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Quality of Life in NSAIDs-Exacerbated Respiratory Disease on or off Intranasal Lysine Aspirin Therapy

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Abstract: *Background*: Intranasal administration of lysine aspirin (LAS) is a safe and effective method for aspirin treatment after desensitisation (ATAD). Changes in quality of life (QoL) in patients on intranasal LAS have not been documented and we aimed to investigate QoL in N-ERD patients on or off nasal ATAD. Moreover, an estimate of the cost burden of intranasal LAS is given. *Methods*: A cross-sectional review was conducted for all challenge-confirmed N-ERD patients who were in follow-up in our rhinology clinic. They were asked to complete a SNOT-22 questionnaire, a visual analogue scale for sense of smell (sVAS). Information on prices of LAS and other consumables used for intranasal ATAD was obtained from our hospital pharmacy to obtain an estimate of the cost burden. *Results*: Thirty-four patients replied to the email (79.1% response rate). Of these, 21 (61.8%) were on intranasal LAS. A statistically significant lower score in the total SNOT-22 was found amongst patients on intranasal LAS ($p = 0.02$). The subanalysis of SNOT-22 domains showed that patients on LAS had statistically significant lower scores in the domains "rhinologic symptoms" ($p = 0.05$), "function" ($p = 0.02$), and "emotion" ($p = 0.01$). No significant differences were observed when looking at sVAS. The cost of 1-year treatment of LAS per person was ≈GBP 180.7 with a daily cost of ≈GBP 0.50. *Conclusions*: This study supports the efficacy of nasal ATAD in the management of N-ERD and suggests that long-term use can lead to QoL improvement with cost benefits.

Keywords: sino-nasal outcome test; quality of life; acetylsalicylic acid lysinate; nasal polyps; sinusitis

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (N-ERD) or aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome characterized by chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and intolerance to aspirin/NSAIDs. It affects approximately 15% of cases of patients with severe asthma, 10% of those with CRSwNP, and 9% of cases with chronic rhinosinusitis (CRS) [1,2]. CRS impacts multiple aspects of health-related quality of life (HRQoL) including mental and physical health, sleep, productivity, cognitive and social functioning, and general health status [3,4]. HRQoL is further worsened in patients with CRSwNP who have asthma [3]. Moreover, CRSwNP in N-ERD is usually refractory to conventional medical management and surgery and often requires several courses of systemic steroids for nasal polyposis and multiple endoscopic sinus surgeries (ESS) [5]. As a result, patients with N-ERD usually have ongoing and more severe sinonasal symptoms when compared to their non-N-ERD counterparts [6]. Chronic nasal symptoms and poor sense of smell are the major drivers of N-ERD patients' reduced HRQoL. Olfactory dysfunction (OD), in particular, is highly prevalent amongst patients with N-ERD and is reported to affect >90% of patients [7]. It is well documented that a reduced sense of smell is associated with depression, feelings of

isolation, emotional distress, changes in weight, cognitive decline, and neurodegeneration in the brain and it is an independent risk factor for death among older adults [8–10].

Aspirin treatment after desensitisation (ATAD) is an effective therapeutic option for CRSwNP in N-ERD and its safe profile and low cost make it an attractive alternative treatment option in case of failure of maximal medical and surgical treatment [6,11,12]. The mechanism behind aspirin desensitisation is not completely understood. It has been shown that aspirin desensitisation modulates deregulated immune responses in N-ERD through decreased levels of pro-inflammatory leukotrienes and their receptors, inhibition of Th2 activation, IL-4 production, and mast cell activation [13]. A recent systematic review and meta-analysis [11] has confirmed that oral ATAD improves HRQoL when compared to placebo. However, oral ATAD is associated with adverse outcomes severe enough to cause drug discontinuation, including major gastrointestinal bleeding, gastritis, asthma exacerbation, and severe rash [11,12]. Intranasal administration of lysine aspirin (LAS) is a faster and safer route for ATAD when compared to oral daily aspirin and has been shown to be equally effective to oral ATAD [14,15].

