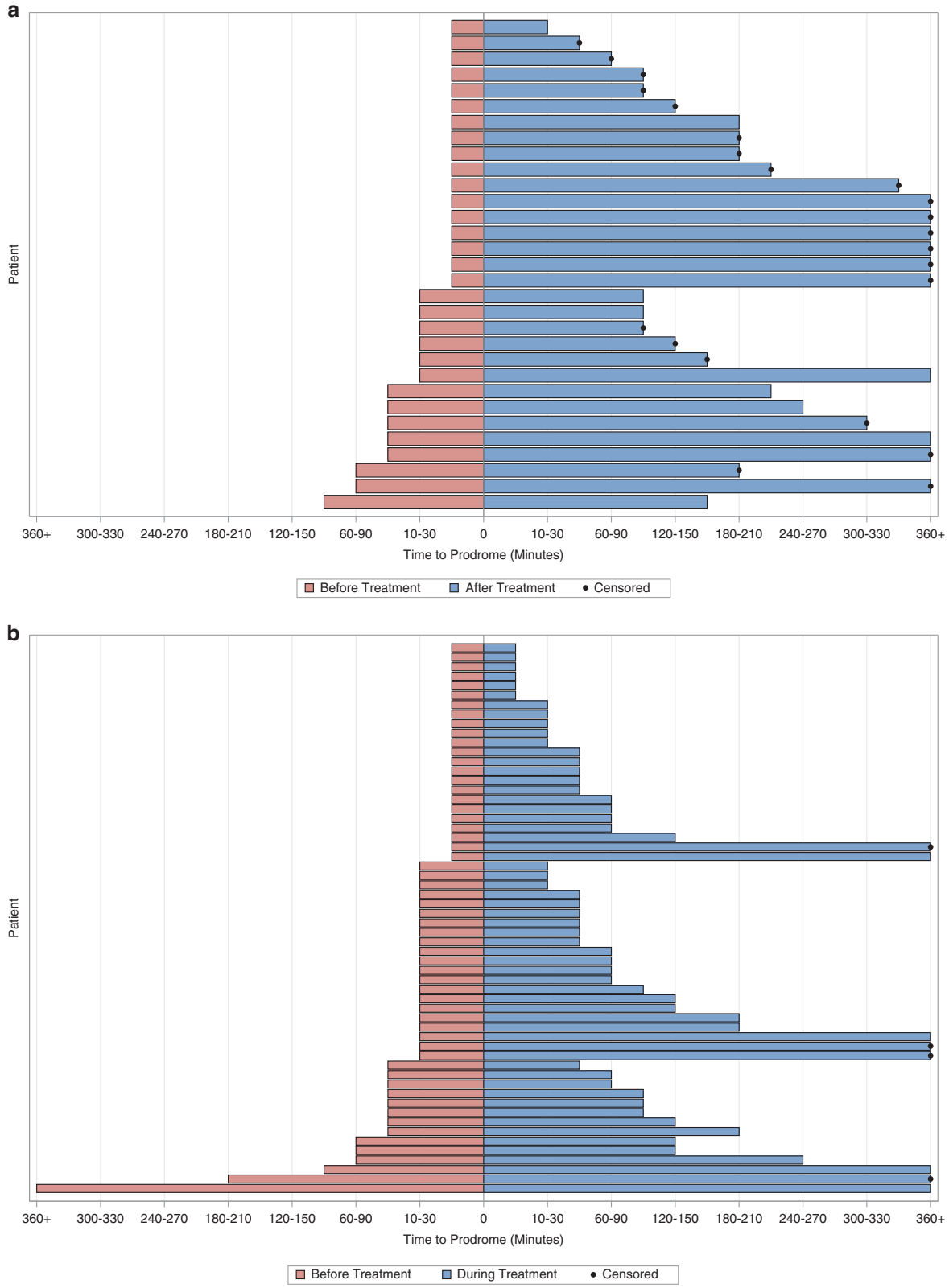


Fig. 1 Time to prodrome before and during afamelanotide treatment for the US and Dutch patients. (**a**) Time to prodrome before and during treatment: US patients. Many patients were afraid to "test their limits" and limited their sun exposure despite experiencing no prodrome. Others stayed out in the sun all day and felt no symptoms. These censored patients are indicated with a black dot at the end of the bar to indicate no prodrome by that time point. (**b**) Time to prodrome before and during treatment: Dutch patients. Some patients stayed out in the sun all day and felt no symptoms. These censored patients are indicated with a black dot at the end of the bar to indicate no prodrome by that time point.

cohorts, a few patients were able to stay out in the sun all day without prodromal symptoms. These censored patients who did not experience a prodrome are indicated in Fig. 1a, b.

