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The role of the foam formulation in improving psoriasis treatment acceptability: a real-life experience and a literature review

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Abstract. – BACKGROUND: Topical therapies represent the first-line treatment for mild-to-moderate psoriasis. Among various topical options, the fixed-dose combination of calcipotriene (Cal) and betamethasone dipropionate (BD) foam (Enstilar®, LEO Pharma, Ballerup, Denmark) showed superior efficacy to Cal and BD monotherapy and ointment and gel formulations. In addition, the Cal/BD foam is the only topical treatment allowed for either reactive treatment of relapse or twice-weekly maintenance use. Since treatment acceptability is crucial to optimize adherence, this paper presents a case series from a multicenter experience using the Cal/BD foam, to further characterize the use of this therapeutic approach. In addition, a narrative review of studies evaluating the acceptability of the Cal/BD foam, even compared with other formulations, is provided.

CASE SERIES: The case series involved adult patients with mild-to-moderate psoriasis treated with the Cal/BD foam from October 2021 to June 2022. A clinical and dermoscopic evaluation of plaques was provided for all patients. Data from the clinical practice report complete clinical resolution of plaques in most patients after 4 weeks of active treatment with the Cal/BD foam, and the dermoscopic clearance after a maximum of 8 weeks. Full adherence to treatment was also reported. Literature evidence suggests that the Cal/BD foam is easy to apply and presents high cosmetic acceptance, rapid onset of action, high efficacy, optimal safety, and a high patient preference. The high satisfaction obtained with Cal/BD foam suggests that this formulation is better accepted than others.

CONCLUSIONS: The Cal/BD foam represents a valuable approach for managing mild-to-moderate psoriasis, both in short and long-term treatment.

Key Words:
Psoriasis, Topical therapy, Calcipotriene/betamethasone dipropionate, Cal/BD foam, Real-life experience, Acceptability, Adherence.

Introduction

Psoriasis is a chronic, immune-mediated skin disorder with inflammatory involvement that substantially diminishes patients' quality of life due to bothersome physical symptoms and considerable psychosocial burden[1,2]. The sustained control of signs and symptoms of the disease represents the main therapeutic goal[3].

Topical therapies are endorsed by current guidelines as first-line treatment for localized, mild-to-moderate psoriasis, which represents the most common form of the disease[4-6]. Among different options, the efficacy and safety of the fixed-dose combination of calcipotriene (Cal) and betamethasone dipropionate (BD) have been confirmed in several trials[5,7-9], representing the main topical therapeutic approach thanks to the synergistic effect of the combination, which allows the accelerating of the onset of efficacy maintaining a good safety profile and high adherence rates.

Although topical treatments have been proven clinically effective in treating psoriasis, patient satisfaction in clinical practice is lower than that generally reported[10-12] for other treatments. In particular, patients with psoriasis consistently report[13,14] that compulsory topical application can be time-consuming and cumbersome. Although they should be strongly motivated to treat their disease, poor adherence is probably higher t han 40%.

The choice of therapy is one of the key factors in improving patient adherence to topical treatment. It has been suggested[13] that the rheological properties of a topical formulation may determine patient preference and treatment adherence, emphasizing the importance of the texture and application characteristics.

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Accordingly, an advancement in the topical treatment of psoriasis was established in 2015 after the approval of a fixed-dose combination of Cal 0.005%/BD 0.064% alcohol- and surfactant-free aerosol foam (Enstilar®, LEO Pharma, Ballerup, Denmark; hereafter called Cal/BD foam) in the EU (in adults) and in the USA (in adults and adolescents)[15,16].

The foam formulation is characterized by a drastic metamorphosis/transformation upon application on the stratum corneum due to the presence of propellants capable of generating, through their rapid evaporation, a supersaturated solution[17]. This modification increases the drug's thermodynamic activity, enhancing skin penetration and, therefore, bioavailability compared with conventional dosage forms[18].

Clinical trials[9,19-24] have shown that the Cal/BD foam has superior efficacy to Cal and BD used in monotherapy and to Cal/BD in ointment and gel formulations while offering a similarly favorable safety profile. In addition, the recent PSO-long trial[7] reported that the regular application of the Cal/BD foam twice-weekly for up to 52 weeks (proactive management) was more effective than the reactive management (which starts as soon as psoriasis relapses) in prolonging the time to first relapse, increasing time to remission and reducing the number of relapses while maintaining a good tolerability and safety profile. On these bases, the Cal/BD foam is the only topical treatment for which the approved label allows reactive treatment of relapse and twice-weekly maintenance use[25].

