Effects of Elexacaftor Tezacaftor Ivacaftor on sinonasal imaging in children with cystic fibrosis

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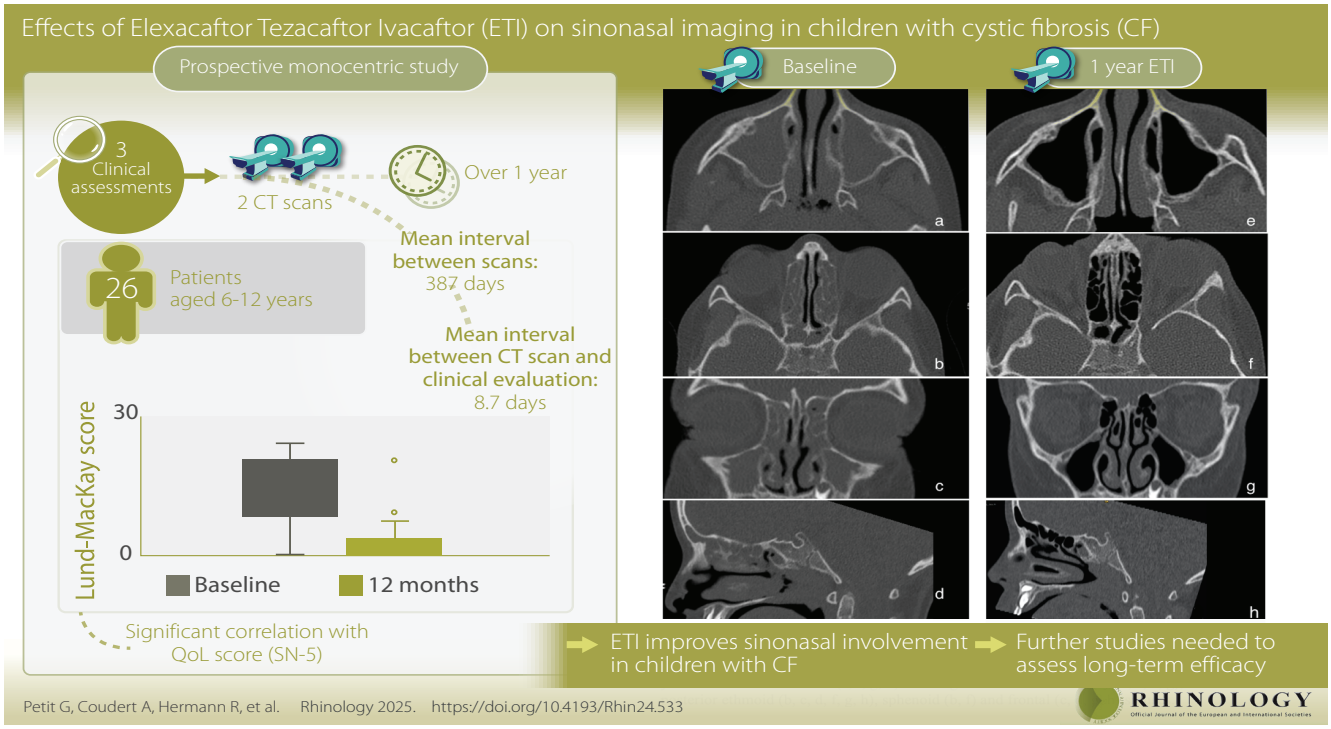

Abstract

Background: New CFTR Modulator triple therapy Elexacaftor-Tezacaftor-Ivacaftor (ETI) has proven efficacy in pulmonary outcomes. However, its qualitative impact via sinonasal imaging in children has not been specifically studied. The aim of our study is to assess the impact of ETI triple therapy through sinus imaging in children with Cystic Fibrosis (CF) aged 6–12 years.