Time to recovery from the prodrome

As shown in Tables 1 and 2, the reported times to recovery or disappearance of the prodromal sensations before treatment occurred in one day or less in 45.2% and 67.2%, and by two days or less in 80.6% and 86.2% of US and Dutch patients, respectively. During treatment, both cohorts had over 90% of patients reporting times to recovery in one day or less; with 93.5% of US and 98.2% of Dutch patients experiencing less or the same prodromal intensity. Before treatment 58.6% of US and 32.8% of Dutch patients reported the prodrome had progressed to pain despite exiting sun exposure, while 93.1% of US and 89.7% of Dutch patients did not progress to pain when they exited the sun during treatment. Recovery times significantly improved during afamelanotide treatment in the US ($p < 0.0001$) and Dutch ($p < 0.0001$) cohorts (Fig. 2a, b). Five Dutch patients did not provide their recovery time during treatment, as noted in the Fig. 2b legend.

Intensity of prodrome

In the US cohort, there was a significant change in the intensity of prodromal symptoms during treatment ($p = 0.04$) with 32.3% (10/31) reporting less intense prodromes on treatment. However, the majority (61.3%, 19/31) of US patients rated the intensity of their prodrome the same during treatment versus before and 6.5% (2/31) reported their prodrome was more intense on treatment (Fig. 3). The Dutch patients treated for up to two years, reported a significant improvement in prodrome intensity during treatment ($p < 0.0001$) with 57.9% (33/57) of patients stating that the intensity of symptoms was less during treatment compared to before treatment, and only one patient (1.8%) reported more intense prodromal symptoms on treatment.

Pain after prodrome

Despite little reported change in prodrome intensity in the US cohort, changes in the incidence of pain after prodrome were notable. Prior to treatment 58.6% (17/29) of US patients reported that their prodrome led to pain even if they got out of the sun immediately, compared to only 6.9% (2/29) during treatment ($p = 0.0001$, Table 1). The same improvement was seen in the Dutch patients whose percentage of prodrome progression to pain decreased from 32.8% (19/58) prior to treatment to 10.3% (6/58) during treatment ($p = 0.0008$, Table 2).

DISCUSSION

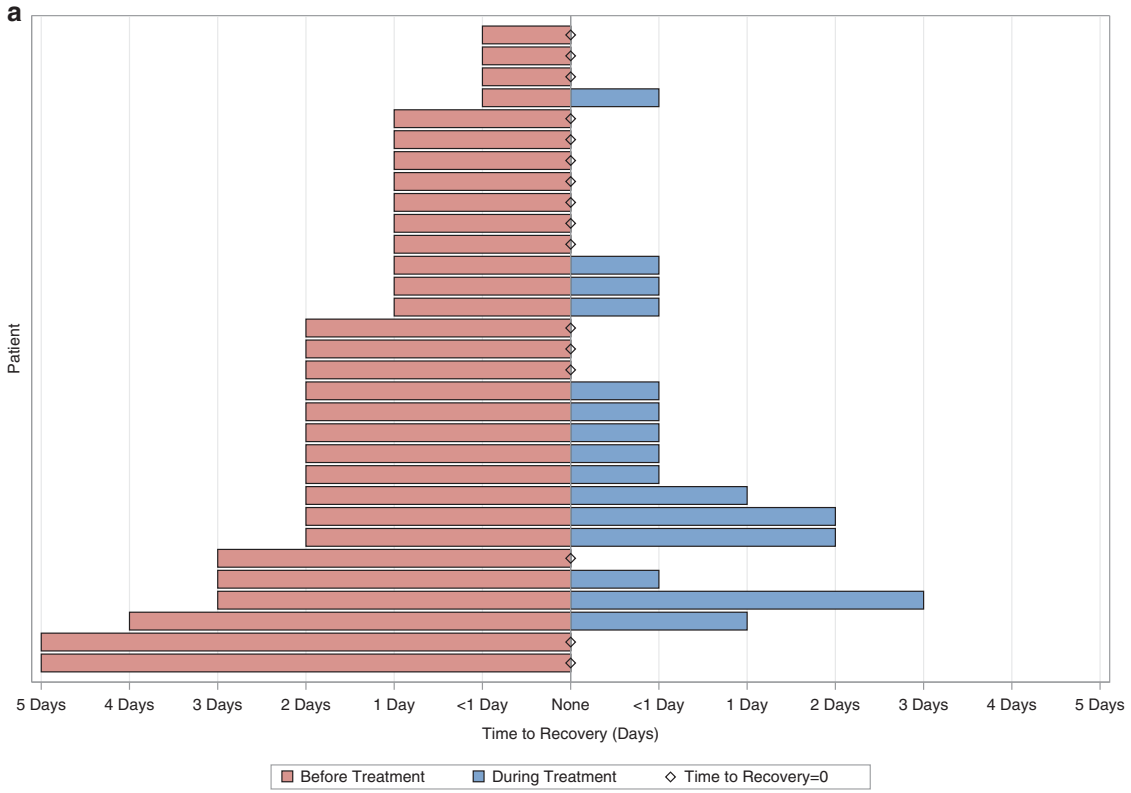
The European and US randomized, placebo-controlled trials for afamelanotide, which used hours in direct sunlight without pain as an endpoint,[18] showed modest increases in sun exposure in the afamelanotide-treated group. The small improvement in the phase 3 trial endpoints could be explained by the fact that patients had deliberately adapted their lifestyles to avoid sunlight and the resulting phototoxic pain. The EU trial had a significantly longer duration of pain-free time in treated versus placebo patients; however, only after nine months of treatment. Lacking strong primary endpoint results, the drug was approved under the EMA's "exceptional circumstances" provision, and was not approved by the FDA until October 2019. Thus, these clinical trials indicated that an improved primary endpoint is needed that measures treatment effectiveness.

