LETTER TO THE EDITOR

Nasal budesonide efficacy for nasal nitric oxide and nasal obstruction in rhinitis

To the Editor,

Nasal nitric oxide (nNO) is a non-invasive tool that may be helpful in evaluating the inflammatory status in the upper airways (1). Previous studies report that nNO is elevated in children with allergic rhinitis (AR) (2), especially in perennial sensitized subjects (3), and that it may be affected by topical administration of intranasal steroids (INSs) (4).

Clinical studies reported that intranasal budesonide is effective on AR symptoms (5), whereas no data about its effect on nNO in children with persistent allergic rhinitis (PAR) are available to date.

Including nasal cytology (NC) into the diagnostic process may allow to detect and discriminate the cellular components involved in the inflammatory response in AR (6).

Finally, AR has been demonstrated to have a large impact on patient’s life and activities, affecting children’s sleep quality, and leading to daytime somnolence and fatigue (7). Therefore, assessing the burden of disease should be also considered in a comprehensive management of AR.

This study was conducted in 62 children (mean age 9.64 ± 2.06 years) with PAR for at least 1 year. Children were eligible if affected by PAR with characteristic symptoms and a positive skin test (>3 mm wheal) for Dermatophagoides pteronyssinus. Skin-prick tests (SPTs) were performed according to EAACI recommendations with a standard panel of inhalant allergens including a positive (histamine 1%) and a negative (saline) control (ALK-Abelló, Milan, Italy). Allergic sensitization was defined upon a positive skin response after 15 min (i.e., a wheal ≥3 mm larger than the negative control test).

Exclusion criteria included a concomitant allergy to seasonal pollens and treatment with any drugs and/or infection of the upper respiratory tract in the 3 weeks previous to the study. None of the patients were smokers. None of the patients had taken any medication for PAR during the 14 days prior to enrollment. Use of any additional medication for PAR, other than the study medication, was prohibited during the treatment period. All children attended the Paediatric and Pulmonology–Allergology outpatient clinic of the Institute of Biomedicine and Molecular Immunology at the National Research Council of Palermo.

This was a 3-week, randomized, double-blind, placebo-controlled, parallel-group study. Children were randomly allocated to receive a course of (i) a nasal budesonide (NB group), or (ii) a nasal saline solution (NS group). Children in the NB group were treated with budesonide nasal spray (Aircort® nasal spray 50 μg, Italchimici, Pomezia, Rome, Italy) 100 μg twice daily, whereas children in the NS group were treated with a nasal saline solution spray (0.9% sodium chloride solution) twice daily.

Detailed medical history was obtained by parents of all the participants through medical well-trained interviewers (GF, SLG, VM). There were two assessments: at enrollment (T0) and after 3 weeks of treatment (T1). At T0 visit, children underwent physical examination and nNO measurement. Subjective symptoms were assessed through standardized tools such as Total 5 Symptom Score (TSSS) and the Pittsburgh Sleep Quality Index (PSQI). At T1 visit, physical examination, nNO measurement, and subjective symptoms assessment were repeated. Information on adverse events (AEs) was recorded.

The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. The approved study was registered on the central registration system ClinicalTrials.gov (identifier: NCT02409563). Nasal nitric oxide was measured by gently introducing an inert olive into the vestibulum of one nostril, avoiding contact with the nasal mucosa, completely occluding it in order to avoid ambient air sampling. The contralateral nostril was left open. In the seated position, patients were asked to breathe through the mouth, without speaking or swallowing. nNO was measured ‘off line’ by an electrochemical sensor (Hypair FeNO, Sensor Medics, Italy). Air from the nasal cavity was continuously analyzed by the sensor at a sample flow rate of 350 ml/min, during 30 s tidal breathing through resistance, so that the velum was closed to prevent any contamination of nasal air with bronchial air. nNO values were reported as median (IQR) of the three measurements. Only measurements with less than 10% among the three measurements variability were recorded.

The cytologic sampling consisted in the collection of surface cells scraping from the middle portion of the inferior turbinate. The cellular material was spread on a glass slide, fixed by air-drying, and then stained by the method of May–Grunwald–Giemsa. Slides were read using a common optical microscope, at 1000× in oil immersion, equipped with a digital camera. The analysis of rinocitogram involved the reading at least 50 fields, in order to assess the eosinophil count.

