Purified oral cannabidiol for pain management in severe recessive dystrophic epidermolysis bullosa

Sir,

Severe recessive dystrophic epidermolysis bullosa is a rare, genetically inherited skin fragility disorder. It is an autosomal recessive condition caused due to mutations in the COL7A1 gene that codes for collagen VII, the main constituent of anchoring fibrils within the basement membrane zone. Clinical hallmarks of recessive dystrophic epidermolysis bullosa include blister formation, chronic wounding and scarring of the skin and mucous membranes upon minor mechanical stress, thereby causing significant morbidity.[1]

We report a 21-year-old woman suffering from recessive dystrophic epidermolysis bullosa due to heterozygous COL7A1 mutations (344insG, 487delT) which lead to a frameshift and biallelic preterminal stop-codons. Oro-oesophageal blisters, erosions and strictures caused significant odynophagia, dysphagia and dystrophy resulting in undernourishment (body mass index 14.2 kg/m^2). Although clinically indicated, a gastrostomy was refused by the patient because of tomophobia. Neither topical therapy (application of budesonide with 2% lidocaine gel twice daily on the mucous membrane) nor surgical interventions (including two oesophageal dilatations) provided any relief to the patient. Attempts to provide systemic analgesia with metamizole 500 mg up to four times daily and ibuprofen 400 mg up to three times daily could not mitigate disease progression or provide satisfactory symptomatic relief. As long-term analgesic therapy was indicated, the patient refused morphine as well as other analgesic treatments (tramadol hydrochloride, gabapentin, pregabalin, amitriptyline, etc) because of concerns about opiate/drug dependence and their potential side effects. Her general condition thus progressively worsened, resulting in significant restriction in daily life activities and causing severe depression.

As a palliative approach to improve pain control and quality of life, we started administration of oral cannabidiol drops containing 20% phyto-cannabidiol (purity >99.8%, without delta-9-tetrahydrocannabinol) produced according to good manufacturing practice standards. Lacking clinical experience with purified cannabidiol in epidermolysis bullosa, the initial dose of 62 mg (10 drops, 1.6 mg/kg body weight) twice daily was prescribed according to the manufacturer's (Trigal Pharma GmbH, Austria, Vienna) standard dosage recommendations and was maintained for six weeks. As there was an excellent tolerability, the dosage was thereafter increased to 124 mg (20 drops, 3.1 mg/kg body weight) twice daily. This regimen resulted in a clinically relevant symptomatic improvement reflected by a mean pain reduction by three points on a visual analogue scale from baseline range of 4–8 to (range of 1–5 by week 6, (visual analogue scale: 0 = no pain, 10 = worst pain imaginable). In addition, pain peaks of ≥8 which were reported multiple times per week before initiating the treatment were experienced only once during the 92 weeks treatment period. Pain reduction was associated with improved swallowing, thereby ameliorating the patient's self-reported health status, quality of life and emotional state. The self-reported frequency and duration of depressive episodes decreased consistently, from twice a month prior intervention to once a month during the treatment period and from about two weeks to less than five days, respectively. After 36 weeks of treatment, the patient's mother decided to reduce the cannabidiol dose to 93 mg (15 drops, 2.3 mg/kg body weight) twice daily without informing her daughter, in order to determine whether the striking pain reduction would be dose-dependent on cannabidiol intake. Indeed, the patient reported worsening of symptoms within one week after tapering, while a subsequent re-introduction of 124 mg twice daily dose (corresponding to 6.2 mg/kg body weight daily) led to a symptomatic alleviation within two weeks, suggestive of an individual threshold dose for maintenance therapy.

Apart from a macrogol-containing laxative given daily to prevent obstipation, the patient did not take any comedication. Notably, the beneficial effects of cannabidiol were observed in an add-on setting to the analgesic premedication with metamizole and ibuprofen.

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Legal access to medicinal *cannabis* products, including purified good manufacturing practice-grade cannabidiol, is limited in European and non-European countries. However, pharmaceutical grade phyto-cannabidiol had received marketing authorization in the United States already in June 2018 and in the European Community in September 2019.[2] Cannabidiol can be legally prescribed in several countries, including Austria, Australia, Canada, Germany, New Zealand and Switzerland. Nevertheless, the use of cannabinoids in dermatology is still at an experimental stage.[3] Cannabidiol and other cannabinoids are known to have anti-inflammatory and analgesic effects.[4] Data also suggests that they foster wound healing and re-epithelialization by increased expression of platelet-derived growth factor -A and -B,[5] enhancement of keratinocyte migration as well as immunomodulation through downregulation of interleukin-1β, interleukin-6, tumour necrosis factor-α, transforming growth factor-β1 and up-regulation of interferon-γ after activation of the cannabinoid receptor type 2.[6] The literature-based evidence for use of cannabidiol in epidermolysis bullosa, however, is sparse and of rather low quality. For instance, a topical, yet not further specified "cannabidiol-oil" was reported to improve pain and wound healing in three children with epidermolysis bullosa simplex.[7] Another case series comprising three adult epidermolysis bullosa patients - two with intermediate junctional epidermolysis bullosa and one with severe recessive dystrophic epidermolysis bullosa - revealed a considerable reduction of pain and itch after sublingual ingestion of a cannabinoid-based oil, containing cannabidiol and tewtrahydrocannabinol.[8]

The therapeutic impact of cannabidiol, in particular on patients with epidermolysis bullosa, remains rather elusive. For a critical appraisal, the heterogeneous quality of many cannabidiol-oils is a major limitation. This refers to the purity and concentration of the two main cannabinoids, i.e., non-psychotomimetic cannabidiol and psychotomimetic tetrahydrocannabinol. The latter exerts psychoactive side effects including dependence and potentially detrimental effects on the developing brain.[9,10]

In addition, the content of cannabinoids and terpenes may show considerable variations, creating an unpredictable "entourage effect" on the therapeutic outcome.[11] Finally, many of the over-the-counter cannabidiol products are mislabelled and their composition ill-defined and contaminated by pesticides and microbial toxins.[12] Considering these significant shortcomings as well as the limitations of our single-case observation, large-scale, controlled clinical trials are warranted to more comprehensively assess the potential of highly purified cannabidiol to improve pain and overall quality of life alongside an acceptable safety profile in patients with recessive dystrophic epidermolysis bullosa.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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The study was supported by Trigal Pharma GmbH. The company provided cannabidiol for the patient for 4 months. Cannabidiol for the remaining 19 months was sponsored by the non-profit support group DEBRA Austria. There was no other support.

Conflicts of interest

Gerhard Nahler, MD, Ph.D. is an independent consultant. Among others, he consults physicians, the non-profit NGO International Institute for Cannabinoids (ICANNA), the European Industrial Hemp Association (EIHA) and a number of pharmaceutical companies.

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