Based on the interview findings described here, afamelanotide treatment was associated with substantial increases in the TTP measures. In both the US and Dutch cohorts, the results showed a faster time to recovery, decreased pain intensity, and less progression to pain on treatment. Most Dutch patients who were treated with afamelanotide for up to two years reported less intense prodromes, which resolved more rapidly, and they felt less restricted during daily activities. These findings would predict fewer and shorter phototoxic reactions as reported in the previous trials.[18] Overall, the results of both cohorts were comparable.

In the Dutch cohort up to two years of continuous afamelanotide treatment extended patient time outdoors in sun and shade.[15] However, most patients continued to limit sun exposure. Many patients mentioned that they were afraid to test their limits, and continued to restrict their sun exposure, despite not reaching their treatment-extended prodrome. Conversely, one Dutch patient no longer experienced a prodromal warning signal, and fearing phototoxic attacks, stopped treatment. Compared to the earlier used endpoint "time spent outside"[15] average daily TTP can be a more specific endpoint since time spent outside is an endpoint that is influenced by more factors than the EPP specific weather conditions and light intensity. For example, the obligation to travel to work five days a week will result in less time spent outside, although this is totally independent of EPP symptoms. Recently, "phototoxic burn tolerance time" was suggested as a new endpoint,[30] which is in line with our study to introduce a PRO endpoint for upcoming trials. This endpoint is similar to the TTP, which we proposed in an orally presented abstract at the International Congress on Porphyrins and Porphyrias in September 2019.[31] Although the TTP is more specific compared to the phototoxic burn tolerance time, since they used the maximum time spent in sunlight without a phototoxic reaction. Therefore, the average daily TTP can be a more clinical meaningful endpoint.

We were surprised that the time to recovery on "immediately" exiting the sun before treatment reported by most patients varied from several minutes to a day or two. The variability maybe due in part to various solar radiation factors (e.g., latitude, season, weather, photopriming) and individual patient factors (e.g., Fitzpatrick scale, residual ferrochelatase activity, vascular endothelial PPIX levels, previous number of severe attacks which build up layers of laminated membrane around vascular endothelial cells, and possible misunderstanding of the question). In fact, many patients may have misinterpreted this survey question, especially the word "pain" and the phrase "immediately exit sun exposure" and thus may not have fully realized their importance. "Pain" may have been interpreted as the continued discomfort of the prodromal sensations and not the incapacitating pain of a full-blown phototoxic attack. Thus, the questions on the time to recovery and progression to pain were not clear, a limitation of retrospective surveys. Clearly, the time to recovery before treatment needs further and more specific investigation in a cohort of untreated patients. Whatever the actual percentage of untreated patients who immediately exited the sun and subsequently had a full-blown attack, it is notable that during treatment most had prolonged TTPs and did not have full-blown attacks.