Total 5 Symptom Score was obtained for each child and was completed by medical well-trained investigators who interviewed the patient (GF, SLG, VM). AR subjective symptoms were assessed by calculating the sum of the before scores for nasal obstruction, nasal itching, rhinorrhea, sneezing, and ocular itching. Each symptom was scored on a scale from 0 to 3 (0 = absent; 1 = mild, any symptom not causing significant discomfort; 2 = moderate, any symptom causing discomfort but not interfering with daily activity and/or disturbing sleep;
and 3 = severe, any symptoms that interfered with daily activity and sleep pattern). Patients were asked to indicate their own perception about the severity of symptoms during in the last 4 days before the visit. Total score was calculated by adding the scores for all the five domains (maximum score 15).

Pittsburgh Sleep Quality Index was used to measure sleep quality during the previous month. This self-administered questionnaire includes 19 questions about seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. Each component is scored from 0 to 3 so that the global score ranges from 0 to 21. A global score above 5 indicates poor sleep quality; scores larger than 10 indicate a chronic sleep disorder.

The primary end-point was the mean nNO change from baseline to the end of the treatment period. Secondary end-points were the mean change in T5SS total score, T5SS individual symptom score, nasal eosinophil count (0 = ‘none’, 0.5 = ‘occasional’, 1 = ‘few scattered cells, small clumps’, 2 = ‘moderate number, large clumps’, 3 = ‘large clumps not covering the field’, 4 = ‘clumps covering entire field’), and PSQI total score. Concerning T5SS, the mean change from baseline to an intermediate fourteen-day assessment was also available, allowing a more detailed evaluation.

In a previous study on children with AR (4), nNO levels (mean ± s.d.) of 271 ± 21 before and 212 ± 20 after treatment (nasal beclomethasone dipropionate 400 µg daily for ten days) were found. Based on these results, the target sample size of this study consisted of 12 subjects for each treatment group, with a 99% statistical power and a 1% two-sided significance level (Epi Info, version 7.2 CDC-INFO, Atlanta, GA-USA). However, an oversampling of 48 subjects for each treatment group was considered due to the following reasons: (i) we used a lower dose of budesonide (200 µg daily); (ii) our treatment period was longer (twenty-one days); and (iii) we hypothesized a dropout rate of 50%.

All efficacy assessments were carried out on the subjects who completed the study (per-protocol analysis). For both the primary and the secondary end-points, the treatment group (NB) and the placebo (NS) were compared using linear regression models adjusting for age, gender, passive smoke and mold exposure ever, disease duration, and baseline value of the outcome. Comparisons were made in terms of least square (LS) mean differences. Some exploratory analyses were

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**Figure 1** Patient disposition (e/c, entry criteria; ITT, intention-to treat; AEs, adverse events).
also performed through Welch t-tests for difference in mean and chi-square test for difference in variance (not adjusted effects).

Of the 85 screened patients, 62 were randomized to receive either nasal budesonide (NB) 200 μg/b.i.d (n = 31) or the nasal saline solution (NS) (n = 31). In total, 48 patients (77%) completed the study. No AEs were reported (Fig. 1). Demographic and clinical characteristics were similar between the two groups at baseline (Table 1).

In the preliminary exploratory analysis, considering unadjusted (crude) values, the mean reduction in nNO levels was significantly higher for children treated with NB with respect to those treated with NS (−131.4 vs. 411.52, p = 0.034). Indeed, the mean change in nNO was positive for the NS group. Moreover, the standard deviation of the change in nNO was significantly lower for the NB group with respect to the NS group (491 vs 1050, p = 0.001). Adjusting for baseline nNO and the other potential confounders, the treatment effect on nNO was substantially unchanged (−76.38 NB vs. 363.68 NS, p = 0.046); such effect and the adjusted effects for the other outcomes are reported in Table 2. TSSS total score improved to a larger extent in the NB group than in the NS group (LS mean change of −6.22 and −4.77, respectively, p = 0.006). Global improvement was the result of specific improvement in all the nasal symptoms; in particular, the score relevant to nasal congestion improved significantly more for children in the NB group (LS mean difference from placebo: −0.49, p = 0.009). The LS mean change was numerically different also for all the other symptom scores, nasal eosinophil count, and PSQI total score, even if they did not reach statistical significance (Table 2).

At first, we found that children with PAR treated with a 3-week course of nasal budesonide showed a significant change in nNO levels at the end of the treatment period, in comparison with children treated with nasal saline solution. This result is in accordance with previous studies reporting that rhinitic adults and children treated with nasal steroids had significantly lower nNO levels than controls (4). The increased levels of NO in nasal air of patients with rhinitis may be derived from inducible NO synthase (iNOS) in the nasal mucosa, as its upregulated expression was described in nasal biopsies of patients with persistent allergic rhinitis (8). Experimental data suggest that intranasal steroids may reduce production of NO by blocking the transcription factor nuclear factor KB that is critical for transcription of the iNOS gene (9). Hence, our clinical results are in agreement with the expected efficacy of nasal budesonide in reducing nNO. Moreover, these data support the role of nNO as a useful biomarker during INS treatment in AR patients.

