

## Review of results

### *Review of the patient study groups*

This analysis included 4 patient groups of different size (group A – 29 patients, group B – 27 patients, group C – 27 patients and group D – 16 patients). These groups were not homogeneous in terms of age and gender. The process of inclusion of individual patient records was based primarily on the criterion of proportional selection of patients with acute and chronic rhinosinusitis, and only further on the criterion of age and gender.

### ***Disease symptoms before treatment. Comparison of the results obtained during visit 1.***

The analysis included the records of those patients, who at the time of visit 1 were in the initial stage of the disease – acute rhinosinusitis, or in the stage of exacerbation of chronic rhinosinusitis symptoms. Results obtained during visit 1 for each ailment and symptom in all groups are presented in tables 2-25. Average values connected with severity of individual ailments and symptoms in individual patient groups during visit 1 are shown in column one of table 26. The severity of the disease process on a ten-point VAS scale reached similar average values in all analysed groups (6.586 points in group A, 6.741 points in group B, 5.778 points in group C and 6.750 points in group D). The predominant symptoms were: blocked/stuffy nose (on a three-point scale: 1.897 points in group A, 2.148 points in group B, 2.074 points in group C and 2.250 points in group D), runny nose, covering both the “front” and “back” catarrh – trickling down the back wall of the pharynx (on a three-point scale: 1.793 points in group A, 2.111 points in group B, 1.778 points in group C and 2.000 points in group D) and a feeling of bursting face (on a three-point scale: 1.793 points in group A, 1.815 points in group B, 1.111 points in group C and 1.625 points in group D). Smell impairment had slightly lower values on the three-point scale (1.241 points in group A; 1.519 points in group B; 1.296 points in group C and 1.313 points in group D). High values of symptoms evaluated by a physician during physical examination, expressed on a single-point scale were also obtained: oedema of the nasal mucosa (0.931 points in group A, 0.852 points in group B, 0.704 points in group C, 0.813 points in group D) and presence of mucous and purulent secretion (0.621 points in group A, 0.852 points in group B, 0.519 points in group C and 0.938 points in group D). The odour identification test pointed to significant disorders in identification of odoriferous substances (the results of this test expressed on an interval scale were ranked for the purposes of the analysis on a three-point scale; the following average results were obtained: 1.570 points in group A, 1.500 points in group B, 1.296 points in group C and 1.074 points in group D). Distributions of the studied variables in the vast majority deviated from normal distribution (tables 2-25), so non-parametric tests were used for further statistical analysis. In order to compare the average results of the analysed parameters obtained in all patient groups during visit 1, the ANOVA test of Kruskal-Wallis ranks was applied (tables 27-28). This test showed no differences between groups in terms of average values of severity of the disease process on the VAS scale, nasal block, runny nose, impaired smell, oedema of the nasal mucosa and the test results of the odoriferous substance identification test. However, there were statistically significant differences in the severity of the feeling of a bursting nose ( $H = 10.21406$ ;  $p = 0.0168$ ) and presence of mucous and purulent secretion ( $H = 12.38709$ ;  $p = 0.0062$ ). The next stage of the analysis was to find out whether the differences obtained in the Kruskal-Wallis test resulted from differences between groups A and C, and B and D. In order to compare the average values of the parameters analysed between these groups, the *U* Mann-Whitney test was applied (tables 29-32). A comparison of severity of individual ailments and symptoms between groups A and C during visit 1 showed the presence of a statistically significant difference in the severity of feelings of bursting face ( $Z = -2.76155$ ,  $P = 0.005753$ ) and oedema of the nasal mucosa ( $Z = -2.19959$ ,  $P = 0.027837$ ). These average values were significantly lower in patients in group C. The lack of previously identified differences between all groups in terms of oedema of the nasal mucosa could have resulted

from the fact that the result was masked by influence of other groups. A comparison of severity of individual ailments and symptoms between groups B and D during visit 1 did not show any differences between the average results of these groups. The conclusions drawn from this stage of the analysis are as follows.

1). During visit 1, the average values of the severity of the feeling of bursting face and oedema of nasal mucosa are significantly lower in group C as compared to group A. Only the average of the first of these symptoms influenced the outcome of the ANOVA Kruskal-Wallis test, which compares the averages across all groups; the second difference in this test was probably masked by the impact of average values in other groups.