Changes in HRQoL in patients on intranasal LAS have not been documented and in this cross-sectional retrospective study, we aimed to investigate HRQoL in N-ERD patients on or off nasal ATAD. Additionally, a focus on the costs of treatment options currently available for difficult-to-treat CRSwNP in N-ERD patients is also provided.

2. Materials and Methods

Due to pandemic restrictions, in the months of October-November 2020, we reviewed all our challenge-confirmed N-ERD patients who were in follow-up in our rhinology clinic through a remote telephone consultation. As part of that, they were sent an email in which they were asked to fill out a SNOT-22 questionnaire, a disease-specific HRQoL questionnaire for use in CRS [16]. This questionnaire has a recall period of 2 weeks (i.e., symptoms are rated as these have been over the last 2 weeks) and evaluates 5 main domains including sinonasal (8 items), ear/facial (4 items), sleep (4 items), function (3 items), and emotion (3 items) with each item scoring from 0 ("no problems") to 5 points ("problem as bad as it can be") leading to a total score ranging from 0 to 110 [16,17]. In each case, higher scores represent worse HRQoL. Moreover, patients are asked to tick up to 5 "most important" items that they feel are affecting their QoL the most. To determine the portion of respondents who complained of OD at the time of the consultation, the answer to item 21 of the SNOT-22, which asks patients to rate their sense of taste/smell, was analysed separately. Patients were also asked to self-assess their olfaction during the last 2 weeks using a visual analogue scale (sVAS—0 represents 'sense of smell absent' and 10 'sense of smell not affected') and to report which medications they were taking at the moment of which the questionnaire was completed. Other relevant data were retrieved using our hospital medical system. Information on prices of LAS and other consumables used for intranasal ATAD was obtained from our hospital pharmacy to obtain an estimate of the cost burden. The study was conducted in accordance with the 1996 Helsinki Declaration and approved by the Research Ethics Committee (Ref: 06/Q0301/6).

Statistical Analysis

Quantitative variables were summarized using median and interquartile range (P25–P75), whereas qualitative variables were described with frequency and percentage. Comparisons of general characteristics and findings between groups were performed using the T-test for quantitative variables if normally distributed, or the Mann–Whitney U test if not, while the Pearson chi-square test was used for categorical variables. *p*-values have been calculated for all tests, and 5% was considered as the critical level of significance. A post hoc power analysis has been calculated using the SNOT-22 total score as the main outcome and keeping the alpha level at 0.05.

3. Results

Of the 43 patients on follow-up, 34 were remotely reviewed (79.1% response rate) between 14 October 2020 and 29 November 2020 and sent back to us their questionnaires (SNOT-22 and sVAS) along with the other information requested. Of the 34 respondents, 21 patients (61.8%) were on intranasal LAS with a median length of LAS treatment of 44 months (range 10–180 months). The median time from sinus surgery to LAS initiation was 16 months (range 3–48 months). Four patients initially tried intranasal LAS but then stopped because of no improvement in their nasal symptoms and were included in the group of patients "not on LAS". The remaining patients refused intranasal LAS and did not start any aspirin desensitisation treatment. Similarly, these patients were included in the group of patients "not on LAS". Characteristics of the population are reported in Table 1.

Table 1. Characteristics of the whole population and according to intranasal lysine aspirin (LAS) use. Level of significance $p \leq 0.05$. Significant p values in bold. * Eosinophils normal range: 0.0–0.4 $\times$ 10^9/L.

