Dual and triple modulator therapy for chronic rhinosinusitis in cystic fibrosis patients*

Saartje Uyttebroek1,2, Claire ClaeysSENS1,2, Mark Jorissen1,2, Lieven Dupont3,4, Laura Van Gerven1,2,5

Abstract

Background: The introduction of CFTR modulators has changed the landscape in the treatment of cystic fibrosis (CF) and early case series have shown improvements in sinonasal outcomes in this patient population.

Methodology: A real-world data study was performed to evaluate the impact of dual therapy with tezacaftor/ivacaftor (TEZ/IVA) and triple therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on CF-related chronic rhinosinusitis (CRS), by comparing subjective and objective outcome measures at baseline, 12 months after treatment with TEZ/IVA and six months after treatment with ELX/TEZ/IVA.

Results: In total, 43 CF patients, with a mean age of 32 years, were included. After triple therapy, significant improvements in overall visual analogue scale, SNOT-22, Lund Kennedy, nasal polyps, and Lund-Mackay scores were observed, whereas no beneficial effect could be seen in patients treated with dual therapy. Bacterial upper airway colonization did not differ pre- and post-modulator therapy in the present study. The number of responders to dual and triple therapy is 23.8% and 63.2% of the patients, respectively.

Conclusions: Triple therapy with ELX/TEZ/IVA is superior to dual therapy with TEZ/IVA in the treatment of CF-CRS, as significantly reduced sinonasal complaints, nasal endoscopy and CT scores were observed after triple therapy, whereas this was not the case for dual therapy.

Key words: CFTR, chronic rhinosinusitis, CRS, cystic fibrosis, modulator

Graphical abstract

Impact of CFTR modulators on cystic fibrosis-related chronic rhinosinusitis

Prospective study
Data collection before and 6-12 months after start of modulator therapy

Cystic fibrosis patients 18 years old (n=43)

SNOT-22
VAS
Endoscopy scores
Microbiology
CT sinuses

Dual therapy
Ivacaftor (CFTR potentiator) + Tezacaftor (CFTR corrector)

No change in VAS, SNOT-22, nasal endoscopy scores, nasal polyp size, CT scores and bacterial colonization 12 months after dual therapy

Triple therapy
Ivacaftor (CFTR potentiator) + Tezacaftor Elexacaftor (CFTR correctors)

VAS and SNOT-22 scores nasal endoscopy score nasal polyp size CT scores 6 months after triple therapy No change in bacterial colonization

Abbreviations
CFTR- Cystic Fibrosis Transmembrane Conductance Regulator
SNOT-22- SinoNasal Outcome Test
VAS- Visual Analogue Scale
CT- Computed Tomography
Introduction

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators, small molecules that are able to restore the functionality of the impaired CFTR channel in cystic fibrosis (CF) patients, were approved in Europe in 2012 and have been changing lives of CF patients ever since (1). CFTR modulators are usually classified in two subgroups: CFTR potentiators and correctors. Potentiators (e.g. ivacaftor) improve ion transport at the level of the plasma membrane, whereas correctors (e.g. lumacaftor, tezacaftor and exelcaftor) improve CFTR processing and trafficking to the plasma membrane (1). The exact molecular mechanisms of action of these modulators remain unknown.

In Europe, four modulators have been approved for use in CF patients: ivacaftor in monotherapy (IVA, marketed under trade name Kalydec®), combination treatment of ivacaftor with tezacaftor (TEZ/IVA, marketed under trade name Symkevi/Kalydeco®), ivacaftor with lumacaftor (LUM/IVA, marketed under trade name Orkambi®) and triple combination of ivacaftor with tezacaftor and elexacaftor (ELX/TEZ/IVA, marketed under trade name Kalydeco®), ivacaftor with lumacaftor (LUM/IVA, marketed under trade name Orkambi®) and triple combination of ivacaftor with tezacaftor and elexacaftor (ELX/TEZ/IVA, marketed under trade name Kalydeco®). In Belgium, reimbursement of TEZ/IVA was approved in 2021 for patients with at least one gating mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R) (3). Reimbursement for ELX/TEZ/IVA has been available since September 2022, for patients with at least one ΔF508 mutation (5).

Both randomized controlled trials and real-world data studies have shown that modulators significantly improve pulmonary function, nutritional status, quality of life and sweat chloride, compared to placebo. Furthermore, these modulators decrease lower airway colonization with Pseudomonas aeruginosa and Staphylococcus aureus and secondary reduce the number of intravenous antibiotic courses and need for maintenance treatments (including long-term macrolides and dornase alfa) (5-10).

