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COMMENTARY

The Patient Perspective: A Matter of Minutes

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This article describes how patient input can contribute to medical product research and development processes, regulatory reviews, health technology assessments and reimbursement decision-making. It builds directly from my presentation in the symposium, "Patient preferences in the medical treatment lifecycle" at the 10th Meeting of the International Academy of Health Preference Research (IAHPR) in Basel, Switzerland, on the 13th of July 2019 [1, 2]. I thank the meeting co-chairs, organizers, attendees and my fellow panelists, including Professor Hans Hillege, MD, PhD, MSc, who was also present at the European Medicines Agency (EMA) meeting in September 2014, when regulatory approval for afamelanotide to treat adults with erythropoietic protoporphyria, an ultra-rare disease that causes severe intolerance to light, was discussed. At the symposium, Professor Hillege mentioned that it was one of the few cases to his knowledge whereby a meeting with patients overturned a unanimous negative opinion. Five years after the EMA approval, patient access to afamelanotide remains limited. What happened?

1 The Disease

Erythropoietic protoporphyria is an inborn disorder of heme biosynthesis that belongs to a group of diseases known as porphyrias. It causes severe intolerance to the visible radiation components of light due to an accumulation of the phototoxic heme precursor protoporphyrin IX in erythrocytes and endothelial cells of the blood vessels beneath the skin [3–6]. Within minutes after exposure to light, especially outdoors, individuals with EPP experience phototoxic reactions that cause severely painful and incapacitating burning sensations in their skin. This occurs even when it is overcast, or with some forms of artificial light. Despite the excruciating and sustained intensity of these sensations, external cutaneous manifestations are rare and symptoms remain invisible. When a reaction is particularly pronounced, swelling, edema, skin lesions, erosions, and crusting may appear hours and days later. Burning sensations can take several days to resolve, during which patients hide from all light sources to avoid exacerbation.

Conventional ultraviolet-protecting measures such as topical sunscreens are of no use, thus patients need to cover their skin extensively and to stay indoors. During early childhood, individuals with EPP typically experience frequent traumatizing reactions and, consequently, develop a deeply ingrained fear of sunlight, adopting a lifelong behavior of light avoidance. Moreover, because of the invisible nature of the disease, patients experience difficulties in communicating the nature and severity of their condition. Consequently, they are labeled as malingerers and suffer ridicule because of their light avoidance behavior. This adds psychological distress and social isolation to the physical effects of EPP, further impacting quality of life, schooling, employment opportunities, family, and social activities [7–10].

2 The Journey Begins

I am a porphyria advocate and biochemist, and I myself have EPP. Like many other patients, I had tried all types of remedies throughout my life [11], all to no avail. Then, in early 2006, I read about a synthetic analog of the alpha-melanocyte-stimulating hormone, which is currently known as afamelanotide [12]. I spoke about it with Prof. Elisabeth Minder, porphyria expert at the Municipal Hospital Triemli in Zurich, Switzerland, and we both agreed that it might have potential in treating EPP. By September 2006, Clinuvel Pharmaceuticals, the manufacturer of afamelanotide, initiated the first clinical trial in EPP under the supervision of Prof. Minder. I was one of the study subjects. After gradually overcoming my lifelong

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fear of the sun, I realized my tolerance to light dramatically increased, as it did for other subjects under treatment in this first trial [13].

In the next few years, additional trials in Europe and the USA followed. Real-world evidence was collected in Italy and Switzerland from patients benefiting from special access schemes. During this period of about 5 years, patient testimonies steadily trickled in at patient meetings, through social media and by word of mouth, all pointing to a life-changing experience for those receiving treatment. By the time the manufacturer of afamelanotide submitted an application to EMA for marketing authorization in early 2012 [14], the porphyria patient community was full of hope and eagerly looking forward to a rapid approval of the drug. Naturally, the EMA had little knowledge of the severity and life-limiting nature of EPP, a poorly understood ultra-rare disease burdened by the additional challenge of 'invisibility'. To overcome this understandable hurdle, the porphyria patient community actively engaged with the EMA, offering to educate the agency about EPP and the benefits experienced by patients receiving afamelanotide treatment. After numerous exchanges, in April 2014, an EPP patient and carer delegation finally had the opportunity to speak at an EMA ad hoc expert group meeting. In September 2014, two patients with EPP were invited to the plenary meeting of the EMA Committee for Medicinal Products for Human Use (CHMP) to discuss the benefits and risks of afamelanotide [15–17]. It was the first time in the EMA's history that patients were involved in the CHMP assessment of the benefits and risks of a medicine, paving the way for a more systematic inclusion of the patient perspective in the EMA's medicine evaluation process [18].

The culmination of this phase of involvement from patients with EPP came on 24 October, 2014, when the EMA recommended afamelanotide for marketing authorization under exceptional circumstances [19]. The EMA's recommendation recognized the challenges in assessing the efficacy and the lack of therapeutic alternatives in EPP. It was supported by patients and expert physicians consistently reporting improvements in quality of life and by the data from long-term use of the therapy in the Italian and Swiss patient cohorts [20, 21]. The porphyria patient community was thrilled by this outcome and hopeful of quick access to the therapy. However, little did we know that this was just the beginning of a long and tortuous journey. What happened?