	Whole n = 34	On LAS n = 21	Not on LAS n = 13	*p*-Value
General characteristics				
Age, median [P25–P75], yr	49.0 [38.0–56.8]	48.0 [37.0–59.0]	50.0 [38.0–56.0]	0.50
Sex, No (%)				
Female	17 (50.0%)	10 (47.6%)	7 (53.8%)	0.72
Male	17 (50.0%)	11 (52.4%)	6 (46.2%)	
Onset CRSwNP, median [P25–P75], yr	27.0 [18.8–36.8]	25.0 [17.0–35.0]	28.0 [24.0–34.5]	0.39
Onset nasal polyps, median [P25–P75], yr	30.0 [24.0–40.0]	31.0 [24.0–41.0]	30.0 [25.0–38.5]	0.34
Onset asthma, median [P25–P75], yr	30.0 [25.0–40.0]	29.0 [19.5–40.0]	34.5 [28.5–40.0]	0.22
Numbers of previous ESS, median [P25–P75]	3.0 [2.0–4.5]	3.0 [1.5–3.5]	4.0 [2.0–5.5]	0.34
Routine medications				
Long-term nasal CS drops, No. (%)	32 (94.1%)	20 (95.2%)	12 (92.3%)	0.75
Nasal douche, No. (%)	34 (100%)	21(100%)	13 (100%)	1
ICS, No. (%)	12 (35.3%)	5 (23.8%)	7 (53.8%)	0.09
LABA, No. (%)	2 (5.9%)	1 (4.8%)	1 (7.7%)	0.75
ICS + LABA, No. (%)	19 (55.9%)	14 (66.7%)	5 (38.5%)	0.07
SABA, No. (%)	13 (38.2%)	7 (33.3%)	6 (46.2%)	0.52
Anticholinergic inhaler, No. (%)	1 (2.9%)	0 (0.0%)	1 (7.7%)	0.21
Long-term macrolides, No. (%)	2 (5.9%)	1 (4.8%)	1 (7.7%)	0.75
Antileukotrienes, No. (%)	13 (38.2%)	9 (42.9%)	4 (30.8%)	0.41
Oral antihistamines, No. (%)	14 (41.2%)	9 (42.9%)	5 (38.5%)	0.71
Laboratory findings and testing				
Eosinophils, median [P25–P75], ×109/L *	0.5 [0.4–0.7]	0.6 [0.4–0.9]	0.4 [0.3–0.7]	0.28
Missing	11	7	4	
Skin prick test, No (%)				
Negative	10 (41.7%)	4 (19.0%)	6 (46.2%)	0.12
One allergen	3 (12.5%)	1 (4.8%)	2 (15.4%)	
Two allergens	5 (20.8%)	4 (19.0%)	1 (7.7%)	
Multiple allergens	6 (25.0%)	5 (23.8%)	1 (7.7%)	
Missing	10	7	3	

CRSwNP: chronic rhinosinusitis with nasal polyps; ESS: endoscopic sinus surgery; CS: corticosteroids; ICS: inhaled corticosteroids; LABA: long-acting β2-adrenergic; SABA: short-acting β2-adrenergic; ANCA: antineutrophil cytoplasmic antibodies.

The most affected SNOT-22 domain was "rhinologic symptoms" and the question with the highest score (worst symptom) overall was "loss of smell or taste". "Loss of smell or taste" was also the most frequently ticked "most important item" by respondents (20/34; 58.8%), followed by nasal obstruction (12/34; 35.3%), thick nasal discharge (8/34; 23.5%) and post-nasal discharge (8/34; 23.5%) (Figure 1). Only 2 patients, both amongst those using LAS, reported in question 21 of the SNOT-22 that they had "no problem" with their

sense of smell, while 27 patients (81.8%) confirmed to have at least a moderate problem with their sense of smell. Similarly, 18 patients (52.9%) reported at least a moderate nasal blockage and 12 patients (35.3%) reported this to be one of the most affected items.

