Olfactory dysfunction in adult cystic fibrosis patients*

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Olfactory dysfunction (OD) is a frequent yet underrecognized manifestation of chronic rhinosinusitis (CRS) in cystic fibrosis (CF) [(1)]. Despite widespread reports of OD in CF, the impact of CFTR modulator therapy on smell outcomes remains unclear. We conducted a prospective study to evaluate olfactory function changes in CF-related CRS patients, as defined by EPOS2020 [(2)], following 12 months of elexacaftor/tezacaftor/ivacaftor (ETI) therapy, exploring clinical and biological correlates. The study was approved by the local ethics committee (CEAVC 22454). From 120 ETI-treated CF patients at the University Hospital of Careggi, 45 adults (mean age: 37.5 years; 55.6% female) diagnosed with CRS completed pre- and post-treatment assessments, including olfactory evaluation via the 16-item Sniffin' Sticks Identification Test (SSIT) for its feasibility and longitudinal applicability. After one year, 25 hyposmic patients improved to normosmia, and 9 normosmic patients maintained their status totaling 34 responders (75.6%). Conversely, 8 patients remained hyposmic and 3 normosmic deteriorated, yielding 11 non-responders (24.4%). Mean SSIT scores significantly increased from 9.6 to 12.0 (p=0.002), raising normosmia rate from 26.7% to 75.6%. No significant differences were found between patients with and without nasal polyps, nor between heterozygous and homozygous delF508 genotypes.

These findings differ from prior studies showing limited smell improvement after ETI [(2–4)]. We hypothesize that the improvement stems from enhanced mucociliary clearance, improved airflow to the olfactory cleft, and reduced sinonasal inflammation, supported by significant reductions in SNOT-22 (53.9 to 22.8, p<0.001), modified Lund-Kennedy scores [mLKS] (4.9 to 2.4, p<0.001), and Lund-Mackay scores [LMS] (15.8 to 7.1, p<0.001). However, recent evidence suggests that OD in CF may involve intrinsic olfactory epithelium alterations and impaired neurogenesis, possibly explaining heterogeneity in response [(5)]. Interestingly greater radiological improvement was seen in patients without nasal polyps versus those with polyps (–9.8 vs. –7.3, p=0.006) (Table 1a). Yet, no significant differences in SNOT-22, NPS, mLKS, and LMS were found between OD responders and non-responders, or between genotype groups, underscoring the limitations of standard sinonasal metrics in predicting olfactory outcomes (Table 1b). Notably, responders showed greater improvement in pulmonary function (FEV1 +16.9% vs. +8.0%, p=0.041). Although not significant, responders also exhibited a decrease in peripheral blood eosinophil counts (–62.5 vs. +0.46 cells/µL). While Th1-driven inflammation is notoriously predominant in CF-related CRS, this finding may suggest a potential contribution of type 2 inflammation [(6)]. This is consistent with a case report by Le Bon et al. reporting overall improvement following ETI but OD amelioration only after the addition of dupilumab [(9)]. Discrepancies across studies may reflect differences in olfactory testing. For example, the 16-item SSIT defines normosmia as ≥12 (75% correct), whereas the 40-item University of Pennsylvania Smell Identification Test (UPSIT) sets the normosmia threshold at >33 for men (82.5%) and >34 for women (85.0%) [(3,10)]. Furthermore, a 40-item test may detect subtler changes in OD that a shorter 16-item SSIT could underestimate. We should also recognize that an identification test may be less sensitive than a threshold test in assessing OD in CF patients [(7)]. Finally, lower baseline SSIT scores may reflect more severe disease, with greater potential for improvement.

In conclusion, CRS significantly impacts CF patients' quality of life, particularly through OD. Our findings challenge the perception of OD as a static feature of CF and suggest responsiveness to ETI. The observed improvement supports incorporating olfactory testing into routine monitoring, especially when conventional sinonasal scores do not capture functional recovery.

Multicentric studies using comprehensive olfactory testing are needed to explore OD implications in patient-centered outcomes.

Table 1. BMI, pulmonary function, blood eosinophils, and mean rhinological scores at baseline and after 12 months of ETI; followed by mean changes in rhinological scores after 12 months of ETI in patients with and without improvement in olfactory dysfunction.

Factor (mean, SD)	Pre-treatment	Post-treatment	P value
BMI	20.9 (±2.7)	22.2 (±2.1)	<0.001
FEV1%	46.7 (±19.9)	61.4 (±21.1)	<0.001
FVC%	66.7 (±16.2)	79.1 (±15.7)	<0.001
FEV1/FVC	68.7 (±17.8)	76.6 (±17.1)	0.001
Blood eosinophil	232.6 (±178.5)	193.1 (±109.7)	0.017
SNOT22	53.9 (±16.8)	22.8 (±13.8)	<0.001
NCS	1.5 (±0.7)	0.7 (±0.7)	<0.001
mLKs	4.9 (±1.6)	2.4 (±2.0)	<0.001
NPS	1.0 (±1.7)	0.7 (±0.7)	0.015
LMs	15.8 (±3.9)	7.1(±3.2)	<0.001
VAS reduced smell	3.7 (±2.3)	2.4 (±2.4)	0.034
SSIT	9.6 (±3.8)	12.0 (±3.6)	0.002

Table 1a. BMI body mass index SNOT-22 SinoNasal outcome test-22; NPS nasal polyp score; NCS nasal congestion score, mLKS modified Lund–Kennedy score; LMS Lund–Mackay score; VAS visual analog scale; SSIT Sniffin' Sticks identification test.

Factor (mean, SD)	Responders	Non responders	P value
ΔBMI	0.6 (±3.84)	1.8 (±2.3)	0.218
ΔFEV1	16.9 (±13.6)	8.0 (±11.0)	0.041
ΔFVC	13.3 (±13.0)	9.5 (±12.2)	0.392
ΔBlood eosinophil	-62.5 (±194.5)	0.46 (±122.0)	0.215
ΔSNOT22	-31.5 (±21.8)	-29.7 (±19.4)	0.801
ΔNCS	-0.9 (±0.9)	-0.6 (±0.8)	0.193
ΔmLKs	-2.6 (±1.9)	-2.2 (±1.7)	0.513
ΔNPS	-0.4 (±0.9)	-0.2 (±0.8)	-0.517
ΔLMs	-5.2 (±5.8)	-6.7 (±5.0)	0.420
ΔVAS reduced smell	-2.0 (±2.8)	1.73 (±3.7)	0.009

Table 1b. A negative value indicates a decrease in the score. ΔSNOT-22 changes in SinoNasal Outcome Test-22; ΔNPS percentage changes in nasal polyp score; ΔNCS percentage change in nasal congestion score; ΔmLKS percentage changes in modified Lund–Kennedy Score; ΔLMS percentage changes in Lund–Mackay Score; ΔVAS: changes in visual analog scale; ΔSSIT percentage changes in Sniffin' Sticks identification test.

Authorship contribution

AM: writing, editing; PO: writing, reviewing, editing; LM: data collection and analysis; AR: data collection and analysis; SB: editing, reviewing; GM: editing, reviewing.

Conflict of interest

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

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