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Effects of Elexacaftor-Tezacaftor-Ivacaftor on Nasal and Sinus Symptoms in Children With Cystic Fibrosis

Guillaume Petit | Aurélie Coudert | Ruben Hermann | Eric Truy | Maxime Bonjour | Philippe Reix | Sonia Ayari

Hôpital Femme Mère Enfant, Hospices Civils de Lyon, 59 Boulevard Pinel, Lyon, France

Correspondence: Guillaume Petit (guillaume.petit01@chu-lyon.fr)

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ABSTRACT

Background: New CFTR Modulator triple therapy Elexacaftor-Ivacaftor-Tezacaftor (ETI) prove efficacy in pulmonary outcomes. However, its impact on nasal sinus symptoms in children has not been specifically studied. The aim of this study is to evaluate the impact of this therapy on nasal sinus symptomatology in children aged 6–12 years.

Methods: A prospective, single-center cohort study was conducted over a 12-month follow-up period in children aged 6–12 years at the initiation of ETI therapy. The primary outcome was evolution of the SN-5 score, a validated pediatric questionnaire measuring quality of life related to nasal sinus symptoms. A decrease of 0.5 points is considered clinically significant. Secondary outcomes included changes in clinical examination findings (obstructive turbinate hypertrophy, polyps, presence of pus in the middle meatus, and externalized mucocele), quality of life measured by the Visual Analog Scale (VAS), and number of antibiotic courses during the study period.

Results: Twenty-six patients were included between March and September 2023, with no lost to follow-up. The initial mean SN-5 score was 2.88 (95% CI {1.91; 3.85}). After 1 year, the mean SN-5 score was significantly lower (1.41, 95% CI {1.00; 1.88}, Delta = 1.47, $p < 0.001$). The VAS related to symptoms also improved (Delta = 1.7, $p < 0.001$), and the number of antibiotic courses decreased (25 vs. 69, $p < 0.001$). A trend toward improvement in clinical examination parameters was observed.

Conclusion: ETI therapy appears to significantly improve nasal sinus symptoms in children aged 6–12 years, as evidenced by improved quality-of-life scales and reduced antibiotic use.

1 | Introduction

Cystic fibrosis can result from a multitude of genetic mutations in the CFTR gene, encoding the CFTR protein [1]. Hundreds of mutation combinations are possible, making it challenging to develop individualized targeted treatments. Two main types of treatments have been described: "correctors," acting on abnormalities in CFTR protein production or maturation to make it functional, and "potentiators," increasing the probability of opening the apical membrane of epithelial cells, thereby enhancing the presence of the protein at the apical pole of the cell [2, 3]. A triple therapy has emerged and is now widely used due to its efficacy. This therapy consists of a next-generation corrector (Elexacaftor), another corretor (Tezacaftor) and a potentiator (Ivacaftor). Results of various studies favor safety and excellent efficacy in improving pulmonary parameters in patients, including exacerbations, peak expiratory flow, and antibiotic use [4–6]. The significance of Elexacaftor Tezacaftor Ivacaftor (ETI) therapy lies in its potential use for patients with at least one class II mutation (e.g., p.Phe508del) and a mutation leading to minimal or absent CFTR production ("minimal function" mutation).

The quality of life of children with cystic fibrosis is compromised by insidious but disabling symptoms affecting the nasal sinus mucosa [7], especially in children [8], even as early as the age of

6. Moreover, MRI detects early onset and progression of the severity of chronic rhinosinusitis from infancy to school age [9].

From a clinical perspective, two recent meta-analysis about nine studies favored a clinical and radiological improvement in adults treated with ETI therapy, with a significant improvement in the SNOT-22 score (at least 10 points out of 110) and overall quality of life score [10, 11]. Four studies reported specific results about radiologic improvements in adults with ETI therapy [12–15]. However, the impact on naso sinus symptoms has not been specifically studied in the pediatric population between 6 and 12.

The aim of this study is to evaluate the impact of ETI therapy on nasal sinus symptomatology in children aged 6–12 years.

The primary outcome is the evolution of the SN-5 score, a validated pediatric quality-of-life questionnaire related to nasal sinus symptoms.

Secondary outcomes include changes in clinical examination findings, quality of life assessed by the Visual Analog Scale (VAS), and number of antibiotic courses during the study period.