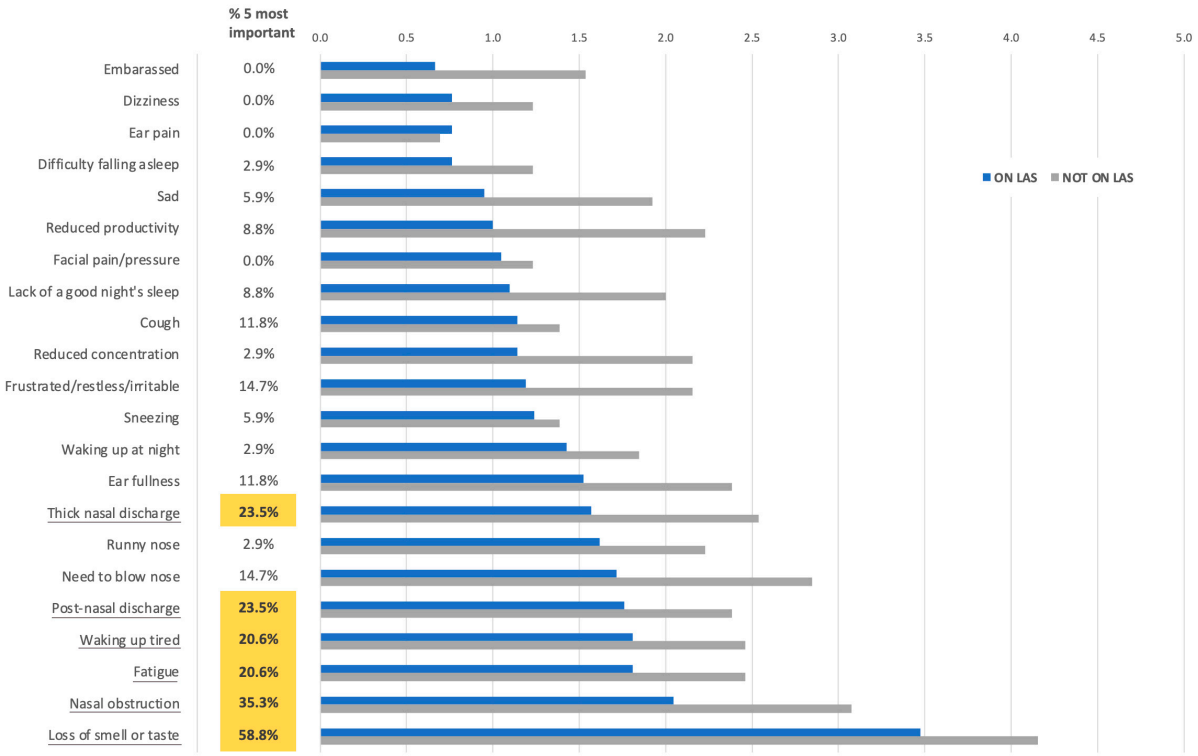

Figure 1. Average score for each SNOT-22 item in patients on or off intranasal lysine aspirin (LAS). "% 5 most important" represents the percentage of patients who considered each item as one of the 5 most important items. The most frequently reported items in the population are highlighted in ochre and underlined. Please note that due to similar scores in 4 items, we highlighted 6 most important items. SNOT-22: 22-item Sino-Nasal Outcome Test; LAS: lysine aspirin.

No statistically significant differences were noted in terms of general characteristics, laboratory findings, or routine medications when comparing those patients who were on intranasal LAS or not (Table 1). A statistically significant lower score in the total SNOT-22 was found in patients on intranasal LAS (p = 0.02). Moreover, when we performed a subanalysis of the SNOT-22 domains (rhinologic symptoms, ear/facial, sleep dysfunction, function, and emotion), as previously described [17], patients on LAS showed statistically significant lower scores in the domains "rhinologic symptoms" (p = 0.05), "function" (p = 0.02) and "emotion" (p = 0.01) (Figure 2; Table 2). No significant differences were observed when looking at the sVAS or the SNOT-22 item "decreased sense of smell/taste" (Table 2).

When looking at the prices of intranasal ATAD, the price of a box containing 20 sachets of lysine acetylsalicylate (=20 days treatment) is GBP 8.30, while the price of one box of sodium chloride 0.9% containing 20 ampules (each of 10 mL), used to mix with the LAS sachet to prepare the solution, is GBP 1.60. Other expenses include the use of a reusable glass bottle and a dropper pipette to instil the solution in the nose (one-time expense of ≈GBP 1). This brings the cost of a 1-year treatment of LAS per person to ≈GBP 180.7 and a daily cost of ≈GBP 0.50.