Since treatment acceptability is crucial to optimize adherence, particularly in long-term treatments, this paper presents a case series from a multicenter experience using the Cal/BD foam, to further characterize the use of this therapeutic approach. In addition, a narrative review of studies evaluating the acceptability of the Cal/BD foam, even compared with other formulations, is provided.

Case Series

This case series involved adult patients with mild-to-moderate psoriasis treated with the Cal/BD foam from October 2021 to June 2022 at the specialist Medical-Surgical Clinic "Myskin" (Lecce, Italy), Gasparini Dermatology Center (Terni, Italy) and Dermatological Clinic of Perugia (Italy). Patients were treated with the Cal/BD foam according to doses and modalities defined in the summary of product characteristics (SmPC)[26]. The case series description focused on clinical and dermoscopic evaluations of plaques, which were collected from clinical records for all patients. The dermoscopic evaluations were performed to assess the vascular pattern (dotted, globular) and the degree of silver scales' presence. The presence of scarring and structureless areas was also assessed to evaluate atrophy during the treatment. Due to the retrospective nature of this case series, treatment regimens, and patient education were not standardized.

The study was conducted in accordance with the ethical principles of the revised version of the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). All patients provided written informed consent to treatment and the publication of clinical data and images. The retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Cases Description

Eight patients (50% females; mean±SD age: 61±13 years) with mild-to-moderate psoriasis were treated with one daily Cal/BD foam application for 4 weeks. Three patients presented with plaques in two different body areas. The main clinical characteristics of patients are reported in Table I.

At the first visit, all patients presented with erythematous and/or erythematous and desquamative plaques (Figure 1A, T0). Dermoscopic examination reported a monoform punctiform vascular pattern in all patients, with silver scales in half of the cases (Figure 1B, T0).

Table I. Main clinical characteristics of patients.

Characteristics	n (%)
BSA:	
• <25%	• 4 (50)
• <10%	• 4 (50)
Lesion site:	
• Lower limbs	• 4 (50)
• Scalp	• 2 (25)
• Hands/foot	• 2 (25)
• Trunk	• 1 (12)
• Upper limbs	• 1 (12)
Comorbidities:	
• Hypertension	• 3 (36)
• Diabetes	• 1 (12)
• None	• 4 (50)

BSA: Body surface area.