2 | Methods

We conducted a prospective, single-center, non-randomized open label study at the Hospices Civils de Lyon, the study's promoters. Ethical approval from the Ethics Committee was obtained on February 24, 2023 ("Comité de protection des personnes Ouest IV", Maison de la Recherche en Santé, 53 chaussée de la Madeleine, 44000 NANTES France, approval study NCT05581056) for a study classified as RIPH3 (involving human subjects and non-interventional). Recruitment was carried out over a 6-month period starting on March 3, 2023, with a 1-year follow-up duration. Three evaluations of the impact of nasosinus symptoms and clinical examination parameters were performed during this period: at baseline, 6 months, and 1 year after treatment initiation. Potential study participants were identified at the Lyon Cystic Fibrosis Reference Center at the Femme Mere Enfant Hospital as part of their regular medical follow-up. Patients and legal guardians were informed of the protocol by an investigating physician, and non-opposition was obtained from parents and children.

To be included, children had to be aged between 6 and 12 years, with a compatible genotype and treated or scheduled to be treated with ETI therapy within 1 month of inclusion.

Children were not included in case of their refusal or legal guardian to participate in the study, if not covered by National Health Service or under legal protection or if legal guardians do not speak French.

Sinus surgery during the observation period or poor tolerance of the treatment (on pulmonologist's assessment) excluded patients from the study.

Age at inclusion, gender, genotypes, weight and previous CFTR modulator therapy were initially recorded.

2.1 | Assessment of Nasosinus Symptoms

2.1.1 | Regular Assessment of Quality of Life

An assessment of quality of life related to nasosinus involvement is necessary for patient evaluation. Among many scales available, the SN-5 is a validated pediatric questionnaire [16] evaluating the quality of life of children with nasosinus symptoms, including a French version [17].

The SN-5 questionnaire (Appendix) consists of five questions assessing the five major categories of symptoms related to nasosinus involvement: number of infections, nasal obstruction, allergic symptoms, emotional impact, and activity limitation. These five items are scored on a scale of 1–7. The scoring is as follows: Never (1 point), Rarely (2 points), Occasionally (3 points), Sometimes (4 points), Often (5 points), Almost always (6 points), Always (7 points). An average score is then calculated, questioning the five items, scored out of 7. The higher the average, the poorer the child's quality of life. We only studied the overall mean SN-5 score.

A global quality of life score out of 10 is also included, called Visual Analogic Score in our study.

2.1.2 | Regular Clinical Evaluation

A clinical examination with nasofibroscopy was performed to assess polyps, mucosal hypertrophy, especially in the turbinates, purulent secretions, and externalized mucocele (defined as defined as a periorbital edema or swelling), as well as monitoring their evolution. The grading of the polyps was performed using the LildHoldt and Johansson classification [18]: 0 no polyp, I small polyp not reaching the lower edge of the middle turbinate, II polyps extending from the upper margins to the lower margins of the inferior turbinate, III polyps extending below the lower margins of the inferior turbinate. Score from both nasal cavities (right and left) were then added. For mucosal hypertrophy, the data were scored at the turbinate level using the following scale: 0 no obstruction, 1 partial obstruction, 2 total obstruction. Score from both nasal cavities (right and left) were also added

Number of antibiotic therapies administered systemically were recorded retrospectively, based on cohort follow-up data prospectively recorded and specifically noticed in the patients' medical records by referring pulmonologist.

2.2 | Statistical Analysis

Data analysis was conducted on an intention-to-treat basis for both the primary and secondary outcome measures.

The primary outcome measure analysis is based on the analysis of a quantitative variable, the mean SN-5 score in each patient before treatment initiation and 1 year after treatment initiation.

This statistical analysis involves a comparison of two paired means: the mean SN-5 score before treatment initiation and

the mean SN-5 score at 1 year after treatment initiation in patients.

The null hypothesis assumes no treatment effect. In previous studies, after external validation, a change of at least 0.5 points in the SN-5 score is used as a threshold to consider at least a slight clinical change [16]. Considering a common standard deviation of 1 of the SN-5 score, 34 patients are required to detect an expected mean difference of 0.5 before the introduction of treatment and the evaluation time for the SN-5 score, with 80% power. This estimation used a two-sided Student paired t-test for equal variances at a 5% alpha level (O'Brien, R.G. 1993). Therefore 40 patients should be included to account for potential dropout. Additionally, we chose a 1-year follow-up period to avoid seasonal bias.

The expected initial mean score was 3, which has been observed in several studies after standard treatment of nasosinus manifestations in cystic fibrosis population (nasal lavages, adenoidectomy) [19–21]. However, due to significant variations between studies, each patient is considered their own control.