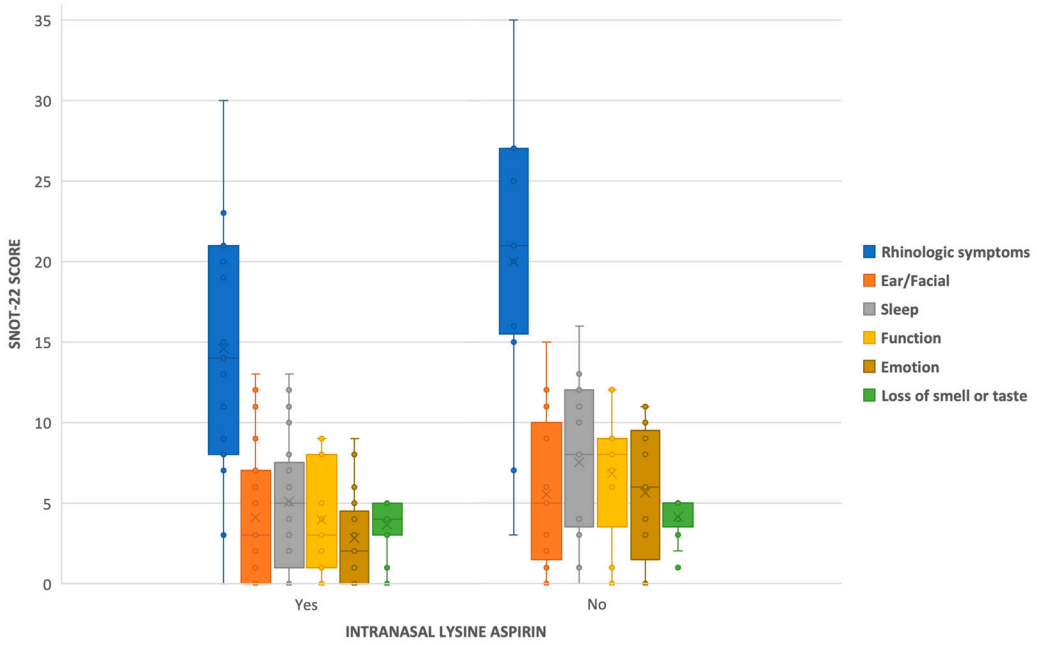

Figure 2. Box plots showing SNOT-22 domain scores in patients on or off intranasal lysine aspirin. SNOT-22: 22-item Sino-Nasal Outcome Test.

Table 2. Patient-reported outcome measures (PROMs) in the whole population and according to intranasal lysine aspirin (LAS) use. Level of significance $p \leq 0.05$. Significant p values in bold. $^{+}$ This item is already included in the "rhinologic symptoms" and, thus, has not been considered when calculating the total SNOT-22 score.

	Whole n = 34	**On LAS n = 21**	**Not on LAS n = 13**	***p*-Value**
sVAS, median [P25–P75]	0.0 [0.0–3.0]	0.5 [0.0–3.0]	0.0 [0.0–2.5]	0.67
Missing	3	1	2	
SNOT-22 score, median [P25-P75]				
Rhinologic symptoms	19.0 [11.0–21.0]	14.5 [8.5–21.0]	21.0 [16.0–27.0]	**0.05**
Ear/Facial symptoms	3.0 [1.0–7.0]	3.0 [0.5–7.0]	5.0 [2.0–9.0]	0.22
Sleep dysfunction	5.5 [2.3–10.0]	5.0 [2.0–7.0]	8.0 [4.0–12.0]	0.07
Function status	4.5 [1.0–8.8]	3.0 [1.0–8.0]	8.0 [6.0–9.0]	**0.02**
Emotion status	3.0 [0.3–6.0]	2.0 [0.0–4.0]	6.0 [3.0–9.0]	**0.01**
Decreased sense of smell/taste $^{+}$	5.0 [3.0–5.0]	4.0 [3.0–5.0]	5.0 [4.0–5.0]	0.41
Total SNOT-22 score	36.0 [24.0–51.0]	29.0 [19.5–43.5]	49.0 [29.0–62.0]	**0.02**
Missing	1	1	0	

sVAS: visual analogue scale for sense of smell; SNOT-22: 22-item Sino-Nasal Outcome Test.