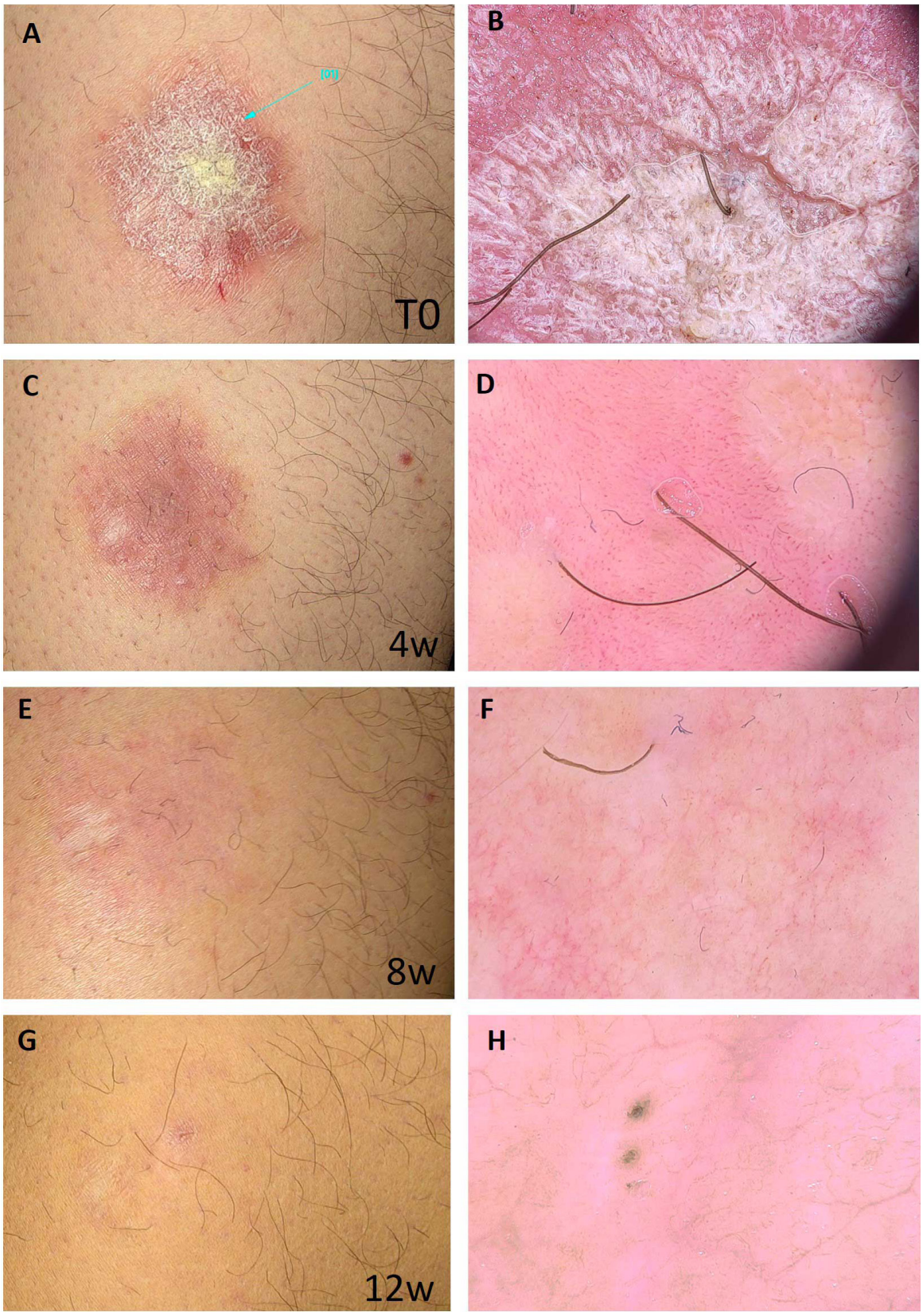

Figure 1. Representative psoriasis plaques images (**A,C,E,G**) and related dermoscopic examinations (**B,D,F,H**) at the baseline (T0, **A-B**) and after 4 weeks (4w, **C-D**), 8 weeks (8w, **E-F**) and 12 weeks (12w, **G-H**) of the Cal/BD foam treatment.

After 4 weeks of treatment, clinical and dermoscopic resolution of psoriasis plaques was reported in three patients. A proactive therapeutic regimen (application of the Cal/BD foam twice a week) was prescribed. The improvement in the clinical and dermoscopic presentation of plaques was not satisfactory in three other patients who continued the once-daily application for 4 weeks (Figure 1C and 1D – 4 weeks).

One patient with psoriasis plaques on the heel and forefoot reported complete clinical resolution in both areas and, simultaneously, the presence of a monoform punctiform vascular pattern on the forefoot at the dermoscopic analysis. Therefore, while a proactive regimen was prescribed for the heel, a once-daily application was continued on the forefoot.

Similarly, another patient reported complete clinical and dermoscopic resolution of psoriasis plaques on the scalp and the presence of erythematous and desquamative plaques with a monoform punctiform vascular pattern on lower limbs. The reactive regimen was continued on lower limbs, while a proactive scheme was applied for psoriasis plaques on the scalp.

At the 8-week visit, the three patients who continued the once-daily application of the Cal/BD foam reported complete clinical and dermoscopic resolution of plaques (Figure 1E, Figure 1F – 8 weeks), which persisted for up to 12 weeks in two of them (Figure 1G, Figure 1H – 12 weeks), after 4 weeks of proactive treatment. Patients were advised to continue the proactive treatment regimen to maintain the clinical and dermoscopic results. One patient with complete resolution at the 4-week visit maintained the clinical results up to the 12-week visit after 8 weeks of proactive treatment.

Dermoscopic analyses showed the absence of cutaneous atrophy during both active and proactive treatment of psoriasis with the Cal/BD foam in all patients. No patients reported adverse events during the treatment period or discontinued the treatment, reporting full adherence to the Cal/BD foam therapeutic scheme.

Literature Review

A literature search was conducted on PubMed, using different combinations of pertinent keywords (psoriasis AND fixed-dose combination of the Cal/BD foam; a fixed-dose combination of the Cal/BD foam AND patient satisfaction; the Cal/BD foam AND adherence), considering original research papers from 2015 to 2022, without any limitations in language. Documents from the authors' collection of the literature were also considered. Articles were selected for inclusion according to their relevance to the topic, as judged by the authors. The narrative description of the papers was provided in chronological order.

Results

Seven original articles[12,22,27-31] evaluating the acceptability of the Cal/BD foam treatment were retrieved from the PubMed search. These were four observational studies[12,27-29], two clinical trials[22,30], and one survey[31]. In the two clinical trials, the comparator treatment was the Cal/BD gel. A summary of the main characteristics of the study is provided in Table II.

