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ORIGINAL ARTICLE

High concentration of topical amitriptyline for treating chemotherapy-induced neuropathies

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Abstract

Purpose Chemotherapy-induced peripheral neuropathy (CIPN) is a devastating pain condition of cancer therapy that may force chemotherapy dose reduction or discontinuation. Since treatment options for CIPN are quite limited, we investigated the effect of 10% amitriptyline cream on neuropathic pain.

Patients and methods This pilot study enrolled patients with hematological or solid tumors presenting hands and feet CIPN (for less than 1 month without previous treatment for CIPN [Group 1]; for more than 1 month with previous treatment [Group 2]). Patients applied 10% amitriptyline cream twice a day. Pain intensity was evaluated at 1, 2, and 4 weeks then monthly up to 1 year. The primary endpoint was change from baseline to 4-week treatment in median pain score assessed by visual analogue scale (VAS).

Results Overall, 44 patients were enrolled. Median (range) age was 67 (46–80) years, 34% were female. The majority (88.6%) had hematological malignancies, and the most commonly used chemotherapeutic agents were bortezomib and oxaliplatin. The median (range) VAS pain score decreased from 7 (4–9) at baseline to 2 (0–4) after 4-week topical treatment. No difference was seen between Group 1 and Group 2. Reduced initial chemotherapy doses in 11 patients as well as chemotherapy discontinued in 5 patients at baseline were resumed after treatment with 10% amitriptyline cream.

Conclusion Considering the limited efficacy of conventional systemic treatments in CIPN and their safety profile, 10% topical amitriptyline appears to be a good candidate for first-line CIPN therapy, allowing continuation of chemotherapy at effective doses. The results are worth to be confirmed in a placebo-controlled clinical trial.

Keywords CIPN · Neuropathy · Pain · Amitriptyline cream · Supportive care

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most devastating pain conditions and most common side effects of cancer therapy with a reported overall incidence of 38% [1]. Symptoms are characterized by spontaneous or evoked pain reported as electric shock-like sensations, burning, paresthesia, dysesthesia, allodynia, or hyperalgesia [2].

Julien Rossignol and Benoit Cozzi are the first co-authors.

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Predominantly located at hands and feet, these peripheral neuropathies may have a detrimental effect on patients' motor function and quality of life (QoL), and generate a substantial challenge for healthcare professionals. CIPN can have significant repercussions on patient management as it may force chemotherapy (CT) dose reduction or even discontinuation leading to loss in efficacy and thus a missed therapeutic chance in the context of serious diseases [3].

Currently, the treatment options for CIPN are quite limited. Duloxetine, a serotonin and norepinephrine dual reuptake inhibitor, was shown to improve the symptoms of established CIPN, in a randomized, double-blind, placebo-controlled, crossover phase III trial involving 231 patients with taxane- or platinum-associated CIPN. Patients who received duloxetine as initial therapy reported a greater mean decrease in average pain of 1.06 compared with 0.34 in the placebo arm ($p = 0.003$) [4]. Other oral antidepressants, by contrast, have not shown a similar benefit. In an 8-week, double-blind, randomized, placebo-controlled, parallel-group study, oral amitriptyline was administered in 44 patients with CIPN at an initial starting dose of 10 mg/day followed by a dose escalation of 10 mg per week up to a maximum target dose of 50 mg/day. Results from this study showed that amitriptyline may improve QoL even though no significant effect on pain and other neuropathic symptoms was achieved, which was thought due to low dose of the amitriptyline (the American Academy of Neurology recommends 25 up to 100 mg/day) and small sample size [5].