4. Discussion

The SNOT-22 is a patient-reported outcome measure (PROM) commonly used to assess the impact of CRS on HRQoL and can be a useful tool to evaluate the benefits of a treatment on patients' health [16,17]. In our study, the median SNOT-22 score in N-ERD patients on nasal LAS was 20 points lower than in those off LAS and this was statistically significant ($p = 0.02$). So far, several studies have confirmed an improvement in the reported sinonasal symptoms in patients undergoing oral ATAD, as well as in the long term. Swierczynska-Krepa et al. [18] found a statistically significant improvement in the SNOT-20 score in a placebo-controlled randomized trial of ASA desensitisation in ASA-tolerant and ASA-intolerant asthmatics. Esmaeilzadeh et al. [19] found a statistically significant improvement in SNOT-22 in the desensitisation arm at 6 months when comparing 16 ASA desensitisation patients to 16 controls. Mortazavi et al. [20] observed a significant improvement in the SNOT-22 score in 19 patients randomized to ASA when compared to 19 receiving a placebo.

Fruth et al. [21] reported improved QoL scores on the Rhinosinusitis Disability Index in 18 ASA-desensitised patients compared to 13 controls at 36 months after sinus surgery. Similar results were found by Rozsasi et al. [22] using modified validated QoL questionnaires. In a previous study, Cooper et al. [23] observed a significant decrease in the SNOT-22 median score of an average of 10 points after 6 months of maintenance therapy. However, to the best of our knowledge, this is the first study evaluating the HRQoL in patients on intranasal ATAD using LAS. Interestingly, the 20-unit difference found in the total score of the SNOT-22 in our N-ERD patients on and off nasal LAS was higher than that observed in patients on oral ATAD in a recent meta-analysis (difference of 10.27 units) [11]. The lower SNOT-22 scores found in our patients on intranasal LAS could also be related to better tolerability of nasal ATAD compared to the oral one. In fact, it is well-known that people on oral ATAD can develop symptoms affecting the skin, gut, or lungs, and in previous studies conducted by our team, we confirmed a lower rate of side effects in patients using intranasal LAS when compared to those on oral aspirin, including lower risk of gastrointestinal bleeding or urticarial rash [14,15]. Nevertheless, up to 30% of patients may not respond to ATAD [12]. In a previous audit on intranasal LAS, our team found that 18.7% of patients reported no efficacy following intranasal ATAD at their 3-month follow-up. With this in mind, a common issue is to determine how long a patient should be trialled before considering him to be a non-responder to ATAD. In this regard, a total score of 20 at the SNOT-22 has been defined to be the threshold to distinguish responders (SNOT-22 < 20) from non-responders (SNOT-22 $\geq$ 20) [24]. Moreover, a recent study from Tripathi et al. [25] found that the SNOT-22 score obtained at 6 months post-desensitisation had the greatest predictive value for long-term outcomes at 24 months post-desensitisation, with an OR of 16.5, proposing a 6-month time point of ATAD as a predictor for long-term success. In our practice, we tend to consider a patient a good responder to the treatment when their SNOT-22 score significantly improves from baseline (SNOT-22 before treatment). In this regard, the minimal clinically important difference (MCID) for the SNOT-22 total score has been reported to be 8.9 points and this is the minimal improvement in the SNOT-22 total score we usually seek for in order to consider a patient a responder to the treatment. In our population, 11.8% (4/34) were previously considered non-responders to intranasal ATAD (based on our medical records), although this percentage could have been higher considering that the remaining 9 patients never started intranasal LAS.