Comparison between the two mean SN-5 scores was performed using a paired Student's *t*-test.

For the evaluation of secondary criteria, a description with mean and standard deviation or number and percentage, depending on continuous or categorical/binary variables, was carried out. For the secondary outcomes, either Fisher's exact test or the Wilcoxon test was performed depending on the type of data collected.

3 | Results

Twenty-six patients were included between March 3, 2023 and September 3, 2023 (Figure 1). No one was excluded from our study. 86,4% of patients were F508del/F508del, and the other 13.6% were heterozygous for F508del. In heterozygous population, 75% were F508del/Minimal Function (MF) and 25% were F508del/Residual Function (RF). 96.2% of patients were already on dual therapy with a CFTR potentiator and a CFTR corrector. Four children had undergone previous endonasal sinus surgery. Sinonasal surgeries were performed at least 3 years before initial evaluation, limiting impact on SN-5 initial evaluation (Table 1).

Concerning the primary endpoint, initial SN-5 mean score was 2.88 (95% CI {1.91; 3.85}). At 1 year, the mean SN-5 score was significantly lower with an average of 1.41 (95% CI {1.00; 1.88}, $\Delta = 1.47$, $p < 0.01$, Figure 2). The mean score at 6 months was 1.75 (95% CI {1.00; 2.59}) (Table 2 and Figure 2).

Concerning secondary endpoints, the Visual Analog Scale (VAS) related to quality of life also shew a significant improvement ($\Delta = 1.77$, $p < 0.01$, Figure 3), and the number of antibiotic courses over the year was substantially reduced (69 in the year before treatment compared to 25 in the first year of treatment, $p < 0.01$). All children (100%) had a maximum of two antibiotic courses during the year, compared to 53.8% in the previous year.

Regarding clinical examination findings, obstructive turbinate hypertrophy was statistically decreased in the children at the end of the study, with 1.4 point difference in the mean score. No

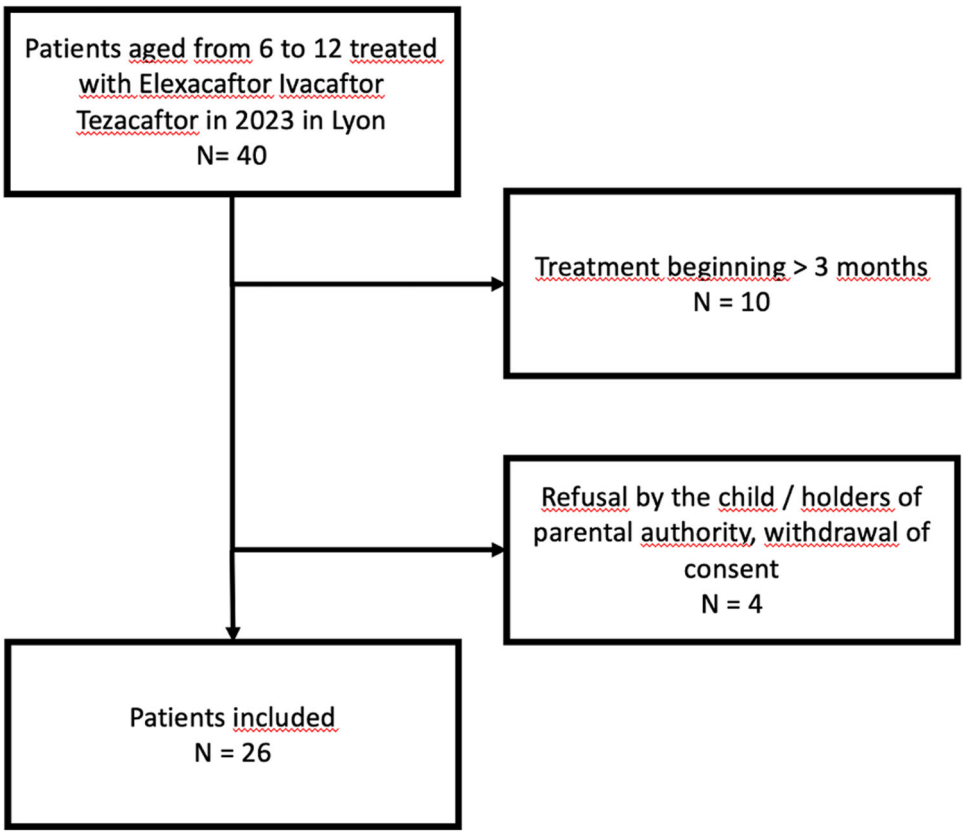

FIGURE 1 | Flow chart.