Methods: This prospective, single-center study, covered children with CF aged 6-12 years, all undergoing annual low-dose CT scans of the sinuses and lungs. The main objective of our study is the evaluation of the evolution of the modified Lund-Mac Kay (mLMK) score. Evaluations occurred at baseline and after one year of ETI therapy. Secondary objectives included the identification of potential associations between mLMK score and Sinus and Nasal Quality of Life Survey Score (SN-5) score, as well as examination of mLMK score changes in individual sinuses.

Results: 26 patients were enrolled in our study. The median mLMK score significantly improved after one year of ETI therapy. Significant correlation was observed between mLMK and SN-5 scores.

Conclusion: This study highlights ETI's efficacy in improving sinonasal involvement in children aged 6 to 12 with CF. This is in line with the observations of clinical improvement, and presents an alternative to sinus surgery, thus potentially leading to a reduction in surgical interventions.

Key words: cystic fibrosis, Elexacaftor Ivacaftor Tezacaftor, CFTR modulators, Lund-MacKay, children

Introduction

Cystic fibrosis (CF) can result from a multitude of genetic mutations in the CFTR gene, by encoding the CFTR protein [1]. Hundreds of mutation combinations are possible, making it challenging to develop individualised targeted treatments. A triple therapy has emerged and is now widely used due to its efficacy, it consists of a next-generation corrector, elexacaftor, an additional corrector, tezacaftor, and a potentiator, ivacaftor, collectively known as elexacaftor-tezacaftor-ivacaftor (ETI). Results of various studies have reflected a good safety profile, as well as its excellent efficacy in improving pulmonary parameters in patients, including exacerbations, peak expiratory flow, and antibiotic use [2–4]. However the quality of life of patients with CF is also compromised by insidious and disabling symptoms affecting the sinonasal mucosa [5], especially in children (6), sometimes as early as the age of 6. Two recent meta-analyses have shown clinical improvement in quality of life in both adults and children [7,8] with ETI therapy. Moreover, sinonasal involvement can be assessed clinically via quality of life scales such as SN-5 in children and through radiologic parameters. In fact, Wucherpfennig et al. demonstrated the high frequency of sinonasal opacification in children affected by CF [9]. They described a gradual worsening from infancy to preschool and school ages, resulting in almost all sinuses (71-99%) opacified in magnetic resonance imaging from 6 to 12 years old. They also noticed a slight improvement of sinus opacification with less effective treatment, the Ivacaftor and Lumacaftor dual therapy. In adults, results of ETI therapy seem to be encouraging as highlighted by four studies that published specific results about radiologic improvements, based on Lund-Mac Kay (LMK) score [10-14]. The pediatric population between 6 and 12 years of age has not been specifically studied. Moreover, the correlation between LMK score and clinical evaluation in CF remains unclear. For some authors, there is no correlation between clinical and radiological findings on patients affected by CF, and CT-scans should only be performed with a surgical purpose, on either in adults [15] or children [16]. Since calculating the LMK score requires the presence of fully developed sinuses [17], it could not be used in our study due to the young age of our cohort, as some sinuses may still be underdeveloped. We also based our evaluations on the modified LMK (mLMK) score, which accounts for undeveloped sinuses [18].

The aim of this study is to evaluate the impact of ETI therapy on sinonasal imaging in children aged 6 to 12 years. The primary outcome is the evolution of the mLMK score that is a validated radiologic score for sinonasal imaging after one year treatment with ETI therapy [17]. Secondary outcomes will assess the correlation between mLMK score and patient reported quality of life, as measured by the Sinus and Nasal Quality of Life Survey (SN-5) questionnaire, and sub-group analysis from all components from mLMK: maxillary, ethmoid, sphenoid, frontal sinuses and ostiomeatal complex.

Materials and methods

This prospective, single-center, non-randomized open label study was conducted in a tertiary care center. The study was registered in a public trial registry, ClinicalTrials.gov NCT05581056, with an approval from the Ethics Committee obtained on 24/02/2023 and a ratification for use of imaging data ("Comité de protection des personnes Ouest IV", France). Recruitment was carried out over a six-month period starting on 03/03/2023, with one year follow-up duration.