So far, the effects of topical amitriptyline in the treatment of CIPN have been evaluated in two randomized, double-blind, placebo-controlled trials [6, 7]. Both trials assessed topical amitriptyline administered in low concentrations (< 5%). The first trial evaluated a combination gel consisting of amitriptyline 3%, ketamine 1.5%, and baclofen 0.8% versus placebo in 208 patients with CIPN. During 4 weeks, the patients applied the gel to at most four areas, around 1.5 mL on each area, twice daily. The sensory neuropathy subscale (primary endpoint) as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN20 (EORTC QLQ-CIPN-20) showed a trend in favor of the active arm, with a mean ± standard deviation (SD) change from baseline at 4 weeks of 8.1 ± 15.1 for the baclofen + amitriptyline + ketamine arm versus 3.8 ± 15.5 for the placebo arm, and an effect size of about 0.28 for the active arm over placebo ($p = 0.053$). For the motor neuropathy subscale, the mean ± SD change from baseline was 7.1 ± 13.7 and 1.8 ± 14.1, respectively, for an effect size of about 0.38 over placebo ($p = 0.021$). The greatest improvements were related to the symptoms of tingling, cramping, and shooting/burning pain in the hands as well as difficulty in holding a pen. There were no reported toxicities associated with the topical combination and no evidence of systemic toxicity (Barton et al. 2011). A related combination of ketamine and amitriptyline was further studied in a phase III, multicenter, randomized, double-blind, placebo-controlled study. A total of 462 cancer survivors with CIPN were treated with either a 2% ketamine plus 4% amitriptyline cream or a placebo for 6 weeks. The ketamine and amitriptyline treatment did not significantly reduce the pain, numbness, and tingling scores compared to the placebo group ($p = 0.363$). Despite the frequency and diversity of adverse effects with the amitriptyline/ketamine cream ($n = 147$), no significant difference was observed compared to the placebo group ($n = 158$) suggesting that these effects were not related to the treatment [7].

Furthermore, in five case reports of topical amitriptyline cream (5% or 10%) used to treat neuropathy from a variety of pathologies, there was a reduction in pain in all five cases associated with the application of the cream [8–11]. To our knowledge, 10% amitriptyline cream is the highest described dosage of topical amitriptyline to date. However, this dosage was only studied in a few cases of neuropathic pain unrelated to CIPN (diabetic neuropathic pain, pain due to chronic idiopathic axonal polyneuropathy, and pain due to multiple sclerosis) [10, 11]. The purpose of this present pilot study was to obtain preliminary information on the efficacy and safety of a monotherapy of 10% amitriptyline cream in the treatment of patients with newly diagnosed CIPN or CIPN that did not respond to previous pharmacologic treatment.

Patients and methods

Eligibility criteria

Patients were eligible for this study if they were receiving neurotoxic CT and had CIPN symptoms, such as numbness, burning, tingling, or pain. Eligible patients were at least 18 years of age, and had > Grade I sensory CIPN based on the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 grading scale. Patients with hematological malignancies (lymphoma, myeloma, mastocytosis, etc.), or solid tumors (e.g., lung, gastrointestinal [GI] cancers) were eligible for the study. CIPN had to be limited to the hands and/or feet where the cream could be applied. Karnofsky performance status eligibility was ≥ 50%. Patients were excluded if they had any known hypersensitivity to amitriptyline, a history of neuropathy from other causes (i.e., diabetes, thyroid dysfunction, B12 vitamin deficiency, or alcohol abuse), open skin lesions in the region the cream was to be applied, or were concurrently treated with any agent with suspected efficacy for neuropathy, such as anticonvulsants or tricyclic antidepressants. There was no exclusion criterion related to type of CT.

Study design and treatment

This pilot study was an open-label, non-comparative, uncontrolled, prospective clinical trial conducted at the Pain Management Department at the Necker Hospital, Paris, France. Eligible patients who signed the informed consent were instructed to apply 1 g of 10% amitriptyline cream (oil-in-water emulsion), with a measuring device, twice a day to each area with pain, burning, numbness, and/or tingling. Patients were asked to apply the cream thinly to the affected areas and gently rub it in. They were told to wait 30 min before handwashing without need for footwashing. Patients were required to maintain topical amitriptyline treatment during the whole CT course and up to 1 year. The amitriptyline cream was compounded at Delpech Pharmacy in Paris, France.

Patients were contacted by phone or by email at 48 h after the first application of topical amitriptyline to monitor safety. They were afterwards routinely evaluated to assess pain intensity after 1, 2, and 4 weeks and then monthly up to 1 year, during clinical outpatient visits. Pain intensity was measured before and after the application of topical amitriptyline, using the visual analogue scale (VAS) with a score ranging from 0 (no pain) to 10 (worst possible pain). Moreover, patients were also questioned about the intensity of other CIPN symptoms, such as numbness, burning, tingling, and electric shock sensation before and after the application of the cream. Adverse events were also assessed by asking the patients about any systemic or local side effects. All adverse events were reported regardless of whether they were deemed to be related to the treatment as per the investigator's assessment. They were graded using NCI-CTCAE version 4.0. Patients were required to maintain topical amitriptyline treatment during the whole CT course, and were followed-up for up to 1 year after treatment initiation with topical amitriptyline. Compliance was assessed by contacting the patients by phone or email at 48 h and at 1 week after the first application of topical amitriptyline, and at subsequent outpatient visits.