2) No differences between groups A and C, and B and D in terms of the average result of Presence of mucous and purulent secretion in the *U* Mann-Whitney test shows that the earlier result of the Kruskal-Wallis test (difference between groups A, B, C, and D) were affected by the differences other than the differences between the results in groups A and C, and B and D.

3) No statistically significant differences were found between the average values of results obtained in groups B and D during visit 1.

***Disease symptoms after 7-14 days of treatment. Comparison of remission of individual ailments and symptoms within individual groups and between group A and C, and B and D.***

Examinations conducted during visit 2 (respectively after 7 days of VR treatment and after 7-14 days of NVR treatment) showed significant improvement in all measured symptoms in groups A and B and the majority of symptoms in groups C and D (table 26, column 2). In order to compare the remission of individual ailments and symptoms within the studied patient groups, the Wilcoxon's pair sequence test was used. The analysis of average results for individual groups showed a high statistically significant improvement in all the examined parameters (i.e. decrease in severity of individual ailments and symptoms, as well as improvement of the identification of odoriferous substances) after 7-14 days of treatment of patient groups receiving Nasodren: in group A (table 33) and in group B (table 34). A significant improvement in most of the tested parameters was also obtained in group C, an exception being the result of presence of mucous and purulent secretion ( $T = 1.883294$ ,  $p = 0.059661$ , table 35); in group D, a statistically significant improvement in most of the parameters was achieved, with the exception of improving the smell function in the odoriferous substance identification test ( $T = 1.213560$ ,  $p = 0.224917$ , table 36).

In order to compare the remission of individual ailments and symptoms between groups A and C, and B and D (the differences between the results obtained during visit 1 and 2 in individual group were compared – the values of these differences are shown in column 3 of table 26), the *U* Mann-Whitney test was used. A comparison of average results between groups A and C showed the presence of statistically significant differences between the fall in the severity of the disease process on the VAS scale ( $Z = -2.21827$ ,  $p = 0.026537$ ), a weakened feeling of bursting face ( $Z = -3.18234$ ,  $p = 0.001461$ ) and oedema of the nasal mucosa ( $Z = -2.10040$ ,  $p = 0.035695$ ). The values of these differences were statistically significantly higher in group A as compared with group C (table 37). No differences were found between the fall in the remaining parameters under analysis in groups A and C. A comparison of average results of differences between groups B and D showed statistically significant differences between the decrease in the fall in presence of mucous and purulent secretion ( $Z = 2.018993$ ,  $p = 0.043489$ ) and the change in the result of the odoriferous substance recognition test ( $Z = 2.355927$ ,  $p = 0.018477$ ). The value of the first of these differences was significantly higher in group D, while the other value – in group B (table 38). There were no differences between the fall of the other parameters analysed in groups B and D.

The conclusions drawn from this stage of the analysis are as follows:

- 1) In groups of patients receiving Nasodren (A and B) after 7-14 days of treatment, a statistically significant improvement was achieved in terms of all the parameters analysed. Similar, but not identical results were obtained in groups of patients not receiving Nasodren. There was a significant improvement in group C in all the analysed results except for presence of mucous and purulent secretion, while in group D there was a statistically significant improvement in all the results, except for the result of odoriferous substance recognition test.
- 2) Compared with group C, in group A there was a significantly greater improvement in the analysed results (expressed as a greater decrease in the value of the evaluated parameters): the severity of the disease process on the VAS scale, a feeling of bursting face and oedema of the mucous membranes of the nose. There were no significant differences between the changes of other parameters in the compared groups, including the result of presence of mucous and purulent secretion (despite the previously observed differences in the Wilcoxon's test). The latter can be explained by a small difference between the decrease in the severity of this symptom and a wide discrepancy of this result in groups A and C.
- 3) Compared with group D, in group B there was a significantly greater improvement in the results of the odoriferous substance identification test (expressed as an increase in the value of the assessed parameter) and a significantly less improvement of the result of Presence of mucous and purulent secretion (expressed as a decrease in the value of the assessed parameter). The first of these results corresponds to the lack of improvement in olfactory function, as assessed in the odoriferous substance identification test in group D.
- 4) On the basis of the obtained results, it can be concluded that after 7 days of treatment in patients with AVR, Nasodren causes a statistically significant improvement in all 8 analysed parameters, as compared with the 7 parameters in patients not taking Nasodren. Compared with the patient group not taking Nasodren, a significantly greater improvement was observed in case of 3 analysed parameters (severity of the disease process on the VAS scale, a feeling of bursting face and oedema of the nasal mucosa). After 7-14 days of treatment in patients with ANVR, Nasodren causes a statistically significant improvement in all 8 analysed parameters, as compared with the 7 parameters in patients not taking Nasodren. The improvement of the parameters analysed in patients with ANVR receiving Nasodren is significantly higher in the case of one of these parameters (evaluation of smell), but also significantly lower in the case of one of them (presence of mucous and purulent secretion).