Shortly after the introduction of IVA, the first reports indicated not only amelioration in pulmonary health but also notable improvements in cystic fibrosis-related secondary chronic rhinosinusitis (CRS), especially in patients with at least one G551D gating mutation (11). Studies on ELX/TEZ/IVA, both prospective and retrospective, revealed substantial reductions in sinusal complaints and radiographical disease severity (12-19). To date, no clinical data are available on the impact of TEZ/IVA dual therapy on CF-related secondary CRS or the effect of modulator therapy on nasal endoscopy or bacterial upper airway colonization.

As CFTR modulators are increasingly being recognized as the ‘golden standard’ for CF treatment, post-market real-world data studies are needed to provide important long-term data on the safety and effectiveness of these modulators. The main goal of the present study is to assess the impact of dual TEZ/IVA therapy and triple ELX/TEZ/IVA therapy on CF-related secondary chronic rhinosinusitis in the adult CF population at our tertiary hospital.

Materials and methods

Data collection

A monocenter, real-world data study was performed, between January 2020 and October 2023, to evaluate the impact of dual and triple modulator therapy on CF-CRS. At our center, an annual rhinological evaluation by an ENT specialist at the Pneumology outpatient clinic is implemented in the standard-of-care follow-up scheme of CF patients. During this rhinological evaluation, a nasal endoscopy, a sinonasal swab and a CT scan of the sinuses are performed once a year to evaluate the objective severity of CF-CRS. Furthermore, to assess the subjective impact on quality of life of CF-CRS, patients are asked to fill-in questionnaires.

First, a nasal endoscopy, using a rigid 4 mm 30° nasal endoscope, is performed and scored using Lund-Kennedy (score from 0 to 12, Appendix 1) and Modified Davos (score from 0 to 8, Appendix 2) scores. Moreover, a sinonasal swab is performed at the level of the middle meatus, on the side with visually the most pathology, bacterial cultures are grown, and antibiotic sensitivity is assessed. The latter are performed at the Clinical Department of Laboratory Medicine (UZ Leuven) according to CF protocols. Furthermore, a low-dose CT of the sinuses, without intravenous contrast, is performed and scored using the Modified Lund-Mackay scoring system (score from 0 to 24, Appendix 3). Lastly, patients are asked to fill-in a questionnaire, including the SNOT-22 score (score from 0 to 110, Appendix 4) and visual analogue scale (VAS) scores, from 0 to 100mm, on overall sinonasal symptoms, nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, and sense of smell (Appendix 5). Additional data on demographics, rhinological history, and current treatments, and CF genotype and phenotype are collected.

To evaluate the impact of dual and triple therapy on CF-CRS, both objectively and subjectively, data from three consecutive years were collected. In 2020, baseline data were gathered, before the start of modulator therapy. From April 2022 on, ± 12 months after reimbursement of TEZ/IVA in Belgium, outcome measures were repeated to evaluate the impact of dual modulator therapy, and from March 2023 on, ± six months after the reimbursement of ELX/TEZ/IVA in Belgium, data were collected for the last time to evaluate the impact of triple modulator therapy on CF-CRS. Data were stored in a server protected RedCap database.

Lastly, the rate of patients responding – both subjectively and objectively – to modulator therapy was measured based on
SNOT-22 (questionnaire) and Modified Lund-Mackay (CT) scores. A minimal clinically important difference (MCID) was defined, to make a distinction between statistically and clinically significant changes in outcome measures. A MCID in SNOT-22 score was defined as a change in score of >12 points (20), and a MCID in Modified Lund-Mackay score was defined as a change in score of >5 points (21).

The study was approved by the Ethical Committee of UZ/KU Leuven and written informed consent was obtained from all included patients.

Sample size calculation
Sample size calculation was performed to obtain an adequate statistical power to detect significant differences in outcome measures. The analysis was performed using G*Power software (version 3.1.9.7) and was designed to accommodate paired data analysis with a two-sided test, an alpha (significance) level of 0.05, and a desired statistical power of 90%. The Modified Lund-Mackay score was used as outcome parameter to build the power calculation, as previous literature has shown that patient-reported outcome measures poorly correlate with objective disease extent (22).