TABLE 1 | Patient's characteristics at treatment's initiation.

	***N* = 26**
Inclusion's age (years)	
Mean ± Standard deviation {mini; maxi}	8.64 ± {6; 11.7}
Weight (kg)	
Mean ± Standard deviation {mini; maxi}	27.83 ± {15.40–60}
BMI (Body Mass Index, kg/m^2)	
Mean ± Standard deviation {mini; maxi}	17.09 ± 3.11 {15.21–17.53}
Genotypes	
Homozygous p.Phe508del	22 (86.4%)
Heterozygous p.Phe508del/Minimal Function	3 (11.5%)
Heterozygous p.Phe508del/Residual Function	1 (3.8%)
Anterior treatment	
None	1 (3.8%)
LUMACAFTOR/IVACAFTOR	23 (88.4%)
IVACAFTOR/TEZACAFTOR	2 (7.7%)
At least one endonasal sinus surgery	4 (15.3%)

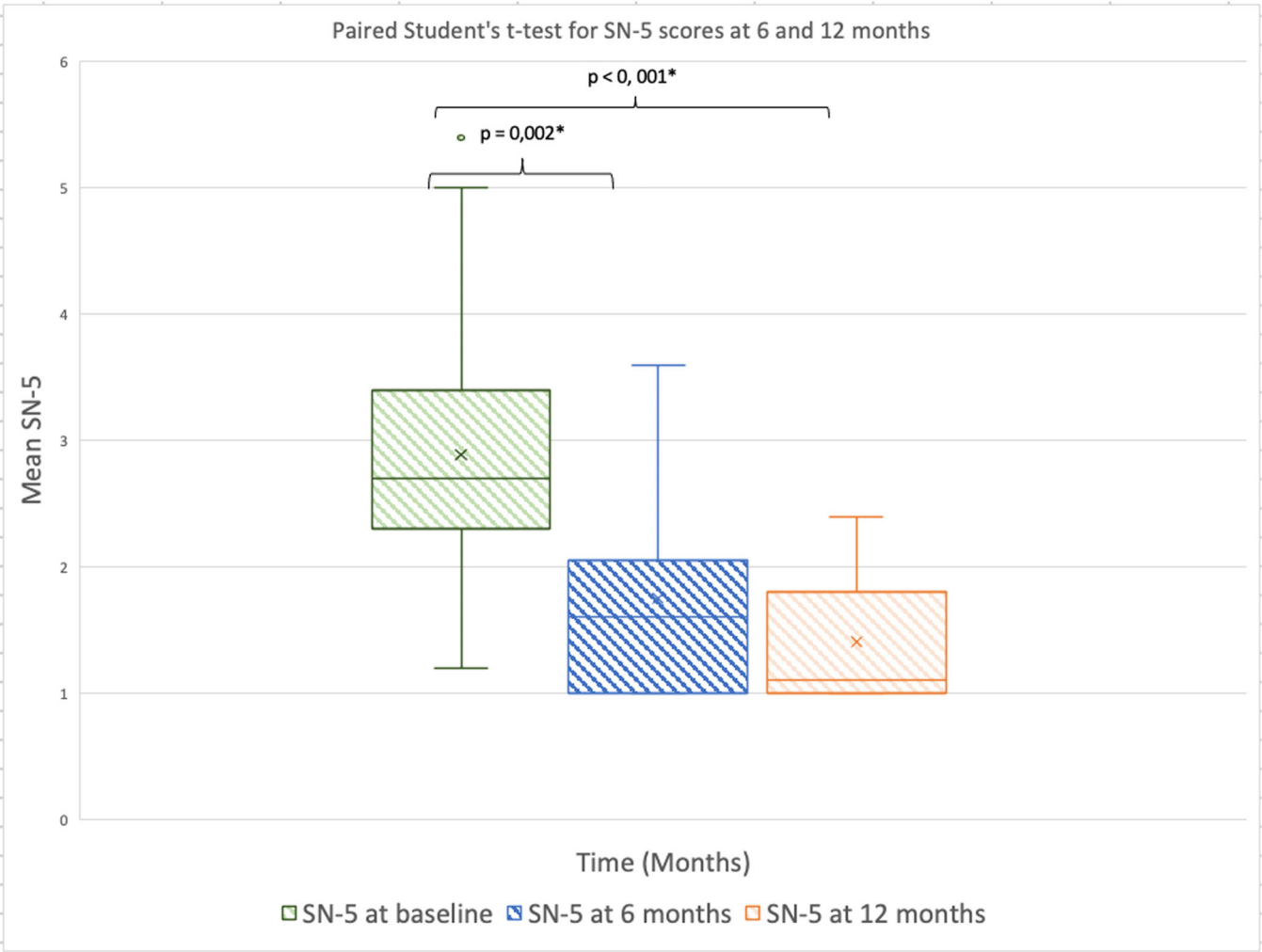

FIGURE 2 | Paired Student's *t*-test for SN-5 scores at 6 and 12 months. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 | SN- 5 at inclusion, 6 months and 12 months follow up.

	Inclusion		6 months		12 months	
	Mean (SD)	Median (Q1–Q3)	Mean (SD)	Median (Q1–Q3)	Mean (SD)	Median (Q1–Q3)
SN-5	2.88 {1.91; 3.85}	2.80 (2.40–3.30)	1.75 {1.00; 1.88}	1.60 (1.00–2.00)	1.41 {1.00; 2.59}	1.10 (1.00–1.80)