Assessing domains and item scores of the SNOT-22 separately can provide clinicians with a better understanding of which individual aspect of CRSwNP has the greatest impact on patients' HRQoL and, thus, offer valuable information in view of personalised treatment decision making. In our study, the domain "rhinologic symptoms" remained the most affected domain across both groups of patients (on or off LAS) with the items "nasal obstruction", "thick nasal discharge", and "post-nasal discharge" reported to be the most important items from our N-ERD respondents. This corroborates previous results of a recent randomized double-blind placebo-controlled study which included patients with CRSwNP considered hard to treat, including patients with N-ERD [26]. Moreover, in our study patients on LAS had significantly lower scores in the rhinologic domain ($p = 0.05$) when compared to their counterparts not on nasal LAS, suggesting that LAS is effective in controlling nasal polyps and the local inflammatory burden, confirming results from our previous retrospective study [14]. We also observed significant improvements in the domains function ($p = 0.02$) and emotion ($p = 0.01$), which could simply reflect the indirect effect of improved sinonasal symptoms on other aspects of health.

Loss of smell in N-ERD negatively impacts QoL and has been reported to be more severe as compared to patients with ASA-tolerant CRSwNP [27]. In our population, more than 80% of the patients reported having at least a moderate problem with their sense of smell at the SNOT-22 and almost 60% of the respondents confirmed this was one of the five most important items affecting their health. This suggests that, from a patient's perspective, OD remains an important marker of disease severity and, thus, a critical outcome measure of treatment efficacy. The cause of OD in N-ERD seems to be multifactorial. Contributing

factors include the high nasal polyp burden and swelling of the sinonasal mucosa in the olfactory area which could cause a physical obstruction preventing odorants from reaching the olfactory epithelium. In addition, the long-standing chronic inflammation within the olfactory epithelium may also be a causative mechanism for OD in these patients [28]. In fact, elevated nasal mucous levels of IL-2, IL-5, and IL-13 have been associated with altered olfaction suggesting a potential immunological cause for OD in these patients [29,30]. A previous review looking at studies evaluating olfactory outcomes following oral ASA desensitisation demonstrated improvements in patient-reported and objective assessments of olfactory function [22,23,31]. Interestingly, in one of these, Sweet et al. [32] compared individuals who were on long-term oral ASA therapy and those who discontinued therapy for a variety of reasons and observed statistically significant improvement in the PROMs while on ASA with a subsequent worsening of symptoms after discontinuation. Although we previously demonstrated improved olfaction in patients on long-term nasal ATAD, as measured by a 6-item identification test (Nez du Vin) [14], in this study there was no statistically significant difference in the patients' reported olfaction (both at the sVAS and the SNOT-22 item "decreased sense of smell/taste") between those on intranasal LAS or not. This could be because subjective olfaction measures are less sensitive than objective ones [33]. In this regard, it is interesting to mention that Landis et al. [34] observed that healthy subjects are usually unable to accurately self-report their sense of smell but the accuracy of this self-assessment improves after undergoing olfactory testing, forcing them to pay conscious attention to their sense of smell.

Despite several studies showing an improvement of HRQoL in N-ERD patients whilst on ATAD, aspirin desensitisation remains an underutilized treatment modality as confirmed by our study of allergists and fellows conducted in the United States in 2016 [35]. More recently, biologics have set their scene on the treatment of severe CRSwNP and, although not specific for N-ERD, they have been shown to be very effective in CRSwNP in N-ERD patients [36,37]. In this regard, dupilumab, an anti-interleukin-4 and -13, has gained increased popularity since its approval as a treatment for severe or refractory CRSwNP in 2019 and several studies have demonstrated effective reduction in both objective and subjective measurements [38–40]. So far, dupilumab is the only biologic showing a difference between aspirin-tolerant and aspirin-intolerant CRSwNP patients with N-ERD patients reporting significantly greater improvement in nasal congestion and SNOT-22 scores after treatment [41]. In a previous study, Buchheit and colleagues [42] reported a higher improvement in the total SNOT-22 score when using dupilumab if compared to our study (mean change of -34.4 and -34.5 at month 1 and 3, respectively; all $p < 0.0001$). Additionally, differently from our results, an improvement in all five SNOT-22 domains at 6 months has also been demonstrated in patients on dupilumab, with the most marked improvements observed for nasal, sleep, and function domains [26]. However, no direct trials with ATAD and biologic therapy in N-ERD patients exist, which makes it difficult to choose the best alternative to use when maximal medical and surgical treatments have failed. Only recently, Tuncay and colleagues [43] conducted an observational real-life study including 59 N-ERD patients receiving ATAD or biologics (either omalizumab or mepolizumab) and found no significant difference in the SNOT-22 scores between patients who received ATAD only and/or biologics although SNOT-22 scores were lower in those who received mepolizumab. Biologics have also been demonstrated to significantly improve olfactory function in several studies [38,44,45]. Moreover, Barroso and colleagues [46] did not show any differences for partial or total improvement in sense of smell when comparing N-ERD (35.7%) and non–N-ERD patients (37%) in patients undergoing long-term treatment with omalizumab, mepolizumab, reslizumab, or benralizumab. However, there remains a need for further studies to demonstrate the effectiveness of biologics more clearly against ATAD for the decision of which biologics are beneficial in patients with both eosinophilia and atopy.