For the subgroup of patients treated with ELX/TEZ/IVA, the estimated sample size was nine, based on the change in mean Lund-Mackay score of -3.6 after six months of treatment as reported by Beswick et al. (12).

Prior to this study, no (pilot) data were available for the TEZ/IVA subgroup. Consequently, the power analysis was conducted using the baseline Modified Lund-Mackay scores from our pre-existing patient registry, which consisted of 122 patients with a mean score of 11.69 and a standard deviation of 6.31 (22). To detect a MCID of >5, power analysis revealed an estimated sample size requirement of 19 participants for this specific subgroup.

Statistical analysis
Data analysis was performed using GraphPad Prism software (version 9.4.1.). Descriptive data, including mean and standard deviation (SD) for quantitative data with a Gaussian distribution, and median and interquartile range for skewed data, were calculated. The normality of data was assessed by the Shapiro-Wilk test (version 9.4.1.) and was designed to accommodate paired data analysis with a two-sided test, an alpha (significance) level of 0.05, and a desired statistical power of 90%. The Modified Lund-Mackay score was used as outcome parameter to build the power calculation, as previous literature has shown that patient-reported outcome measures poorly correlate with objective disease extent (22).

For all statistical tests, differences between the means were calculated and a 95% confidence (CI) interval was established. The difference was considered statistically significant when p-values were < 0.05 (two-sided testing).

Results
Demographical data
Between January 1st 2020 and October 1st 2023, 43 adult CF patients were included, of which 26 males and 17 females with a mean age of 32 (SD ± 9) years at inclusion. The majority of the patients were homozygous for the ΔF508 mutation (70%), the remaining patients were heterozygous for the ΔF508 mutation. At inclusion, the mean BMI, FEV1% and sweat chloride were 22.3 (SD ± 1) kg/m², 73.4 (SD ± 17)% and 105 (SD ± 15) mmol/L, respectively.

Out of 43 patients, data were available from 25 patients both at baseline and after receiving dual therapy with TEZ/IVA, with an average treatment duration of 14 months (SD ± 2.5). Additionally, baseline and post-ELX/TEZ/IVA treatment data were gathered from 39 patients, with an average treatment duration of 8 months (SD ± 2). No significant baseline and demographic differences were observed in the subgroup of patients treated with TEZ/IVA and ELX/TEZ/IVA (Table 1).

Within the TEZ/IVA treatment subgroup, one patient was treated with lumacaftor prior to dual treatment, and one patient with ivacaftor in monotherapy. The remaining patients (92%) did not receive modulator therapy prior to start of dual therapy. In contrast, in the ELX/TEZ/IVA treatment subgroup, 29 patients (74%) had received prior dual therapy with TEZ/IVA before starting triple therapy. Longitudinal data was available from 20 patients, receiving dual therapy first, followed by triple therapy.

Subjective outcome measures (VAS and SNOT-22 score)
No significant differences in mean VAS scores for total sinonasal symptom were observed after treatment with dual TEZ/IVA therapy (Figure 1A, Table 2). Moreover, for the cardinal sinonasal symptoms (nasal obstruction, postnasal drip, rhinorrhea, facial pain/pressure, and reduced smell), no significant reductions in VAS score were observed compared to baseline (Table 2).
After treatment with ELX/TEZ/IVA, a statistically significant reduction in VAS score for total sinonasal symptom of -10.3 mm (p=0.0011) was observed (Figure 1A, Table 2). Additionally, a significant reduction in VAS score for postnasal drip was objectified...
CFTR modulators in cystic fibrosis-related CRS

(mean change = -11.6 mm, p = 0.0005). No significant changes were noted for the remaining cardinal sinonasal symptoms (Table 2).

In regard to the SNOT-22 score, a significant reduction of -6.8 points (p = 0.0254) was observed, compared to baseline, after treatment with ELX/TEZ/IVA, whereas no differences could be achieved after treatment with TEZ/IVA (Figure 1B, Table 2).

Nasal endoscopy
After treatment with dual TEZ/IVA therapy, no changes in Lund-Kennedy and Modified Davos scores could be observed. In contrast, a significant reduction in Lund-Kennedy and Modified Davos scores of -1.6 (p = 0.0017) and -0.8 points (p = 0.0171), respectively, were noted after ELX/TEZ/IVA treatment (Figure 2, Table 2).