Informed consent was obtained from all patients prior to enrolment in the study. The study was approved by the Research Ethics Committee of the Hôpitaux Universitaires Paris-Ouest (HUPO), and by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL). There was no screening log maintained at the study site.

Study endpoints

The primary endpoint was the reduction in the median pain score at 1 month compared to baseline, as assessed by the VAS (0–10 points). Secondary endpoints included the reduction in the median VAS pain score at 1 month compared to baseline, number of adverse events reported, and the number of patients who resumed initial CT doses after topical amitriptyline treatment.

Statistical analysis

Patients were stratified in two groups: Group 1 encompassing patients with CIPN for less than 1 month who had not previously received any pharmacologic treatment for CIPN (Table SI); Group 2 encompassing patients with CIPN for more than 1 month who had not responded to previous pharmacologic treatment considered for CIPN (antidepressants, anticonvulsants, opioids) (Table SII and SIII). Patients in Group 2 had to discontinue their previous pharmacologic treatment for CIPN before the start of topical amitriptyline treatment without a washout period.

All of the data collected were numeric and were expressed as numbers, percentages, median, and ranges. VAS scores recorded at each study visit were analyzed using the Wilcoxon signed rank test. Two-tailed significance was set at $p < 0.05$. Because of limitations in study design, no between-group comparisons were performed. No formal sample size calculation was done due to the pilot nature of the study; a sample of 44 patients was anticipated to be appropriate for this investigation with the stratification to the two above described groups.

Results

Patients

A total of 44 patients with CIPN were enrolled over a 12-month period in the pilot study and were all treated with topical amitriptyline. Of these patients, 17 were allocated to Group 1, and 27 to Group 2. Baseline characteristics of the study population are summarized in Table 1. The median (range) age of the patients was 67 (46 to 80) years, and 34% of patients were female. Some patients had co-morbidities without pre-existing neuropathy: 2 patients suffered from type 2 diabetes, 1 patient had hypothyroidism, and 3 patients had hypertension. Overall, 39/44 patients (88.6%) had hematological malignancies, whereas 5 patients had solid tumors (lung and GI cancers). Karnofsky performance score ranged from 50 to 80%. The two most commonly used chemotherapeutic agents in this study were bortezomib and oxaliplatin. The median (range) delay between the start of neurotoxic chemotherapy's protocols and the occurrence of CIPN was 4 months (1–15) and the median (range) delay between the first sign of CIPN and the beginning of the treatment with amitriptyline cream was 6 months (1–24). Among the study population, there were 3 patients in Group 2 suffering from CIPN for more than 1 year who exhibited a depressive syndrome associated with neuropathic pain. Moreover, all patients in Group 2 had major functional impairment at baseline (difficulty in grasping, in walking, and in wearing clothes, and inability to wear closed shoes).