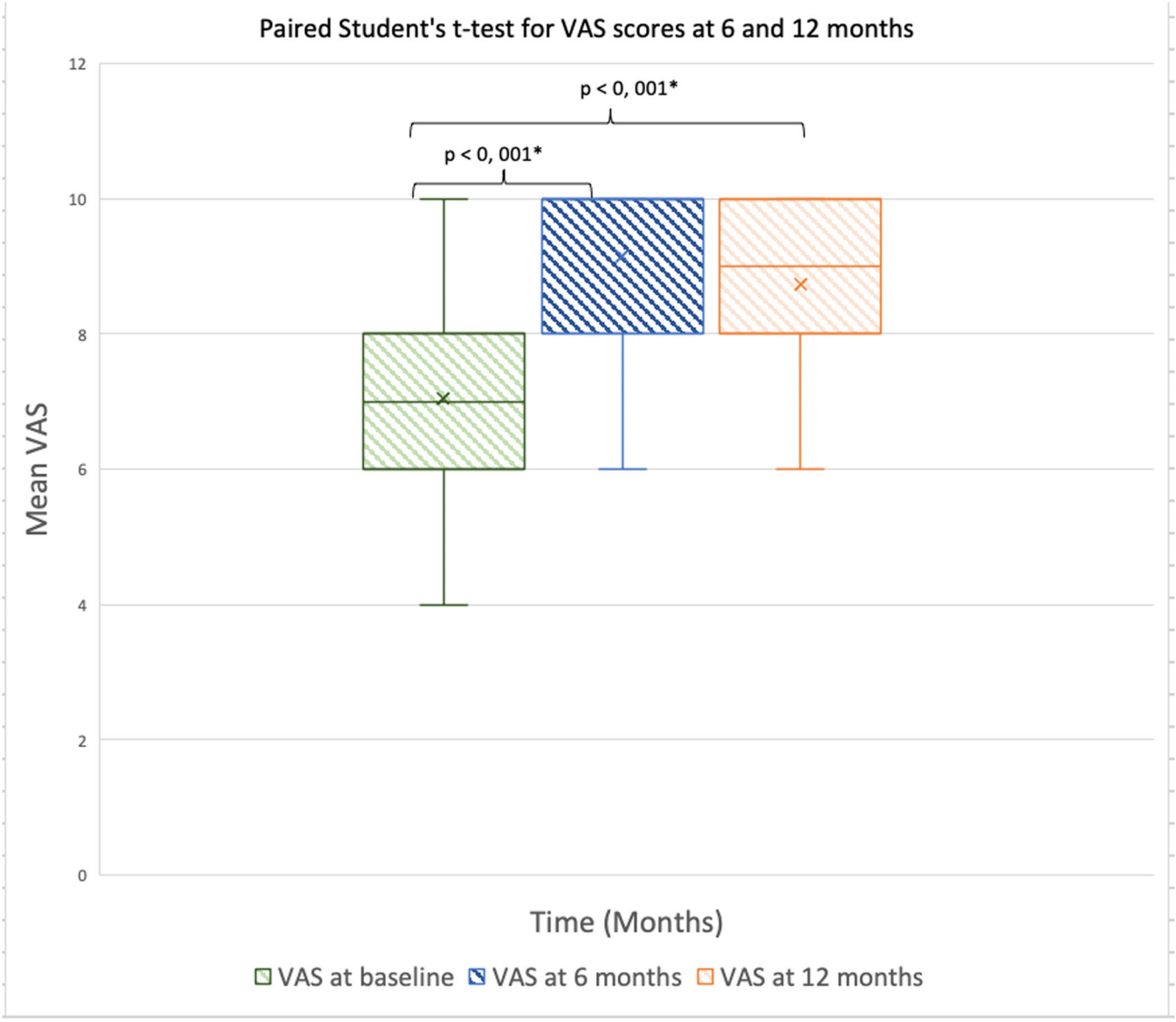

FIGURE 3 | Paired Student's *t*-test for VAS score at 6 and 12 months. [Color figure can be viewed at wileyonlinelibrary.com]

child had pus in the middle meatus, compared to 38% initially. Polyps were present in 11.5% of the children, down from 30.7% initially, and no child presented externalized mucoceles (Table 3).

4 | Discussion

A significant improvement in nasal sinus-related quality of life was observed, as evidenced by the results obtained in the SN-5 and VAS scores. Regarding the SN-5 score, in addition to a statistically significant difference despite the small sample size, a substantial effect size was noted, with a delta of 1.7 points out of 7. It is important to note that, as already described in the literature, we consider a 0.5-point difference on this scale to be clinically relevant [16]. The VAS score also increased by an average of 17% over the year, with a final average close to 9/10. These results are consistent with those previously described in adults [11, 22], as well as with the overall improvement in quality-of-life scales in children treated with ETI therapy [23].

We also observed a decrease in the number of nasal sinus and pulmonary infections. The number of systemic antibiotic courses

TABLE 3 | Clinical examination findings.

Systemic antibiotics (number of courses)	12 months before study	12 months during study	*p*-value
Mean	2.78	0.96	
Median	2.00	0	
Q1–Q3	0.00–4.00	0–1	
Min-Max	0.00–12.00	0–2.00	
Total courses number	69	25	$p < 0.01$*
≤ 2 courses during year (number patients)	14 (53.8%)	26 (100%)	

	Initial assessment	6 months follow up assessment	Final assessment	*p*-value
VAS				
Mean (SD)	7.03 {5.50; 8.56}	9.15 {8.07; 10}	8.73 {7.52; 9.94}	$p < 0.01$*
Obstructive turbinate hypertrophy (mean)				
	2.27 {1.24; 3.30}	1.56 {0.52; 2.60}	0.89 {0.07; 1.67}	$p < 0.01$*
Purulent secretions in middle meatus (presence)				
	10 (38%)	1 (4%)	0	$p < 0.01$*
Nasal polyps (mean)				
	0.58 {0; 1.6}	0.23 {0; 1.04}	0.23 {0; 1.04}	$p = 0.224$