CT scan
In alignment with the endoscopy findings, a statistically significant decrease of 6.3 points (p < 0.0001) in Modified Lund-Mackay scores was seen following ELX/TEZ/IVA treatment, whereas no differences were noted after treatment with TEZ/IVA (Figure 2-3, Table 2).

Bacteriology
In the subgroup of patients treated with dual therapy, longitudinal microbiology data, from the upper airways, are available from 14 out of 25 patients. At baseline, five patients were colonized intranasally with S. aureus. After dual therapy, two patients (2/5) with previous S. aureus colonization were eradicated, while three patients had persisting presence of S. aureus. Notably, among the nine patients who had not been previously colonized with pathogenic bacteria, three acquired new colonizations with S. aureus after commencing dual therapy.

Furthermore, longitudinal microbiology data were available from 34/39 patients treated with ELX/TEZ/IVA. Seventeen out of 34 patients were colonized with pathogenic bacteria intranasally at baseline, including Stenotrophomonas spp. in one patient, Staphylococcus epidermidis in one patient, P. aeruginosa in two patients and S. aureus in thirteen patients. Eradication after triple modulator therapy was seen in 11/17 patients and persistence of the pathogenic bacteria in the remaining patients. In five out of 17 patients without prior presence of pathogenic bacteria, S. aureus could be isolated from the nasal cavity.

Statistically, no differences in number of patients colonized with/without pathogenic bacteria could be found after dual or triple therapy, compared to baseline (Table 2).

Rhinological and antibiotic treatments
Before the start of modulator therapy, 35.7% (15/42) of the patients performed daily nasal irrigations and 47.6% (20/42) applied intranasal corticosteroids on a daily basis. After triple therapy with ELX/TEZ/IVA, no changes were seen in the chronic use of nasal irrigations (mean change = -11.7%, p = 0.3097) and intranasal corticosteroids (mean change = -6.5%, p = 0.6469). No differences in use of oral (mean change = -1 day, p = 0.8955),
intravenous (mean change=-8.5 days, p=0.2088), local (mean change=3 days, p=0.1624) or anti-inflammatory (mean change=-6.3%, p=0.6125) antibiotics could be observed after treatment with dual therapy, compared to baseline. Similar findings were observed after treatment with triple therapy: no significant reduction in number of treatment days with oral (mean change=-8.9 days, p=0.0875), local (mean change=-0.5 days, p=0.1600) and anti-inflammatory (mean change=-3.7%, p=0.6086) antibiotics could be found. Nevertheless, a significant reduction in number of days of intravenous antibiotics was seen six months after the start of triple therapy (mean change= -3.3 days, p=0.0048).

**Longitudinal data**

Longitudinal data was collected from 20 patients, receiving dual therapy first for ±12 months, followed by triple therapy for ±six months (Figure 4).

First, no significant changes were observed in SNOT-22 after dual therapy with TEZ/IVA compared to baseline (mean change=-2.96, 95% CI[-11.2;5.3], p=0.6280). In contrast, a significant reduction was seen after treatment with ELX/TEZ/IVA in comparison to baseline (mean change=-9, 95% CI[-16.6;1.4], p=0.0192). No differences in SNOT-22 score could be observed between dual and triple therapy.

Second, significantly lower Modified Lund Mackay scores were observed after treatment with triple therapy, compared to baseline (mean change=-7.35, 95% CI[-11.1;-3.7], p=0.0002) and to dual therapy (mean change=-5.9, 95% CI[-8.9;-2.9], p=0.0003). No changes were observed after treatment with dual therapy, compared to baseline.

**Rate of responders**

In the TEZ/IVA treated subgroup, only 10.5% of the patients had a change in SNOT-22 of > 12. Moreover, in the ELX/TEZ/IVA subgroup, 22.2% of the patients had a clinically important difference in SNOT-22. A MCID in Modified Lund-Mackay score was observed in 23.8% and 63.2% of the patients treated with dual and triple therapy, respectively.

**Discussion**

CFTR modulators, especially the highly effective triple combination of ELX/TEZ/IVA, have dramatically reduced disease burden in CF-patients and from early-on, data on the impact of modulator therapy on CF-related secondary CRS have been reported. The aim of the present study was to compare efficacy of dual and triple therapy in the treatment of CF-CRS in a real-world data setting. The latter meaning that data are collected over time in patients treated with modulators according to standard-of-care treatment regimen, as proposed by the treating Pulmonologists, and depending on reimbursement criteria in Belgium. Data are collected during routine ENT consultations instead of fixed study visits.