Two evaluations were performed, at baseline and one year after treatment initiation. Potential study participants were identified in our center. As part of their regular medical follow-up and in accordance with local protocol, a low dose CT-scan of the lungs and sinuses is performed at ETI initiation and after the one-year treatment. 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 with ETI therapy. Initial CT-scans were performed at the latest 1 month after therapy initiation. Children were not included in case of their refusal or legal guardians to participate in the study, if not covered by National Health Insurance, if under legal protection or if legal guardians did not speak French, or if ETI therapy was initiated more than 1 month before inclusion. Further, sinus surgery during the observation period or interruption of ETI therapy due to poor tolerance (pulmonologist's assessment) excluded patients from the study. Age at inclusion, gender, genotype, weight and previous CFTR modulator therapy were initially recorded.

Radiological evaluations

Radiological evaluations were performed using mLMK score (17), grading each sinus from 0 to 2 according to this scale: 0 point for no abnormality, 1 point for partial opacification and 2 points for complete opacification. Ostiomeatal complex was also scored according to this scale: not obstructed 0 point and obstructed 2 points. Considering the young age of our patients, sinuses could be undeveloped. In the absence of a sinus, the score of 0 point was attributed, and the corresponding mLMK score was then scaled up to range from 0 to 24 by scaling with the factor 12/n, where n represents a number of scorable (pneumatised) sinuses [18,19]. In case of development of a sinus during study time, we did not include it in the analysis.

CT-scans were performed using Philips Ingenuity 128 barettes, helical acquisition of the sinuses without intravenous contrast injection, followed by multiplanar reconstructions (bone and soft tissue filters), with millimeter slices. The acquisition parameters were 120 kV and 30 mAs. Images were interpreted by a radiologist specialised in pediatric airway imaging, who was blinded to the study. The radiologist detailed data on obstruction of sinuses, but did not grade the mLMK score. Based on his

Table 1. Patient's characteristics at treatment's initiation.

Age at inclusion (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 %)
Delay between 2 CT-Scans (Mean, in days, ± SD)	387.8 (± 22.3)
	N = 26

report and after reviewing the images, ENT physician in charge of the study graded the mLMK score.

Regular assessment of quality of life

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

The SN-5 questionnaire consists of 5 questions that assess the 5 major categories of symptoms related to sinonasal involvement: number of infections, nasal obstruction, allergic symptoms, emotional impact, and activity limitation. These 5 items are scored on a scale of 1 to 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 5 items, ranging from 1 to 7. The higher the average, the poorer the child's quality of life is (Appendix).

SN-5 questionnaire was performed prospectively by ENT trained physician in a dedicated consultation.

Statistical analysis

The primary outcome measure analysis was based on the analysis of a quantitative variable, the median mLMK score of the entire population before treatment initiation and one year after treatment initiation. Alpha risk was fixed on 5%.

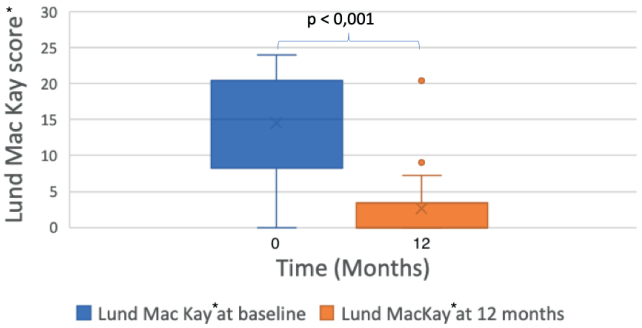

Figure 1. Boxplot of modified Lund Mac Kay score at baseline (blue) and 12 months (orange), with Wilcoxon signed-rank test for paired comparison. * Modified Lund-Mac Kay score.

This statistical analysis involves a comparison of two medians: the median mLMK score at ETI initiation and median mLMK score at one year after treatment initiation. A paired median-comparison of mLMK score was performed with appropriate test (Wilcoxon signed-rank test for paired comparison). The null hypothesis assumes no treatment effect.