It has been suggested that photoprovocation testing provides an objective, reliable, and reproducible efficacy endpoint to demonstrate a treatment effect on EPP patients' light tolerance.[32–34] However, a photoprovocation endpoint requires the subject to return several times to the study site, and for a rare disease like EPP, most patients must travel far to the site, which is both an inconvenience and necessitates time off work. Local expertise is required to ensure the device is properly calibrated and that testing is performed by a well-trained person, and also, importantly, photoprovocation is subject to photopriming, i.e., the effect of the previous days' sun exposure, which may vary from test to test. In contrast, the major strengths of the average daily TTP measure as an efficacy endpoint include the fact that it is a PRO, which the EMA and FDA are currently requesting or requiring for efficacy endpoint measures; the patient can report their TTP daily using a diary or an



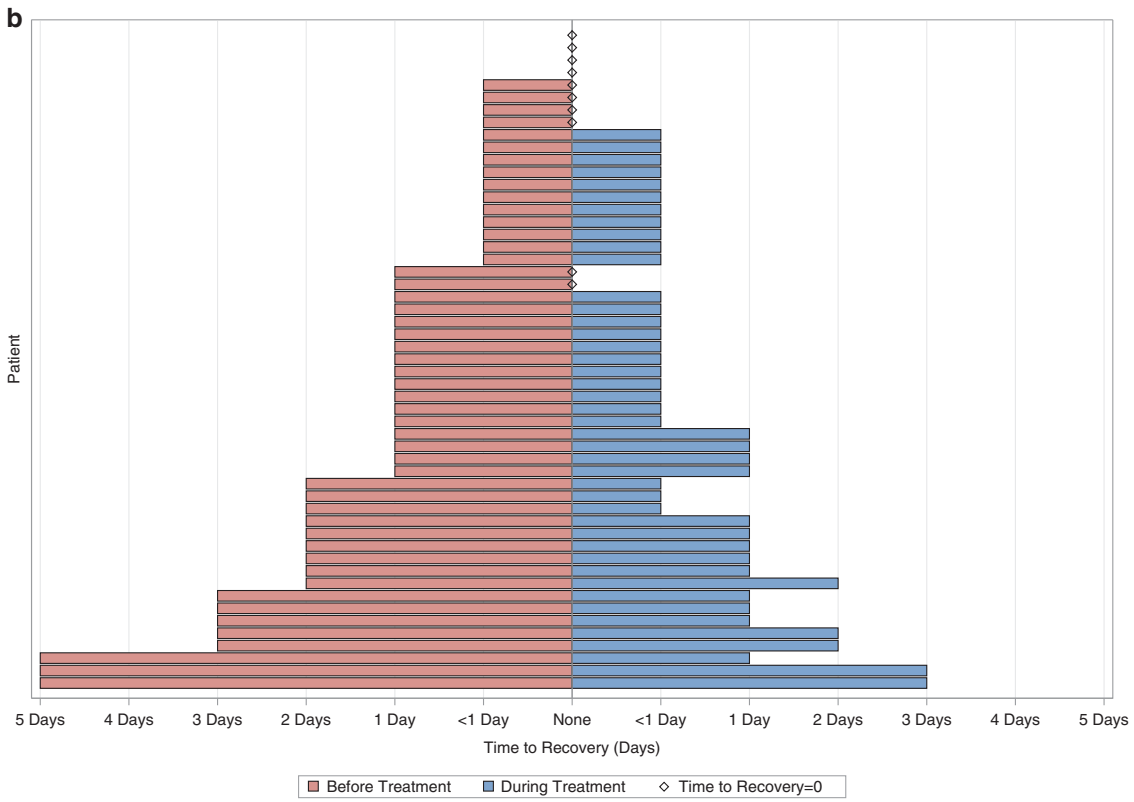


Fig. 2 Time to prodrome recovery before and during treatment for the US and Dutch patients. (**a**) Time to prodrome recovery before and during treatments: US patients ($n = 31$). (**b**) Time to prodrome recovery before and during treatments: Dutch patients ($n = 53$). In the Dutch cohort, one did not answer the question and four said they could not answer the question for the following reported reasons: (1) did not reach the point of requiring recovery time ($n = 2$); (2) "because the prodromal symptoms changed, missing their prodromal warning they did develop painful phototoxic reaction" ($n = 1$); (3) "difficult to answer" ($n = 1$).