Our data showed that ELX/TEZ/IVA significantly reduces sino-nasal symptoms and CT scores, compared to baseline. These findings are in line with previously performed observational
studies, showing that ELX/TEZ/IVA significantly reduces SNOT-22 and Lund-Mackay scores. It should be noted that the magnitude of reduction in SNOT-22 score of -6.8 points is rather limited in comparison to current literature, with a reported mean change in SNOT-22 score ranging from -10.5 to -15 (12-16, 18-19), and might not be clinically meaningful. This might be due to low SNOT-22 scores at baseline (24.4 ± 15.2 points). Moreover, a statistically significant reduction in VAS score for total sinonasal symptom was observed, but when looking at the VAS scores for individual sinonasal symptoms, only a significant reduction could be observed for postnasal drip. No major improvements in nasal patency, sense of smell, facial pain/pressure or anterior rhinorrhea could be observed. But as was the case for the SNOT-22 score, baseline VAS scores were low with a mean score of 32.5 ± 28.8 mm.

Furthermore, our data revealed significantly lower nasal endoscopy (Lund-Kennedy) and nasal polyp scores (Modified Davos) after treatment with ELX/TEZ/IVA. Only one other prospective study reported data on nasal endoscopy appearances, using the Lund-Kennedy score, without looking at specific nasal polyp scores.

For dual therapy with TEZ/IVA, no significant changes in subjective or objective outcome parameters could be observed, compared to baseline. Therefore, dual therapy is inferior to triple therapy in the treatment of CF-CRS. To date, this is the first study reporting clinical rhinological data after TEZ/IVA treatment, and therefore comparison with previous literature is difficult. Previous literature on IVA in monotherapy, in patients with specific gating mutations (G551D or SN1251N), did show significant changes in CT and nasal endoscopy scores. McCormick et al. did see a significant reduction in SNOT-20 score after IVA treatment in 151 patients with at least one G551D mutation, but less than the pre-specified minimal clinically important difference, also due to low baseline values. IVA is a CFTR potentiator that improves the gating function of the CFTR channel and is therefore useful in patients with a gating defect (class III mutations) (1). Class III or gating mutations are defined as mutations in the CFTR gene in which sufficient CFTR protein reaches the plasma membrane, but the gating of the ion channel is impaired and does not function. The lower efficacy rates in our cohort might be due to the absence of patients carrying these specific gating mutations. Eighty-eight % of the patients in the TEZ/IVA subgroup were homozygous for ΔF508, which is representative for the general population. The ΔF508 mutation is defined as a class II mutation, in which the CFTR protein is misfolded and cannot reach the cell surface. The remaining of the patients in our cohort were heterozygous for ΔF508, with one patient carrying a class I (no production of functional CFTR) and two patients carrying a class V mutation (insufficient quantity of

Figure 4. Longitudinal evaluation of SNOT-22 (A) and Modified Lund-Mackay (B) scores at baseline, ±12 months after start of dual therapy with tezacaftor/ivacaftor (TEZ/IVA) and ±6 months after treatment with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). * indicating a statistically significant difference with p-value <0.05.
CFTR channels at the plasma membrane). Nevertheless, studies did show that TEZ/IVA significantly improves lung function in ΔF508 homozygous or heterozygous patients (25, 26), but also for pulmonary outcomes it has been shown that these effects are smaller than seen when treating patients with specific G551D mutations in monotherapy (27). No demographical or baseline (e.g. age, gender, disease severity, previous medical/surgical treatments, genotype) differences between both subgroups could be observed that might explain the difference in efficacy. We hypothesize that the additional effect seen with triple therapy is due to adding a second CFTR corrector elexacaftor, that facilitates folding and translocation of the CFTR protein to the plasma membrane.

The main limitation of this study is its observational design. Previous clinical trials have already extensively studied the effect of ELX/TEZ/IVA and IVA in monotherapy on CF-CRS, and for this subgroup of patients our real-world data offers valuable insights in a more realistic setting. Nevertheless, as this was the first study evaluating the effect of TEZ/IVA, we could not compare our results with existing randomized controlled trials. As the data are, inherently due to the study design, influenced by treatment adherence and compliance, heterogeneity in our patient population with different underlying genotypes and disease severity, and variability in use of maintenance medication for CF-CRS, the effects of TEZ/IVA might be underestimated. Performing a randomized controlled trial with TEZ/IVA would be beneficial to gain more insights in the mechanisms of action of dual therapy, however as triple therapy is now considered the golden standard such study is no longer ethically accepted.