For the evaluation of secondary criteria: a median comparison for paired population (Wilcoxon signed-rank test for paired population) was performed for each sinus using a partition of mLMK score for each sinus (0 point for no abnormality, 1 point for partial opacification and 2 points for complete opacification). We applied Bonferroni correction in order to avoid inflated Type 1 error. As we made 8 analyses, α risk was fixed at 0,00625.

To study an association between mLMK and SN-5 score, the lines were generated using a Generalized Linear Model (GLM) to analyze the relationship between two quantitative scores: the mLMK and the SN-5 score. Given that the variables did not follow a normal distribution and the sample size was relatively small (n < 30), the GLM framework allowed for more flexibility in modeling non-normally distributed data. The fitted line represents the expected values of SN-5 as a function of mLMK.

Results

All patients eligible for our study in our cohort were included, due to low number of participants. Twenty-six patients were included between March 3, 2023 and September 3, 2023. Twenty-five patients (96.2%) were already on dual therapy with a CFTR potentiator and a CFTR corrector. Four children had undergone previous functional endonasal sinus surgery (FESS). None presented bone erosion on CT-scan at inclusion. No one was excluded from our study. Genetic results as well as status for F508del are detailed in Table 1. All patients were under local treatment based on nasal saline irrigation and intra nasal steroid spray at baseline. No complementary endonasal treatment was given under study period.

For the primary endpoint, median initial mLMK score was 15

Table 2. Modified Lund-Mac Kay score at inclusion and 12 months follow-up, and comparison for each component in modified Lund-Mac Kay score.

	Baseline	12 months after ETI initiation		
	Median (IQR)	Median (IQR)	Difference (p value)	
Lund-Mac Kay score	**15 ({8.7; 20.1})**	**0 ({0;3})**	**Δ = 15 (p <0.0001)**	
Studied sinuses	**At baseline (IQR)**	**12 months after ETI initiation**	**Number of sinuses studied**	**p-value**
Maxillary sinuses	3.5 ({0; 4})	0 ({0; 0.75})	52	p <0.001*
Anterior ethmoid	2 ({0; 4})	0 ({0; 0})	52	p <0.001*
Posterior ethmoid	2 ({0; 2.75})	0 ({0; 0})	52	p <0.001*
Frontal	1.50 ({0; 2})	0 ({0; 0})	12	p = 0.17
Sphenoid	2 ({0; 3.25})	0 ({0; 0.5})	34	P = 0.002*
Ostiomeatal complex	2 ({0; 4})	0 ({0; 0})	52	p < 0.001*