Description of Findings

A 4-week observational study (LION study[12]) was conducted in Italy to assess patients' satisfaction with the Cal/BD foam in a real-life setting, involving 256 patients with different grades of psoriasis. The Treatment Satisfaction Questionnaire for Medication (TSQM)-9 median (25^{th}-75^{th} percentile) scores were 83.3 (66.7-88.9) for effectiveness, 77.8 (66.7-88.9) for convenience, and 78.6 (64.3-92.9) for global satisfaction (range from 0 to 100). In particular, 86% of patients were satisfied to extremely satisfied with the effectiveness of the foam treatment and 83% with the foam-induced relief of symptoms; more than 80% of patients rated foam use/planning from easy to extremely easy[12]. Dermatology Life-Quality Index (DLQI) showed significant improvements from visit 1 to visit 2 ($p<0.0001$)[12].

A high adherence rate (82%) to the Cal/BD foam treatment was reported in an observational, multicenter study[27] involving 410 psoriasis patients under daily practice conditions. 71% of patients assessed the foam as very/quite cooling and 59% as very/quite itch relieving; the application was considered very/quite simple by 89%[27]. In the context of the PROPEL[31] study, 449 patients participated in a survey about the experience of applying a medication-free aerosol foam to a single psoriatic plaque. 89% reported that the aerosol foam vehicle was 'appealing overall'. Similarly, a high proportion of patients agreed that the foam vehicle was 'easy to apply' (94%), 'quick to apply' (97%), and 'pleasant on the skin' (91%)[31]. Approximately half of the respondents preferred the foam to the patients' current main topical treatment[31].

Table II. Main characteristics of considered studies evaluating the acceptability of the Cal/BD foam treatment.

Author, year	Study design	Study population	Comparator treatment (if applicable)	Main conclusions on the acceptability
Paul et al[22] 2017	Subgroup analysis of the phase III, prospective, multicenter, investigator-blinded PSO-ABLE study	463 patients	Cal/BD gel	A greater proportion of foam-treated patients compared with gel achieved a Dermatology Life-Quality Index score of 0/1 at weeks 4 (p=0.004), 8, and 12 (p=0.001)
Hong et al[29] 2017	Phase IIIb, prospective, multicenter (Canada/ Germany), open-label, randomized, two-arm crossover study (PSO-INSIGHTFUL study)	213 patients	Cal/BD gel	Based on the Topical Product Usability Questionnaire (TPUQ), overall mean scores were high for both the Cal/BD foam and the gel. The Cal/BD foam was generally preferred by younger patients (aged 18-39 years)
Gerdes et al[26] 2018	Prospective, observational, non-interventional, multicenter study	410 patients	–	• 82% of patients adhered to the Cal/BD aerosol foam therapy until the end of the 4-week observational period and were willing to continue the therapy thereafter
Vender et al[30] 2018	Survey	449 patients	–	89% of patients were highly satisfied with the Cal/BD aerosol foam: • 94% in terms of ease of application • 97% in terms of rapidity of application • 91% in terms of skin sensations Approximately half of the respondents preferred the aerosol foam vehicle to the patients' current main topical.
Velasco et al[27] 2019	Retrospectivey observational study	446 patients	–	85% of patients were highly satisfied with the Cal/BD aerosol foam: • 84% in terms of effectiveness • 84% in terms of symptoms relieve • 83% in terms of rapidity of action 92% in terms of ease of use, ease of planning (94%), and ease of following instructions (90%)
Campanati et al[12] 2021	Real-life multicenter prospective observational cohort study	256 patients	–	More than 90% of patients rated the Cal/BD foam as more effective, easier to use, and better tolerated than previous topical treatments
Jo et al[28] 2022	Prospective, open-label, non-comparative, non-interventional study	218 patients	–	Most of the patients were satisfied with the Cal/BD foam treatment: • 77.0% in terms of effectiveness • 60.0% in terms of ease of use • 73.9% in terms of global satisfaction

In a retrospective observational study[28], 446 patients with psoriasis rated their satisfaction with the Cal/BD aerosol foam using the TSQM-9. Patients were highly satisfied with the product in terms of effectiveness (84%), relief of symptoms (84%), and rapidity of action (83%)[28]. Regarding convenience, patients gave high ratings to ease of use (92%), ease of planning (94%), and

ease of following instructions (90%)[28]. Global satisfaction was also high, with 85% of patients expressing satisfaction[28]. A prospective, open-label, non-comparative, non-interventional study[29] investigated treatment outcomes and satisfaction in adult patients receiving the Cal/BD foam for psoriasis in dermatological centers and outpatient clinics in Korea. Most patients were satisfied with the Cal/BD foam treatment in terms of effectiveness, ease of use, and global satisfaction[29].