3 A Run of the Gauntlet

The lack of scientific instruments, such as specific biomarkers, to objectively measure the extent of phototoxic reactions is the first challenge to assessing the clinical efficacy of therapeutic candidates in EPP. Deeply ingrained light avoidance is another, preventing many patients from fully exploring the potential of therapeutic candidates within the timelines of clinical trials. Seasonal, meteorological, geographical, and occupational variables pose an additional problem, compounding any attempts to normalize light exposure conditions between individual study subjects. Finally, the ultra-rarity of EPP limits the number of patients that can be enrolled in clinical trials, making it harder to generate reliable evidence. Nonetheless, despite all these challenges, the data generated in the afamelanotide trials have consistently revealed significant benefits to patients, who reported in diaries the duration of direct sunlight exposure and phototoxic episodes by scoring pain intensity on an 11-point Likert scale. Duration of direct sunlight exposure on days when no pain was experienced was chosen as the primary endpoint. In the pivotal trial, patients receiving the active drug experienced a statistically significant increase of a median 28.6 h additional time in sunlight as compared with patients receiving placebo over the trial period of 180 days [22]. Now, does this outcome translate into a meaningful change in patients' lives, as suggested by patient testimonies and the evaluation of an EPP-specific quality-of-life questionnaire used in the long-term observational study and as a secondary endpoint in the clinical trials [21, 22]? Evidently, it depends on how the raw data are used. Regrettably, at the time of approval, the data were presented in a manner that still has a negative impact on access to afamelanotide:

> First, the EMA requested a post hoc re-analysis of the data, which reduced the effect from 28.6 to 24.0 h additional time in sunlight [23]. The reasons for this re-analysis remain unexplained.
> Second, the EMA divided the re-calculated 24.0 h by the 180 days of the trial period, translating the therapy's benefit to 8 min of additional direct sunlight exposure per day [23].

It is only a matter of a few minutes, which to the occasional bystander might seem irrelevant. However, for patients, these few minutes matter and make a difference between living the daytime nightmare of EPP and being able to do things that matter in life such as going to work without hiding from the sun, going grocery shopping without experiencing pain, taking your children to school or watching them play out in the sun, walking in the park with a friend, spending time with your family on an outdoors weekend trip and other things that healthy individuals take for granted. They also make the difference in how the benefits of afamelanotide are perceived by regional and national health technology assessment (HTA) bodies, which provide recommendations for the reimbursement of medicines by the healthcare system. Unfortunately, while it was concluded that the overall strength of the evidence could be considered

robust enough to recommend afamelanotide for marketing authorization, the EMA also questioned "whether the apparently small increase in sunlight would translate into a meaningful change in the patients' life" [23]. A fateful statement, which together with the 8-min average misguided HTA bodies. Two prominent examples are Germany's and England's HTA bodies:

> In 2016, Germany's Federal Joint Committee (G-BA) concluded that the additional benefit of the therapy was small, referring to the 8 min reported by the EMA [24].
> In 2018, England's National Institute for Care and Excellence (NICE) recommended against the funding of afamelanotide in the National Health Service, indicating that clinical trial results suggested small benefits of the therapy [25].

Thankfully, in Germany, patients and expert physicians have been able to make a difference again, providing their perspectives and thus contributing to the G-BA changing their assessment from "small benefit" to "not quantifiable." After an arbitration board facilitated a pricing agreement, reimbursement of afamelanotide was granted to patients starting in April 2017 [17]. In England, the International Porphyria Patient Network, the British Porphyria Association, the British Association of Dermatologists, and the manufacturer of afamelanotide appealed the negative recommendation of NICE. After hearing all stakeholders at a meeting held on the 30 July, 2018, an appeal panel upheld six grounds of appeal and remitted the evaluation to NICE on the 9 October, 2018 [26]. In the following months, the appellants submitted additional evidence and discussed it at another NICE committee meeting on the 14 March, 2019 [17]. Eight months after that meeting, as I write this article, EPP patients in the UK and beyond frustratingly have not heard back from NICE.

4 The Patient Perspective

The above are just two examples to illustrate the 5-year run of the gauntlet endured by patients all over Europe to access the treatment since the EMA approval in 2014. Now, critical observers might find fault with how the clinical trials were conducted and blame poor design for all the downstream challenges in patient access. In hindsight, things could indeed have been done better. For example, in addition to patient narratives and qualitative insights, the patient perspective could have been collected through a standardized and scientifically conducted patient preference study to better understand which treatment attributes matter to patients and how much they matter [2, 27, 28]. Plausible attributes could have been: the increase in the time spent outdoors excluding periods with obvious meteorological, occupational, and indoor impediments to light exposure; the extent of the reduction in magnitude of the burning sensations when phototoxic events do occur; quality-of-life improvements specifically relevant to patients with EPP; and the tolerance towards the treatment burden relative to the treatment benefits (Note: afamelanotide is administered once every 2 months as a subcutaneous implant by trained healthcare professionals at sparsely distributed accredited centers, requiring patients to take time off work and often travel long distances at their own expense).