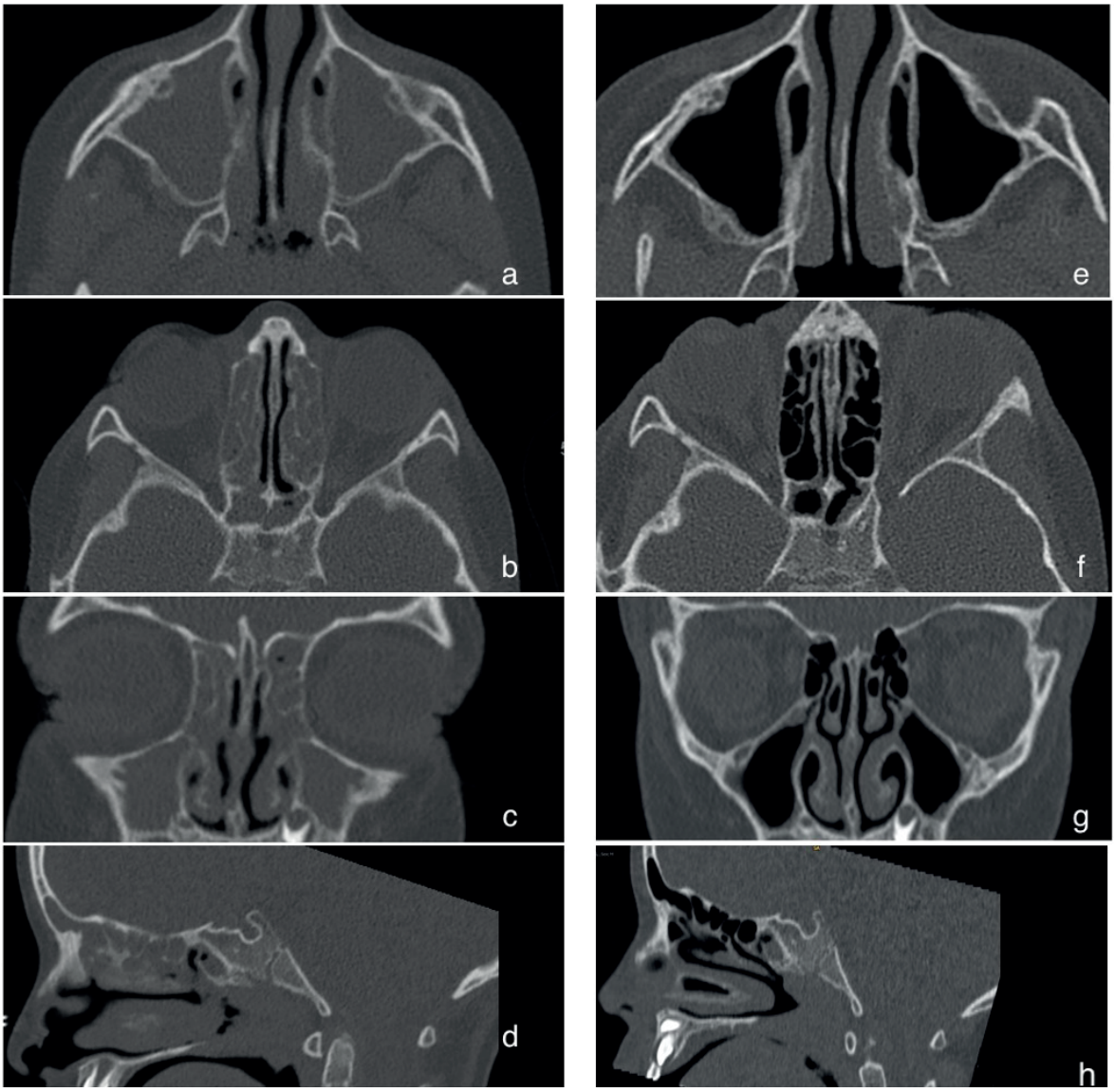

Figure 2. CT-scans in a patient before ETI initiation and after one year of treatment. Axials (a, b, e, f), coronal (c, g) and sagittal (d, h) CT-scan's slices before (a, b, c, d) and after 1 year of treatment with ETI (e, f, g, h) showing evolutions in maxillary (a, c, e, g), anterior and posterior ethmoid (b, c, d, f, g, h), sphenoid (b, f) and frontal (c, d, g, h) sinuses.

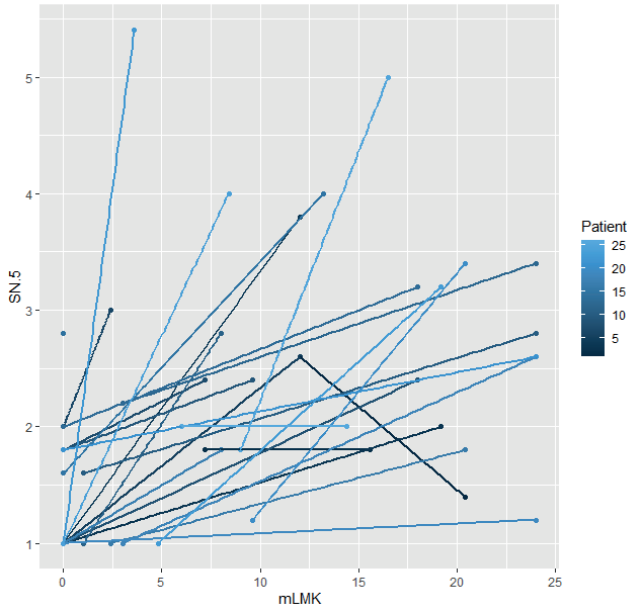

Figure 3. Individual regressions of SN-5 based on mLMK.