Table 1 Patients' baseline characteristics

Characteristic, *n* (%)		Group 1 (*N* = 17)	Group 2 (*N* = 27)	Total (*N* = 44)
Age (years)	45–54	5 (29)	9 (33)	14 (32)
	55–64	4 (24)	2 (8)	6 (13)
	65–74	7 (41)	10 (37)	17 (39)
	≥ 75	1 (6)	6 (22)	7 (16)
	Median (range)	62 (46–79)	67 (46–80)	67 (46–80)
Gender	Male	11 (65)	18 (67)	29 (66)
	Female	6 (35)	9 (33)	15 (34)
Neurotoxic Agent	Oxaliplatin	7 (41)	7 (26)	14 (32)
	Bortezomib	6 (35)	9 (33)	15 (34)
	Vinca alkaloids	1 (6)	7 (26)	8 (18)
	Lenalidomide	2 (12)	1 (4)	3 (7)
	Bendamustine	0 (0)	3 (11)	3 (7)
	Arsenic trioxide	1 (6)	0 (0)	1 (2)
Primary Disease	**Hematologic**	**12 (71)**	**27 (100)**	**39 (88)**
	Mastocytosis	0 (0)	4 (15)	4 (9)
	Myeloma	6 (35)	9 (33)	15 (34)
	Lymphoma	5 (30)	14 (52)	19 (43)
	Acute promyelocytic leukemia	1 (6)	0 (0)	1 (2)
	Solid tumors	**5 (29)**	**0 (0)**	**5 (12)**
	Lung	2 (12)	0 (0)	2 (5)
	Gastrointestinal	3 (17)	0 (0)	3 (7)
CIPN Grade (NCI-CTCAE Version 4.0)	II (moderate symptoms; limiting instrumental ADL)	9 (53)	11 (41)	20 (45)
	III (severe symptoms; limiting self-care ADL)	8 (47)	16 (59)	24 (55)
Pretreatment VAS Pain Score	4–5	2 (12)	3 (11)	5 (11)
	6–7	10 (59)	16 (59)	26 (59)
	8–9	5 (29)	8 (30)	13 (30)
	Median (range)	6 (4–9)	7 (4–9)	5 (2–7)

Percentages are calculated as n/N. Values in bold correspond to the sum of their disease subtypes

ADL activities of daily living, *CIPN* chemotherapy-induced neuropathy, *CTCAE* Common Toxicity Criteria for Adverse Events, *NCI* National Cancer Institute, *SD* standard deviation, *VAS* visual analogue scale

Efficacy

Baseline pain intensity was moderate to severe with a median (range) VAS pain score of 7 (4–9). After 1 week of topical amitriptyline treatment, there was a decrease of at least 3 points in the VAS in all patients. Median pain score reduction in Group 1 was 4 points after 1 week of treatment and 5 points in Group 2. At the 4-week study visit, the median (range) VAS pain score was significantly reduced to 2 ($p < 0.0001$ compared to baseline). Table 2 illustrates the median VAS pain scores at baseline and at the 4-week study visit, and the median changes in pain scores in the whole study population. Figure 1 depicts median VAS pain scores for Group 1 and Group 2 at baseline and after 4 weeks of 10% topical amitriptyline treatment.

Half of the patients (22/44, 50%) were still applying amitriptyline cream at the 1-year study visit, whereas 9 patients (20%) stopped amitriptyline after 1 month of treatment because of total relief of pain and experienced no recrudescence in CIPN symptoms. For patients who continued the treatment over 1 year (mainly patients with myeloma who received long-term neurotoxic chemotherapy's protocols), the median (range) duration was 17 months (12–24) whereas it was 2 months (1–9) for patients who stopped the treatment before the 1-year study visit.

Two patients (one in Group 1 and one in Group 2) seemed to have had a long-lasting post-therapy effect. In fact, these 2 patients prematurely discontinued topical amitriptyline

Table 2 Descriptive statistics for visual analogue scale (VAS) pain scores at baseline and at 4-week visits ($N = 44$)

Study visit	Baseline		Week 4	
Variable	Score range	Patients, *n* (%)	Score range	Patients, *n* (%)
VAS pain scores ranges	4–5	5 (11)	0–1	9 (20)
	6–7	26 (59)	2	21 (48)
	8–9	13 (30)	3–4	14 (32)
Median VAS pain score	7		2	
Median change in pain score from baseline	5			

Percentages are calculated as n/N

VAS visual analogue scale

treatment at 15 days while they were still receiving CT. The patients' VAS pain scores, which were 6 and 9 at baseline, decreased to reach 0 and 1 at the 4-week study visit, respectively, and they did not experience recrudescence in CIPN symptoms at the 6-month study visit (for the patient in Group 1) or at the 1-year study visit (for the patient in Group 2). Two other patients died before the 1-year study visit due to their primary disease.

Safety

Only one patient (in Group 2) with a preexisting atopic dermatitis experienced a local side effect (skin irritation) leading to treatment interruption. No other local or systemic side effects were reported throughout the study, and no major compliance issues were identified.