The second main finding of the current study is about the efficacy of nasal budesonide 3-week treatment in reducing AR symptoms, particularly nasal congestion.

The beneficial effects of budesonide on PAR have been demonstrated in clinical studies (5). Accordingly, our results showed a global improvement in T5SS scores, as the result of specific improvement in all the nasal symptoms; in particular, the score relevant to nasal congestion improved significantly more for children in the NB group after the treatment period. Changes for all the other symptom scores, nasal eosinophil count, and PSQI total score were also observed, even though they did not reach statistical significance.

No studies about the effect of budesonide on nNO in children are available to date. Hence, the current study shows innovative data in this field of research, providing relevant information about budesonide efficacy on both objective (nNO) and subjective (T5SS) outcomes. This combined

### Table 1 Baseline demographic and clinical characteristics of children

<table>
<thead>
<tr>
<th></th>
<th>Nasal Budesonide (n = 31)</th>
<th>Placebo (n = 31)</th>
<th>p-value</th>
<th>Total (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (35%)</td>
<td>11 (35%)</td>
<td></td>
<td>22 (35%)</td>
</tr>
<tr>
<td>Male</td>
<td>20 (65%)</td>
<td>20 (65%)</td>
<td></td>
<td>40 (65%)</td>
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<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td>9.43 (1.79)</td>
<td>9.84 (2.31)</td>
<td></td>
<td>9.64 (2.06)</td>
</tr>
<tr>
<td>Min-max</td>
<td>5–13</td>
<td>5–13</td>
<td></td>
<td>5–13</td>
</tr>
<tr>
<td>BMI, kg/m², mean (s.d.)</td>
<td>19.3 (4.78)</td>
<td>19.28 (3.82)</td>
<td>0.99</td>
<td>19.29 (4.29)</td>
</tr>
<tr>
<td>nNO at baseline, ppb, mean (s.d.)</td>
<td>1137.35 (796.82)</td>
<td>984.74 (774.08)</td>
<td>0.45</td>
<td>1061.05 (782.85)</td>
</tr>
<tr>
<td>Total T5SS score at baseline, mean (s.d.)</td>
<td>7.94 (2.48)</td>
<td>8.74 (3.09)</td>
<td>0.26</td>
<td>8.34 (2.8)</td>
</tr>
<tr>
<td>Total PSQI score at baseline, mean (s.d.)</td>
<td>3.67 (2.77)</td>
<td>3.12 (1.75)</td>
<td>0.39</td>
<td>3.40 (2.32)</td>
</tr>
<tr>
<td>Total IgE, kU/l, mean (s.d.)*</td>
<td>442.2 (452.86)</td>
<td>426.36 (435.95)</td>
<td>0.92</td>
<td>433.51 (436.23)</td>
</tr>
<tr>
<td>Eosinophil count, n/mm³, mean (s.d.)</td>
<td>496.29 (394.97)</td>
<td>421.92 (391.09)</td>
<td>0.67</td>
<td>448.96 (384.74)</td>
</tr>
<tr>
<td>Disease duration, n (%)</td>
<td></td>
<td></td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>≥1 to &lt; 4 years</td>
<td>12 (39%)</td>
<td>10 (32%)</td>
<td></td>
<td>22 (35%)</td>
</tr>
<tr>
<td>≥4 to &lt; 6 years</td>
<td>9 (29%)</td>
<td>10 (32%)</td>
<td></td>
<td>19 (31%)</td>
</tr>
<tr>
<td>≥6 years</td>
<td>10 (32%)</td>
<td>11 (35%)</td>
<td></td>
<td>21 (34%)</td>
</tr>
</tbody>
</table>

BMI, Body mass index; nNO, Nasal nitric oxide; T5SS, Total 5 Symptom Score; PSQI, Pittsburgh Sleep Quality Index; IgE, Immunoglobulin E; p-values are from chi-square (categorical variables) or t-test (quantitative variables).

*Total IgE level was measured by ImmunoCAP system (Thermo Scientific, Uppsala, Sweden).
The present study confirms the anti-inflammatory efficacy of nasal budesonide in children with PAR. After a 3-week treatment period, the significant reduction in nNO levels was observed in conjunction with concomitant improvement in nasal obstruction. As no AEs were reported, we believe that a 3-week course with budesonide nasal spray, 100 μg twice daily, is an effective and well-tolerated treatment in children with PAR.

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