Externalized mucocele (presence)				
	0	0	0	$p = 1$

Note: *p*-values were performed using initial and 12 months assessments.
*Statistically significant at the 0.05.

over the year was reduced by nearly threefold. On average, during the study, treated children experienced less than one infection requiring antibiotics over the past year. These results are consistent with those of the study conducted by *Walter* et al. in patients over 12 years of age [24].

Clinically, despite differences that are not statistically significant for nasal polyps, variations in clinical examination seem to align with the quality-of-life score, showing a trend toward improvement for purulent secretions in middle meatus and in obstructive turbinate hypertrophy. The lack of statistical significance for nasal polyps could have several explanations: the small sample size, the young age from our patients, the post operative status for four of our patients and the reduced percentage of abnormalities. Furthermore, in the specific population that already underwent an endonasal sinus surgery for obstructive nasal polyposis, all were suffering from recurrence of their polyposis at the time of initiation of ETI. Surgery was performed at least 3 years before ETI initiation. During follow-up, we observed complete regression of the polyps in two patients, partial regression in one patient and no progression in the last patient. We can therefore hope that these patients won't need another surgery.

The effect of the triple therapy appears to be rapid, as changes in the quality-of-life scores (SN-5 and VAS) were already significant at the 6-month evaluation ($p < 0.01$). Although the study was not intended to compare different treatments, the marked improvement observed with the introduction of ETI therapy suggests that this treatment might be more effective than the previously recommended dual therapies. Indeed, 96.2% of the children were treated with dual therapy at the beginning of the study, which did not prevent achieving a significant improvement in the SN-5 score.