Nevertheless, the available clinical trial data are sufficient to demonstrate the value of afamelanotide. It should have been self-evident that re-calculating the median clinical effect to one averaged over 180 days would minimize the benefit of afamelanotide during the periods when patients actually need it: when they are outdoors! Which is, of course, not during the entire study period. Patient representatives repeatedly raised this issue but were ignored [17]. In addition, even if we would accept this calculated daily average as an adequate measure of efficacy, it is scientifically inappropriate to deduce that the therapy's benefit is questionable. It is surprising that no one seems to have asked how much time, on average, healthy individuals actually spend outdoors in comparison. Prof. Lesley Rhodes, EPP and photobiology expert at the University of Manchester, raised this crucial point during the NICE appeal hearing. She showed that afamelanotide enables patients with EPP to increase the time they can spend outdoors to the expected normal range for this measure, as determined for healthy indoor workers [29]. This prompted the appeal panel to criticize NICE's conclusion that the benefits of afamelanotide were "small" [26]. Afamelanotide allows patients with EPP to have a second chance in life and start doing things that healthy individuals take for granted. I would not qualify this benefit as "small", either.

As patients, we have gradually overcome our lifelong light avoidance behavior and, together with our expert physicians, have started to learn more about ourselves, our condition, and about what having a normal life means. Supported by this new knowledge, real-world treatment experience could finally be captured in a manner that is better aligned with patient preferences. Soon-to-be-published data will provide even stronger evidence of the effectiveness of afamelanotide. For example, a retrospective study with Swiss patients treated between 2016 and 2018 showed how the tolerance to sunlight *increased from a median of 10 min to a median of 3 h* [30]. Another study of Dutch patients receiving afamelanotide treatment during a 3-year period showed that they could spend an additional 6 h per week exposed to light outdoors [31]. In addition, Dutch and US patients receiving treatment reported a significant increase

in time to prodrome, i.e., the time spent in sunlight until the first symptoms of a phototoxic reaction appear [32]. Finally, using a light-sensing wristwatch, it could be shown how light exposure was nearly normalized in the Dutch patient cohort as compared with healthy controls [33]. In the future, other devices under development could provide us with a better understanding of the interaction between light and patients with EPP [34].

At long last, the patient preference knowledge and real-world evidence gathered during the 5 years since EMA approval contributed to another key milestone on this 14-year-long journey: reviewers at the US Food and Drug Administration unanimously approved afamelanotide to treat patients with EPP on 8 October, 2019 [35–37]. A joyous and rewarding day for patients with porphyria in the USA and beyond who together tirelessly advocated for this moment.

5 A Second Chance

Progress has been made in including the patient perspective more systematically in decision-making processes. The porphyria patient community paving the way for patient inclusion in the EMA CHMP process is a good example of that. There is still a long way to go, however. We need to ensure that patient evidence is considered as authoritative as more conventional forms of evidence, and that it is integrated in decision making. Otherwise, we risk turning patient inclusion into an exercise in tokenism [38] and condemn patients to run the same access gauntlet, unnecessarily withholding effective treatments for years with devastating consequences on patients' health and well-being. In our era of rapid and unprecedented discoveries and as more disease knowledge develops, it is particularly urgent for rare conditions like EPP to foster flexible decision-making processes. As patients, we know best about our own disease. Surrogate decision makers should not have the authority to override patient perspectives, as EMA representatives farsightedly articulated in 2012:

> "Most drug regulators do not have the specific disease experience and do not take the drugs they authorize. Patients, on the contrary, know which outcomes and symptoms matter most to them, and they are the ones who incur the risks from drug treatment. It seems self-evident that patients' value judgements ought to be paramount" [39]

Fast forward to 2019 and, increasingly, senior executives of regulatory and HTA bodies as well as the pharmaceutical industry are publicly voicing their strong support for a more systematic integration of the patient perspective in decision-making processes. Yet it remains a matter of debate how far these good intentions have percolated through the ranks of their organizations [40]. Much more remains to be done. All stakeholders in the healthcare system must work together to ensure patients can better benefit from the life-changing advances of modern medicine.

In our case, it may be just *a matter of minutes*, but only we, who have EPP, truly understand how crucial these few minutes are in enabling us to come out of the daytime nightmare of our condition. As a porphyria advocate, educating decision makers about EPP and the difference these few minutes make has not been an easy journey. I often felt powerless, superfluous, and ignored because while our perspective had been heard, it was not truly assessed in its substance nor integrated into decision making. However, I remain positive because I know that my efforts, and those of my many other fellow advocates, have contributed to a better understanding of EPP and the gradual broadening of access to afamelanotide. Supported by the emerging real-world evidence, we will continue to provide our patient perspective to facilitate further access. Perhaps, even the EMA, NICE, and other skeptical bodies will reconsider their views on the value of this life-changing treatment, giving those who have EPP a second chance to finally step out from the shadows and into life as fully productive and engaged members of society.

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Compliance with Ethical Standards

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