The Cal/BD aerosol foam was compared to the Cal/BD gel in the phase III, randomized, multicenter, investigator-blinded PSO-ABLE study[22]. In a subgroup analysis of the PSO-ABLE study, changes in DLQI were assessed[22]. Results reported that a greater proportion of patients treated with the foam achieved a DLQI score of 0/1 at weeks 4 (p=0.004), 8, and 12 (p=0.001) compared with the gel formulation[22]. Moreover, a greater proportion of patients receiving the Cal/BD foam than the Cal/BD gel thought it was more effective, and easier to apply and generally preferred it over previous topical and systemic therapies[22]. Another phase IIIb, prospective, multicenter, open-label, randomized study (PSO-INSIGHTFUL study)[30] assessed the preferences for the Cal/BD foam or the Cal/BD gel in 213 patients with mild-to-moderate psoriasis. The Topical Product Usability Questionnaire (TPUQ) showed that both the Cal/BD foam and the gel had high scores from the last topical treatment patients received[30].

Discussion

Simplified treatment regimens and proper treatments play a major role in ensuring treatment adherence[5]. The ideal agent should be easy to apply, show high cosmetic acceptance, exhibit rapid onset of action, high efficacy and optimal safety[5].

In our case series, most patients reported complete clinical resolution of plaques after 4 weeks of active treatment with the Cal/BD foam and the dermoscopic clearance after a maximum of 8 weeks. In patients who continued the treatment with a proactive regimen, clinical and dermoscopic results were maintained for up to 12 weeks.

In two patients with different grades of residual disease in different body areas after the first 4 weeks of treatment, the Cal/BD foam was applied according to different therapeutic schemes, suggesting the flexibility of this therapeutic regimen. For instance, these two patients with the residual disease did not present at the 8-week visit: this may suggest that clinical resolution was achieved, and further clinical evaluations were not deemed necessary.

Over the last few decades, dermoscopy has become an invaluable tool in daily dermatological clinical practice for the therapeutic monitoring of skin conditions[32]. Using this tool at the baseline verifies the presence of a monomorphic vascular pattern (similar and reproducible in the different areas of the body), which is an index of psoriasis activity[33]. Indeed, the persistence of vascular structures at dermoscopy at the end of the therapy was strongly associated with relapse (17–21-fold higher risk of disease recurrence), regardless of the degree of improvement, and even with complete/nearly complete clinical healing at the end of the treatment[34]. Accordingly, in this experience, both complete clinical and dermoscopic resolution of psoriasis plaques were required to switch from a reactive to a proactive therapeutic scheme. Dermoscopic analyses also showed the absence of cutaneous atrophy during both active and proactive treatment of psoriasis with the Cal/BD foam, as previously reported[35].

Results[27-31] from the literature review suggest that the Cal/BD foam is endowed with all the properties of an ideal agent and is associated with a high degree of patients' preferences. Moreover, the high patient satisfaction obtained with the Cal/BD foam suggests that the improved cosmetic characteristics of this formulation are better accepted than those of other formulations[22,30]. For instance, preliminary data in a preclinical model suggested that the Cal/BD foam produced a cooling effect on the application area, suggesting a possible calming effect on hitching and burning, which could be hypothesized to favor patients' acceptability[36]. This enhanced acceptability could translate into greater adherence and, ultimately, greater effectiveness of topical treatment, particularly when long-term therapeutic schemes are applied.

Conclusions

Literature evidence suggests that the Cal/BD foam is one of the most manageable of the available topical products for the treatment of psoriasis, and its rapidity of action is reported to promote improved patient adherence to therapy. Most patients consider the Cal/BD foam superior to other topical treatments in terms of ease of use and tolerability, showing a complete adherence to therapy and expressing the will to continue this

treatment. Literature evidence is supported by data from clinical practice, reporting complete clinical resolution of plaques in most patients after 4 weeks of active treatment with the Cal/BD foam and the dermoscopic clearance after a maximum of 8 weeks. Full adherence to treatment has also been reported. In conclusion, based on experiences from clinical practice and literature evidence, the Cal/BD foam can be considered a valuable approach for the management of mild-to-moderate psoriasis, both in short and long-term treatment.

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Conflicts of Interest
None.

Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval
The review of patient data did not require ethical approval in accordance with local/national guidelines.

Informed Consent
All the participants signed an informed consent form.

Authors' Contributions
All Authors contributed to the definition and contextualization of the paper's contents, critically edited the manuscript, and approved its final version for submission.

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