The strengths of our study lie primarily in its prospective design and its exclusive focus on pediatric patients aged 6–12 years. Recent studies have focused on pulmonary symptoms [23] in this population, but none have addressed changes in nasal sinus symptoms, despite their being a common complaint. Moreover, in our study, the data were collected by only two investigators, ensuring reproducibility of the clinical examination.

The value of this study also lies in its focus on the rhinosinusitis impact of cystic fibrosis. This condition is often underestimated by patients, who are accustomed to their symptoms due to their long-standing nature. Indeed, computed tomography studies have shown the presence of objective nasal sinus changes in nearly 100% of patients, with symptomatic complaints in about 20% of children [20]. However, in this study, this impact was demonstrated using a dedicated scale (SN-5). The initially obtained average score was low, at 2.88 (out of 7), consistent with previous studies reporting a score of 3 [19–21]. Our study has some limitations: although the SN-5 score is appropriate for nasal sinus symptoms, the improvement in this score after treatment may be related to the overall effect of the therapy. In fact, ETI therapy treats other symptoms of the disease. Thus, improvements in pulmonary parameters [4–6], digestion, weight gain, and overall health [25], as well as in quality of life itself [26], may have introduced a bias in the assessment within the context of a global improvement in quality of life. The non-randomized and open-label nature of this study may also have introduced bias. However, it seems difficult to avoid this bias given the demonstrated pulmonary benefits of the treatment.

In fact, it did not seem ethical to propose a comparative study (ETI therapy vs. alternative treatment). Moreover, adherence to ETI was not specifically measured. Yet, improvement observed lets us think that it was good. Endly, first evaluation after treatment initiation was realized at 6 months, with already a strong amelioration. This study does not provide informations on the speed of treatment efficacy, which appears to occur between 1 and 4 weeks after its initiation according to data from *Heijerman* et al [27].

Moreover, ETI therapy may alter the nasal sinus disease progression in affected patients. Traditionally, in chronic rhinosinusitis in cystic fibrosis, surgery may be proposed [28] for resistance to medical treatment symptoms. According to data from cystic fibrosis treatment centers, only 3% of affected children undergo surgery, but several well-conducted multicenter studies suggest that nearly one in five children with cystic fibrosis will require endonasal sinus surgery before adulthood (an information bias linked to care outside reference centers). This figure is consistent with the rate of 14.8% obtained in our cohort of children aged 6 to 12 years. This surgery often proves insufficient, and must be repeated at least once in nearly 50% of cases [29]. It also carries a higher risk of complications in patients with cystic fibrosis [30], from minor ones like epistaxis (estimated at 1.6% postoperatively in endonasal sinus surgery [31]) to major ones like osteo-meningeal or orbital breaches. Additionally, these surgeries typically require at least one night of hospitalization and a temporary disruption of school learning. In adults, ETI therapy has already shown its value in reducing the number of nasal sinus surgeries [32]. In our cohort, four patients had already undergone at least one endonasal sinus surgery due to obstructive nasal polyposis. All of them experienced a recurrence of their polyposis at the time of initiating ETI therapy. During follow-up, we observed complete regression of polyps in two patients, partial regression in one patient, and no change in the last patient. We can thus hope that these patients will not require repeat surgery. More broadly, in children, the improvement in nasal sinus symptoms with ETI therapy may eventually reduce the need for primary or secondary endonasal surgeries, making this an important therapeutic and economic consideration.

In addition to the significant functional impact, some studies suggest that chronic nasal sinus involvement may contribute to the development of a bacterial reservoir, which may subsequently be responsible for pulmonary bacterial colonization [33] and thus partly for the poor prognosis of the disease. In adults, two studies have also shown a reduction in *Pseudomonas aeruginosa* carriage in the sinuses under ETI therapy, although this pathogen was not eradicated from the respiratory tract [34, 35]. Our study shows a trend toward reduction in the number of infections requiring systemic antibiotics. Therefore, we can hope for both a reduction in bacterial carriage and a decrease in antibiotic resistance. However, further studies with prolonged follow-up will be necessary to assess the long-term impact of ETI therapy on the bacterial reservoir in the sinuses and on the resistance profile of various bacteria, particularly *Pseudomonas aeruginosa*.

The objective improvement observed during the study was associated with a reduction in the treatments (fewer recurrent antibiotic courses, lighter local treatments). Therefore, if improvement keeps on, it seems reasonable to consider a reduction in specialized follow-ups, which could eventually reduce the number of day hospital visits, decrease school absenteeism, lessen the socioeconomic impact on parents, and thus become a significant public health financial issue.