At baseline, 5 patients (2 in Group 1, and 3 in Group 2) discontinued CT due to intense pain sensation (baseline VAS pain scores ranged from 7 to 9). However, after 1 month of topical amitriptyline application which provided efficient control of pain (reduction of VAS pain score to a range of 0 to 3), CT could be resumed at reduced doses in 4 out of these 5 patients. Moreover, 1 out of the 2 patients in Group 1 who discontinued CT at baseline resumed initial CT doses. Similarly, 11 patients (5 in Group 1 and 6 in Group 2) required CT dose reduction at baseline due to neuropathic pain (baseline VAS pain scores ranged from 5 to 9). The effective pain control that amitriptyline provided after 1 month of treatment allowed to resume initial CT doses in these 11 patients for whom doses were decreased (VAS pain scores ranged from 0 to 3, at the 1-month study visit).

As a result of a protocol deviation regarding amitriptyline administration, some patients ($n = 3$) only received amitriptyline on one side (foot and/or hand) and no treatment was applied on the other side. It was noted that pain was only relieved on the side where amitriptyline was applied, and there was no pain relief in the untreated extremities.

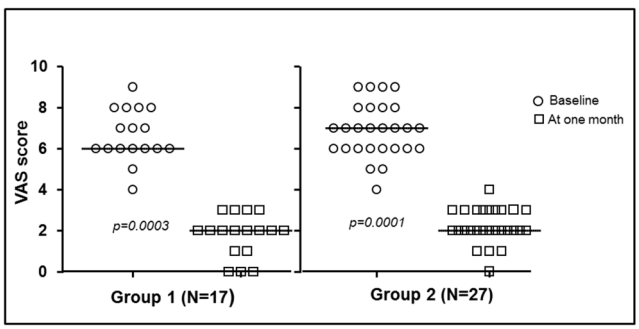

Fig. 1 Median visual analogue scale pain scores for Group 1 and Group 2 at baseline and after 1 month of 10% topical amitriptyline application

Discussion

This prospective, pilot study showed that 10% topical amitriptyline cream alleviated chemotherapy-induced neuropathic pain in cancer patients, with no local or systemic safety concerns. To our knowledge, this pilot study is the first study that has evaluated the efficacy of 10% topical amitriptyline in a large series of patients with CIPN.

The course of CIPN is unpredictable and varies with each CT agent, reflecting their distinctive mechanism of action. CIPN symptoms tend to gradually improve after treatment cessation, but they also may persist or worsen as a result of permanent nerve damage. In general, CT agents cause an axonal peripheral neuropathy by different mechanisms: harming microtubules, interfering with microtubule-based axonal transport, causing mitochondrial dysfunction, causing changes in pain mediator release (like cytokines, growth factors, and ion channels), or cytotoxic effects on DNA. The afferent pain nerve fibers are predominantly affected, and peripheral nerve damage results in their sensitization and spontaneous activity and, consequently, in hyperexcitability in the dorsal column of the spinal cord. Peripheral nerve injury also activates spinal cord non-glial cells to release glutamate and other cytokines, contributing, in this way, to peripheral and central nerve sensitization [3].

So far, there are no pharmacological disease modifiers which could reverse these debilitating cellular alterations.

Hence, treatment of CIPN only consists of supportive measures, focused on pain relief. Anticonvulsants, antidepressants, and opioids, which are considered the conventional pharmacologic treatment for neuropathic pain, have limited efficacy and a poor tolerance profile. They have broad arrays of adverse effects and could lead to drug dependence. Systemic amitriptyline, like all tricyclic antidepressants, has numerous side effects which include anticholinergic effects (dry mouth, blurred vision, mydriasis, increased intra-ocular pressure, constipation, urinary retention, urinary tract dilatation, etc.), cardiovascular reactions (hypotension, tachycardia, syncope, etc.), neuromuscular reactions (confusion, hallucinations, drowsiness, etc.), and other allergic, hematological, GI, or endocrine adverse events [12].