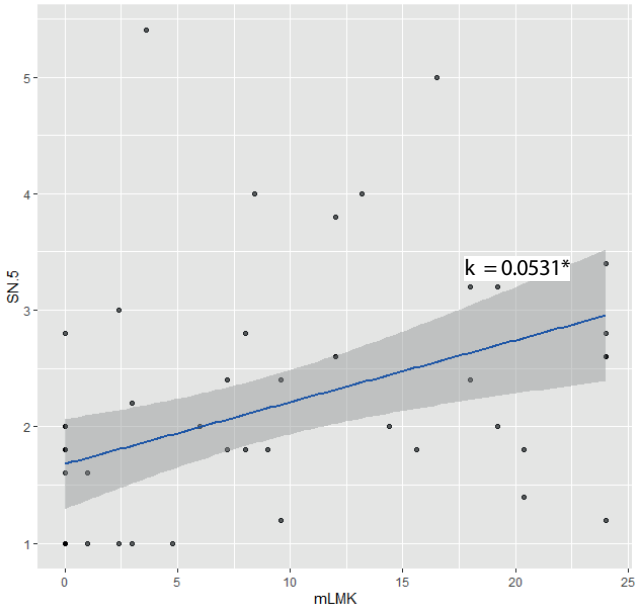

Figure 4. Global regression of SN-5 based on mLMK. k: Generalized linear model coefficient, p = 0.0027.

(IQR {8.7; 20.1}) significatively decreased at one year evaluation with a score of 0 (IQR {0;3}, p < 0.0001) (Table 2 and Figure 1). An example of CT-scan at baseline and after 1 year under treatment with ETI therapy is presented in Figure 2. Mean delay between the two CT-scans evaluations was 387 days (SD=22.3).

For secondary endpoints, we found an improvement of sinus opacification for maxillary sinuses (Δ = 3.5, p <0.001), anterior ethmoid (Δ = 2, p <0.001), posterior ethmoid (Δ = 2, p <0.001), sphenoid sinuses (Δ = 2, p =0.002) and ostiomeatal complexes (Δ = 2, p <0.001). We found an improvement for frontal sinuses (Δ = 1.50, p = 0.06). All results are detailed in Table 2. Initial mean SN-5 score was 2.88, and mean SN-5 score after one year treatment was 1,38.

We graphically displayed the association between mLMK score and SN-5 score in Figures 4 and 5. Generalized linear model coefficient was 0.053 (p=0.0027).

Discussion

To our knowledge, this study is the first to confirm improvement in sinonasal radiological issues in children aged from 6-12 years old with CF after 1 year ETI therapy.

Regarding mLMK score, the mean initial score was 14.54, which is close to those observed in several studies in the pediatric population affected by CF [20,21]. In adults with CF treated with ETI, a significant improvement for radiologic sinonasal evaluation was observed, as evidenced by the results obtained in LMK score [11,12,14]. In our study, a substantial effect size was noted with a delta of 11.95 out of 24, that is more important than described in the adults studies (Δ =3.6 points in study from Beswick et al. [12] and Δ = 2.5 in study from Tagliati et al. [11]). This improvement concerns all sinuses, maxillary, anterior and posterior ethmoid, sphenoid, ostiomeatal complexes and frontal, despite a high frequency of frontal agenesia probably due to young age from our cohort, resulting in the small number of sinuses studied (n=12). According to some authors, a mLMK score ranging from 0 to 5 may be considered within an incidentally "normal" range, and should be factored into clinical decision-making [22,23]. This is confirmed by control groups present in some studies [19]. As the final evaluation after 1 year of ETI reflects an average of 2.59, with a mean SN-5 score of 1.41 close to 1 that is the reference (the best quality of life related to sinonasal symptoms), we could ask ourselves if children with CF will have fewer medical treatments for chronic rhinosinusitis. Moreover, as mLMK score is related to surgical issues, we can expect a massive reduction in endonasal surgical procedures, as it was described in adults [11].
Unlike previous reports, our study seems to identify a correlation between SN-5 score and mLMK score in children with CF. Correlations are established between clinical examination and mLMK score in adults with chronic rhinosinusitis [24–26]. Moreover, correlations were also described between quality of life scales and mLMK score in adults [27] and children with chronic rhinosinusitis [28]. However, in specific population with CF, this association wasn't found neither in adults [15] nor in children [16]. Yet, delay from quality of life evaluations to CT scan in these studies constituted a major evaluation bias. In fact in the 2 mentioned