Conclusion

Triple therapy with elexacaftor/tezacaftor/ivacaftor significantly improves sinonasal symptoms and reduces objective disease severity on nasal endoscopy and CT scan. Dual therapy with tezacaftor/ivacaftor is inferior to triple therapy as no changes could be observed in comparison to baseline. Objectively, 63.2% and 23.8% of the patients with CF-related CRS respond to triple and dual therapy, respectively. No changes in bacterial upper airway colonization could be observed and future studies on this topic are recommended.

Authorship contribution

SU: conceptualization, methodology, investigation, data curation, formal analysis, writing-original draft, visualization, project administration; CC: data curation, formal analysis, writing, review and editing, MJ: writing, review and editing, LD: conceptualization, co-supervision, writing, review and editing, LVG: conceptualization, methodology, resources, supervision, formal analysis, project administration, funding acquisition, writing, review and editing. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

We have no conflicts of interest to declare.

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This manuscript contains online supplementary material
### Appendix 1. Lund-Kennedy scoring system.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severity (0,1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyps, left</td>
<td>0= absent, 1= only in middle meatus, 2= beyond middle meatus</td>
</tr>
<tr>
<td>Polyps, right</td>
<td>0= absent, 1= only in middle meatus, 2= beyond middle meatus</td>
</tr>
<tr>
<td>Edema, left</td>
<td>0= absent, 1= mild, 2= severe</td>
</tr>
<tr>
<td>Edema, right</td>
<td>0= absent, 1= mild, 2= severe</td>
</tr>
<tr>
<td>Discharge, left</td>
<td>0= no discharge, 1= clear, thin discharge, 2= thick, purulent discharge</td>
</tr>
<tr>
<td>Discharge, right</td>
<td>0= no discharge, 1= clear, thin discharge, 2= thick, purulent discharge</td>
</tr>
</tbody>
</table>

**Total score**: Score ranging from 0 to 12 out of 12

### Appendix 2. Modified Davos scoring system.

<table>
<thead>
<tr>
<th>Polyp Score (left, right)</th>
<th>Polyp Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No polyps</td>
</tr>
<tr>
<td>1</td>
<td>Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate</td>
</tr>
<tr>
<td>2</td>
<td>Polyps reaching below the lower border of the middle turbinate</td>
</tr>
<tr>
<td>3</td>
<td>Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate</td>
</tr>
<tr>
<td>4</td>
<td>Large polyps causing complete obstruction of the inferior nasal cavity</td>
</tr>
</tbody>
</table>

**Total Modified Davos score**: Score ranging from 0-8 (left and right combined)

### Appendix 3. Lund-Mackay and Modified Lund Mackay scoring system.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severity (0,1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary sinus, left</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Maxillary sinus, right</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Anterior ethmoid, left</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Anterior ethmoid, right</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Posterior ethmoid, left</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Posterior ethmoid, right</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Frontal sinus, left</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Frontal sinus, right</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Sphenoid sinus, left</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Sphenoid sinus, right</td>
<td>0= no abnormality, 1= partial opacification, 2= total opacification</td>
</tr>
<tr>
<td>Ostiomeatal complex, left</td>
<td>0= not obstructed, 2= obstructed</td>
</tr>
<tr>
<td>Ostiomeatal complex, right</td>
<td>0= not obstructed, 2= obstructed</td>
</tr>
</tbody>
</table>

**Total score**: Score ranging from 0 to 24 out of 24

**Modified Lund-Mackay score**: Lund Mackay score x 24 / (24- 2x number of aplastic sinuses)
Appendix 4. 22-item Sinonasal Outcome Test (SNOT-22).

<table>
<thead>
<tr>
<th></th>
<th>No problem</th>
<th>Very mild problem</th>
<th>Mild or slight problem</th>
<th>Moderate problem</th>
<th>Severe problem</th>
<th>Problem as bad as it can be</th>
<th>Most important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need to blow nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>O</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>O</td>
</tr>
<tr>
<td>Runny nose</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>O</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>O</td>
</tr>
<tr>
<td>Post nasal discharge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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Appendix 5. Visual Analogue Scale (VAS) scores.

- Total sinus symptoms
- Nasal blockage
- Headache/pressure on the face
- Loss of smell
- Postnasal discharge
- Runny Nose