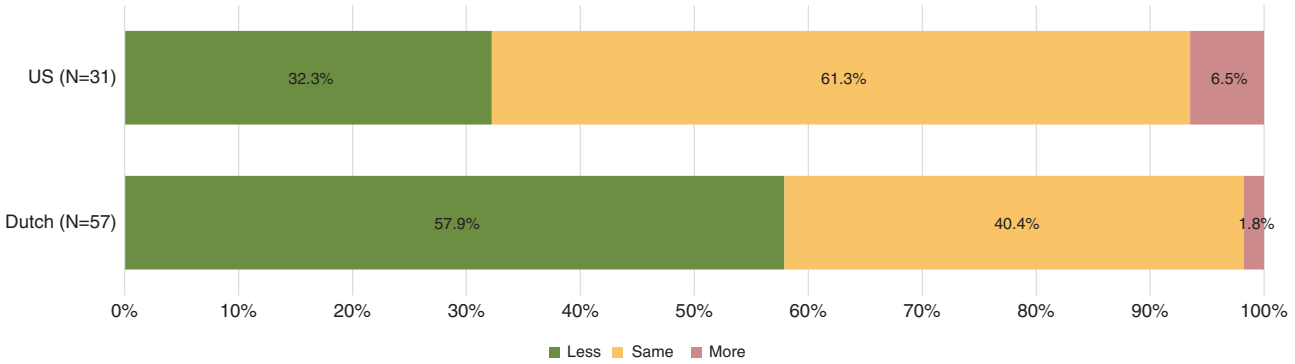


Fig. 3 Intensity of prodrome during treatment compared to before treatment for the US and Ducth patients. Intensity of prodrome during treatment compared to before treatment.

electronic device that can record time of day and time outside without a prodrome, weather conditions such as direct sunlight, cloudy, overcast, etc.; and it will indicate the previous days exposure relevant to concerns about photopriming.

Since the TTP does not challenge the patients to continue exposure to the point of a phototoxic reaction, it would provide for a safer, patient-compatible efficacy measure. Therefore, it is suggested that the average daily TTP would be a preferable primary endpoint to evaluate the efficacy of future treatments for EPP. In fact, a recent randomized, placebo-controlled phase 2 trial in EPP patients of an oral melanocortin 1 receptor agonist, dersimelagon, used the average daily TTP as the primary endpoint, as well as to assess correlations of the endpoint with other clinical and quality of life measures. The recently reported results showed significant improvement compared to placebo in average daily time to first prodromal symptom with sunlight exposure at both doses tested after 16 weeks of treatment ($p = 0.008$, and $p = 0.003$, respectively).[35,36] These results indicate that the average daily TTP can provide an effective primary efficacy endpoint for future EPP treatments that avoids patients' ingrained fear of pain.

Limitations

In the US cohort the time between the clinical trials (2014) and the time of the survey (2018) may be subject to recall bias. As afamelanotide was not approved in the United States at the time of the survey, participants may have been more likely to report positive results on treatment. However, this effect is unlikely since the US cohort results are comparable to the Dutch cohort, most of whom have been on the drug for up to two years. Also, the smaller effect in the Dutch cohort in time to recovery could be explained by recall bias. Further characterization of the time to recovery before treatment is needed.

Conclusion

Afamelanotide treatment for patients with EPP was associated with substantially increased TTP, decreased intensity over time, and improved recovery from the prodromal symptoms. Therefore, TTP could provide an improved efficacy endpoint for treatment effect that is both safer and more relevant to the experience and expectations of the EPP patients. Future studies will determine if TTP can provide an effective primary endpoint for treatments designed for EPP, allowing patients to avoid incapacitating pain attacks.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author (R.J.D. or D.W.), upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization: R.J.D., K.W., D.W., J.G.L. Data curation: J.R.O., D.W. Formal analysis: J.R.O. Funding acquisition: R.J.D. Investigation: K.W., E.J.E.v.B., D.W. Methodology: R.J.D., H.N., J.R.O., D.W., J.G.L.; Supervision: R.J.D. Visualization: J.R.O., D.W. Writing—original draft: R.J.D., D.W. Writing—review & editing: D.W., J.G.L., J.R.O., M.B., M.A.E.M.W., J.H.P.W., K.W., H.N., R.J.D.

COMPETING INTERESTS

J.G.L. report financial support from Clinuvel to cover expenses incurred for data entry for the European Medicines Agency–directed afamelanotide registry. J.H.P.W. reports grants and travel fees from Clinuvel during the conduct of the study. R.J.D. is a consultant for Mitsubishi Tanabe Pharma America. The other authors declare no competing interests.

ETHICS DECLARATION

In the US study, patients were interviewed over the phone by a single study coordinator from the American Porphyria Foundation (APF). The principles of the Declaration of Helsinki were followed, and patients provided oral consent at the time of interview. In the Dutch study, patients were interviewed in-person by a specialized nurse during clinic visits. Patients provided written informed consent at the time of interview or earlier. The study adhered to the principles of the Declaration of Helsinki. Institutional review board approval was not required for the preliminary interviews as the APF receives no federal funds. The follow-up study was approved by the Medical Ethics Review Board of the Erasmus MC Rotterdam.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41436-021-01176-z.

Correspondence and requests for materials should be addressed to R.J.D.

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