studies, mean delay from quality of life scale (SNOT-22 in adults and SN-5 in children) to CT-scan evaluation was 30.5 days [15] (in adults with CF) or 19.5 months (in children with CF) [16], when SNOT-22 score evaluates the past 14 days and SN-5 the past 28 days. In our study, the mean delay between SN-5 score and CT-scan was 8.4 days (1.62 if we remove 2 patients that waited 90 days between SN-5 evaluation and CT-scan), and 20 of our 26 patients had SN-5 evaluation and CT-scan on the same day. Also, our evaluations may be more representative of CT-scan. This questions the role of CT-scan in the follow up of our patients. In fact, despite the specific nature of chronic rhinosinusitis in CF, with poorly symptomatic patients in opposition with sinus opacification in CT-scans, as it was described by Krajewska et al. in their pediatric study [29], clinical improvement seems to be correlate with radiological improvement. Our model draws a curve between SN-5 and mLMK scores with a slope of 0,05. As we consider a 0.5-point difference on SN-5 scale to be clinically relevant [16], wide variations (> 10 points) in mLMK score, such as those described in our study, could be considered clinically relevant.

A strong point from our study relies on evaluations performed and interpreted by a radiologist specialised in pediatric airway imaging, blinded from our study, limiting evaluation bias. Proofreading by ENT physician not blinded did not identify differences with his interpretation, and so did not interfere in results. A second strong point relies in performing evaluations during hospital shifts, and thus limiting the loss due to delayed follow-ups and reducing delay from SN-5 score to mLMK score.
There was no control group in this study because none were available. All the patients aged 6 to 12 years old with a treatment-compatible mutation received ETI therapy. Comparing data with children with non-compatible mutations would have constituted a major evaluation bias, since the variety of mutations is largely discussed of the variety of clinical expressions [30–33]. However, our study has some limitations. The SN-5 score was assessed by an ENT specialist who was not blinded to the study, introducing a potential evaluation bias. Moreover, the small size of our cohort necessitates validation of our results in larger populations.

ETI therapy seems to be effective in the most severe patients too. There were 4 patients (15%) that underwent a FESS before ETI initiation. These patients were considered in recurrence for their symptomatic chronic rhinosinusitis, clinically and radiologically. In this specific population, mLMK score was also greatly improved, with a mean diminution of 11.2/24. This positive outcome in the postoperative population confirms that the efficacy of ETI therapy does not appear to be limited by prior FESS, as observed in adult cohorts, where postoperative patients constitute 40% to 80% of the population [12,34]. Moreover, since the median mLMK reduction seems to be similar in the postoperative population and the overall population, FESS alone cannot account for the difference in effect size between adult and pediatric cohorts.

In addition to the significant morphological 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 [35] and thus partly for the poor prognosis of the disease. In adults, three studies have also shown a reduction in *Pseudomonas aeruginosa* carriage in the nasal sinuses under ETI therapy, although this pathogen was not eradicated from the respiratory tract [36,37]. Therefore, while we observed less retention in sinuses, we can hope for a reduction in bacterial carriage, it's chronic feature and pulmonary impact. 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, particularly *Pseudomonas aeruginosa*, shown to be eradicated in 11 of 17 colonized patients in the Uyttebroek et al. study [34].