Since the use of systemic tricyclic antidepressants is associated with several toxicities, a topical treatment option could be beneficial for patients with CIPN. Moreover, topical administration of effective agents would reduce systemic adsorption and side effects while maximizing local dosage and treatment effects [7]. Several studies on topical amitriptyline have been conducted, and they have produced mixed results concerning the treatment of neuropathic pain [11]. In the double-blind, placebo-controlled trial conducted by Barton et al. [6] which evaluated the effects of a combination gel containing 3% amitriptyline in 208 patients with CIPN, the gel resulted in a trend toward more improvement in sensory neuropathy and a statistically significant improvement in motor neuropathy as measured by the EORTC QLQ-CIPN20 ($p = 0.021$). Blood samples were taken from four patients treated with topical amitriptyline, and amitriptyline levels could be detected in the plasma in only 1 out of 4 patients, but levels were well below systemic therapeutic values, implying that topical amitriptyline has very little systemic absorption [6]. In the five case reports evaluating 5% topical amitriptyline (in 2 patients suffering from intractable neuropathic pain) or 10% topical amitriptyline (in 3 patients with diabetic neuropathic pain, pain due to chronic idiopathic axonal polyneuropathy, and pain due to multiple sclerosis), topical amitriptyline also produced positive results in patients with peripheral neuropathy related to other etiologies than CIPN [8–11]. These cases also suggested that topical amitriptyline has an analgesic dose-response effect.

Despite all the reported positive outcomes associated with topical amitriptyline, Gewandter et al. [7] reported in their double-blind, placebo-controlled clinical trial that 2% ketamine plus 4% amitriptyline cream did not alleviate chemotherapy-induced pain, numbness, and tingling in cancer survivors compared to placebo ($p = 0.363$). These findings suggest that concentrations of topical amitriptyline higher than 4% may be well tolerated and beneficial to patients with CIPN and are worth investigation [7]. Our study, which described the efficacy and safety of medium- to long-term treatment with 10% topical amitriptyline cream in 44 patients with CIPN, supports this hypothesis.

Interestingly, though pathological lesions are different according to the CT agents, patients in our study experienced a similar efficacy from topical amitriptyline. The mechanism involved is still unknown but preclinical work has demonstrated that local administration of amitriptyline produces peripheral antinociceptive and antihyperalgesic actions in models of inflammatory and neuropathic pain in rats [13, 14]. These peripheral actions are mediated, in part, by an interaction with endogenous adenosine, most likely an inhibition of the cellular uptake of adenosine, with a consequent activation of adenosine A1 receptors on sensory nerve terminals. A local anesthetic action for amitriptyline seems to be also involved and could explain the residual action of topical amitriptyline [13]. Moreover, amitriptyline also blocks sodium channels. Sodium channel blockade by amitriptyline prevents excessive nociceptor discharge by blocking the action potential, similar to a local anesthetic such as lidocaine (which is more potent than amitriptyline). Furthermore, there is evidence that sodium channels are involved in modulating N-methyl-D-aspartate (NMDA) receptors; thus, topical amitriptyline could also possibly act indirectly on NMDA receptors [15]. Patients in our study did not experience recrudescence in CIPN symptoms for several months after discontinuing topical amitriptyline treatment. This suggests that topical amitriptyline may have a long-lasting post-therapeutic effect.

This exploratory study provides promising clinical results which should be interpreted with caution due to several limitations such as the small sample size, and particularly the lack of a control group. However, the results suggest that treatment with topical amitriptyline may have the potential to be of considerable importance to cancer patients suffering from CIPN. Based on these valuable clinical results, a larger, randomized, placebo-controlled clinical trial is warranted.

Considering the limited efficacy of conventional systemic treatments in CIPN and their safety profile, 10% topical amitriptyline appears to be a good candidate for first-line CIPN therapy investigation. If our results are confirmed, its use would avoid systemic side effects reported with oral drugs and allow the continuation of CT course at effective doses, thus preventing a loss of opportunity in the management of the underlying malignant disease.

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Authors' contributions CG designed and conducted the study, enrolled patients, analyzed the data, and wrote the manuscript. JR, SH, and BC enrolled and monitored patients, and collected the data. OH and MLV referred patients, and contributed to the review of the data and the manuscript. FL contributed to the review of the data and the manuscript.

Compliance with ethical standards

Informed consent was obtained from all patients prior to enrolment in the study. The study was approved by the Research Ethics Committee of the Hôpitaux Universitaires Paris-Ouest (HUPO), and by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL).

CG is acknowledged as inventor of a patent application owned by the compagny Algo Therapeutix SAS.

The authors have full control of all primary data and agree to allow the journal to review their data if requested.

Conflicts of interest The authors declare that they have no conflicts of interest.

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