5 | Conclusion

Results of this prospective study appear to confirm a trend towards improved quality of life related to nasal-sinus symptoms in the pediatric population treated with ETI therapy. However, long-term studies are needed to assess the durability of the treatment effect over time, its impact on follow-up imaging, and the evolution of indications for nasal-sinus surgery.

Author Contributions

Guillaume Petit: conceptualization, data curation, formal analysis, visualization, writing–original draft, methodology, investigation, writing–review and editing. **Aurélie Coudert:** supervision, writing–review and editing, investigation. **Ruben Hermann:** writing–review and editing. **Eric Truy:** writing–review and editing, supervision. **Maxime Bonjour:** conceptualization, formal analysis, methodology. **Philippe Reix:** investigation, validation, writing–review and editing. **Sonia Ayari:** conceptualization, data curation, writing–original draft, supervision, investigation, validation, writing–review and editing.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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Appendix A

INFECTION SINUSIENNE : écoulement nasal ou par l'arrière dans la gorge, mauvaise haleine, toux pendant la journée, maux de tête, douleur faciale continue ou pulsatile. Est-ce que cela a été un problème pour votre enfant au cours des 4 dernières semaines ?

☐ Jamais ☐ Exceptionnellement ☐ Parfois ☐ Presque tout le temps
☐ Rarement ☐ Souvent ☐ Tout le temps

OBSTRUCTION NASALE : nez bouché ou encombré, congestion nasale, diminution ou perte de l'odorat, difficulté à respirer la bouche fermée. Est-ce que cela a été un problème pour votre enfant au cours des 4 dernières semaines ?

☐ Jamais ☐ Exceptionnellement ☐ Parfois ☐ Presque tout le temps
☐ Rarement ☐ Souvent ☐ Tout le temps

SYMPTÔMES ALLERGIQUES : éternuements, nez ou yeux qui grattent, besoin de se frotter le nez ou les yeux, yeux qui larmoient. Est-ce que cela a été un problème pour votre enfant au cours des 4 dernières semaines ?

☐ Jamais ☐ Exceptionnellement ☐ Parfois ☐ Presque tout le temps
☐ Rarement ☐ Souvent ☐ Tout le temps

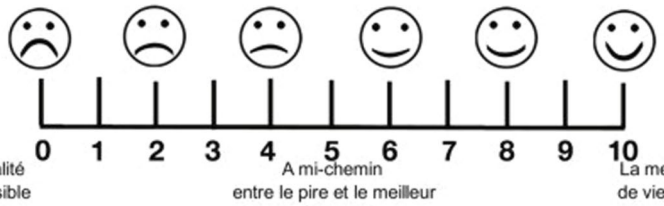
RETENTISSEMENT EMOTIONEL : irritabilité, frustration, tristesse, agitation ou trouble du sommeil à cause de ses problèmes de nez ou de sinus. Est-ce que cela a été un problème pour votre enfant au cours des 4 dernières semaines ?

☐ Jamais ☐ Exceptionnellement ☐ Parfois ☐ Presque tout le temps
☐ Rarement ☐ Souvent ☐ Tout le temps

LIMITATION DES ACTIVITES : absentéisme scolaire, retentissement sur les activités périscolaires, réduction du temps consacré à la famille et aux amis à cause de ses problèmes de nez ou de sinus. Est-ce que cela a été un problème pour votre enfant au cours des 4 dernières semaines ?

☐ Jamais ☐ Exceptionnellement ☐ Parfois ☐ Presque tout le temps
☐ Rarement ☐ Souvent ☐ Tout le temps

AU TOTAL, Comment évalueriez-vous la qualité de vie de votre enfant compte-tenu de ses problèmes de nez ou de sinus ? (entourez un chiffre)



PARTIE MEDICALE :

☐ État de base *(pré thérapeutique)* ☐ Suivi à la semaine [ ] *(post thérapeutique)* ☐ État de base *(pré opératoire)* ☐ Suivi à la semaine [ ] *(post opératoire)* *Score de chacune des 5 questions (1-7)*

ETIQUETTE PATIENT, date [ ] **SN5-score** : somme totale /5

Gargula, Stéphane, Romain Luscan, David Drummond, Françoise Denoyelle, Vincent Couloigner, Nicolas Leboulanger, et François Simon. «French Translation and Validation of the Sinus and Nasal Quality of Life Survey (SN-5) in Children». *International Journal of Pediatric Otorhinolaryngology* 145 (juin 2021): 110706. https://doi.org/10.1016/j.ijporl.2021.110706.