Conclusion

Results of this prospective study confirms improvement in mLMK score, a radiological issue, in the pediatric population aged 6 to 12 with CF one year after ETI therapy initiation. It also questions correlation between clinical and radiological improvements. However, long-term studies are needed to assess the durability of the treatment effect over time, and need for FESS.

Conflict of interest

We declare no conflict of interest.

Funding

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Authors' contributions

GP: conceptualization, data curation, formal analysis, visualization, writing, original draft, methodology, investigation, writing, review & editing; SA: conceptualization, data curation, writing, original draft, supervision, investigation, validation, writing, review & editing; AC: supervision, writing, review & editing, investigation; RH: writing, review & editing; ET: writing, review & editing, supervision; MB: conceptualization, formal analysis, methodology; PR: investigation, validation, writing, review & editing.

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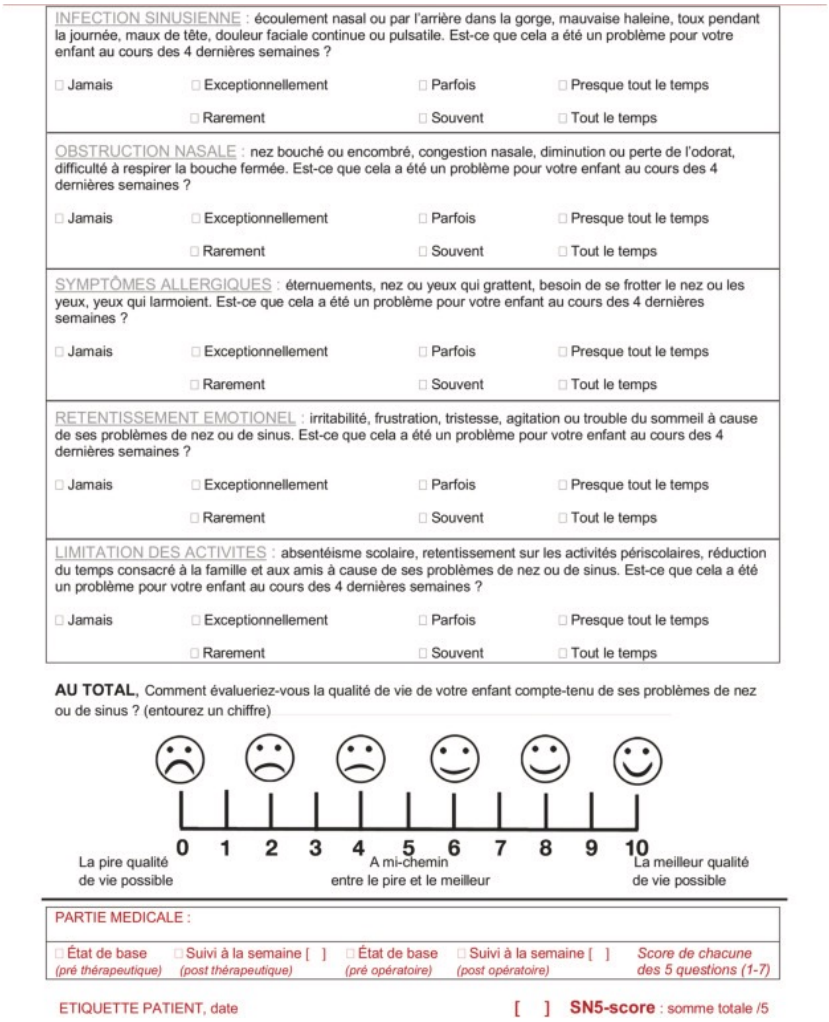
SUPPLEMENTARY MATERIAL

Appendix



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

Stéphane Gargula, Romain Luscan, David Drummond, Françoise Denoyelle, Vincent Couloigner, Nicolas Leboulanger, 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: 110706. https://doi.org/10.1016/j.ijporl.2021.110706.