In spite of its superb effects in controlling CRSwNP and improving HRQoL, also in N-ERD patients, dupilumab is over a hundred times more expensive than ATAD which poses questions about the appropriate use of healthcare resources. In fact, the cost of ATAD is less

than USD 100 per year compared to Th2 biologic therapy, which is estimated to be USD 30.000 to USD 40.000 per patient per year corresponds to a multimillion dollars per patient per year for biologic treatment [41,47]. Moreover, a study from Shaker et al. [48] found that ambulatory desensitisation for N-ERD could save USD 6.768 per "quality-adjusted life year" (QALY), and ATAD remained cost effective with less than USD 50,000 per QALY saved. The cost of intranasal LAS is slightly higher than oral aspirin being roughly GBP 180 per year which is mainly related to the fact that LAS has to be imported from France (LAS is currently not sold in the United Kingdom). However, this cost is again derisory if compared to the yearly cost of biologics. Considering its safety profile, its effectiveness, and its relatively low costs, ATAD should be considered as one of the first-line therapies, if no contraindication, in N-ERD patients with uncontrolled CRSwNP. Nonetheless, the role of endoscopic sinus surgery, in particular of large cavity sinus surgery, with post-operative ATAD should also be taken into account when treating recalcitrant CRSwNP in patients with N-ERD [49,50]. In this regard, a recent cost-effectiveness analysis comparing dupilumab and ATAD for CRSwNP in N-ERD showed that dupilumab treatment can be cost-effective when offered as salvage therapy after failing ATAD after ESS [51]. This offers new insights into when to recommend biologic therapy in a cost-effective manner within the available treatment options.

Limitations of the Study

Our study is slightly unpowered (post hoc power of 50.4%) and, therefore, results should be interpreted in view of this limitation. The main reason for this relies on the large data dispersion (i.e., interquartile range) observed in the SNOT-22 total scores for both groups which reflects the high variability in the severity of symptoms reported by our N-ERD patients. Other limitations of this study are those that are intrinsically inherent to the use of self-reporting outcomes (i.e., PROMs) including changing internal standards (recalibration), changing priorities (reprioritization), and changing interpretations (reconceptualization) [52], which are particularly present when assessing the efficacy of a treatment and especially in chronic conditions like CRS [53,54]. Moreover, for both the SNOT-22 and sVAS, patients were asked to rate their symptoms as these had been over the 2 weeks before questionnaire administration, which inevitably introduced a recall bias. However, it must be considered that all these biases are present when evaluating quality of life using SNOT-22 and/or other PROMs.

5. Conclusions

N-ERD has significant financial and HRQoL detriment to sufferers.

This first study, in which HRQoL was evaluated in patients on long-term intranasal LAS, supports the efficacy of nasal ATAD in the management of N-ERD and suggests that long-term use can lead to QoL improvement.

Since nasal LAS has fewer comorbidities than oral ATAD and is cheaper than monoclonal antibodies we suggest that these results should be confirmed in larger populations. In addition, these results can provide evidence to policymakers looking to support cost-effective treatment options for CRSwNP in N-ERD.

Nevertheless, when choosing the best alternative for uncontrolled CRSwNP amongst the available options, the pros and cons of each treatment should be tailored, taking into account the patient's comorbidities and disease profile in an attempt to offer a more personalised therapy.

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