**Correlations between the parameters analysed in all the patients treated collectively and in groups A and C, and B and D.**

The analysis of the correlation between different parameters was performed by examining the *R* Spearman's rank order correlation coefficients between the average values of the analysed variables. Correlations between individual ailments and symptoms in patients treated collectively are shown in: table 39 (visit 1) and table 40 (visit 2). During visit 1, the occurrence of a positive correlation between the severity of the disease process on the VAS scale and the following parameters was observed: the feeling of bursting face ( $R = 0.308$ ,  $p = 0.002$ ), impaired smell ( $R = 0.308$ ,  $p = 0.002$ ) and presence of mucous and purulent secretion ( $R = 0.301$ ,  $p = 0.002$ ). It was also found that positive correlation exists between the feeling of bursting face and oedema of the nasal mucosa ( $R = 0.263$ ,  $p = 0.008$ ), between presence of mucous and purulent secretion and impaired smell ( $R = 0.245$ ,  $p = 0.015$ ), as well as between presence of mucous and purulent secretion and negative correlation between presence of mucous and purulent secretion and the result of the odoriferous substance identification test ( $R = -0.358$ ,  $p = 0.0003$ ). During visit 2, a correlation between the severity of the disease

process on the VAS scale and all other ailments and symptoms was observed, except for the results of the odoriferous substance recognition test, between the nasal block and all the other analysed parameters (positive for ailments and symptoms; negative for the results of the odoriferous substance identification test), between runny nose and all the other analysed parameters (positive for ailments and symptoms; negative for the results of the odoriferous substance identification test), positive correlations between the feeling of bursting face and: impaired smell and presence of mucous and purulent secretion, negative correlation between impaired smell and the result of the odoriferous substance identification test, a positive correlation between presence of mucous and purulent secretion and oedema of the nasal mucosa, and a negative correlation between the oedema of the nasal mucosa and the result of the odoriferous substance identification test.

Correlations between individual ailments and symptoms in patients from groups A and C are shown in: table 41 (visit 1) and table 43 (visit 2). During visit 1, in group A there was a negative correlation between runny nose and presence of mucous and purulent secretion ( $R = -0.403$ ,  $p = 0.030$ ), between the feeling of bursting face and impaired smell ( $R = -0.406$ ,  $p = 0.029$ ), a positive correlation between the feeling of bursting face and odour recognition test result ( $R = 0.422$ ,  $p = 0.023$ ) and a negative correlation between the impairment of smell and the result of odoriferous substance recognition test ( $R = -0.371$ ,  $p = 0.048$ ). In group C a positive correlation between the severity of the disease process on the VAS scale and the impairment of smell was observed ( $R = 0.573$ ,  $p = 0.002$ ), a negative correlation was found between the severity on the VAS scale and the result of the odour identification test ( $R = -0.446$ ,  $p = 0.020$ ), a positive correlation was found between runny nose and the feeling of bursting face ( $R = 0.573$ ,  $p = 0.002$ ), and a negative correlation between runny nose and presence of mucous and purulent secretion ( $R = -0.402$ ,  $p = 0.037$ ). In addition, there were also: a positive correlation between the severity of the disease on the VAS scale in group C and impaired smell in group A ( $R = 0.520$ ,  $p = 0.005$ ), a negative correlation between nasal block in group C and impaired smell in group A ( $R = -0.423$ ,  $p = 0.028$ ), a negative correlation between the feeling of bursting face in group C and impaired smell in group A ( $R = -0.385$ ,  $p = 0.047$ ), a negative correlation between presence of mucous and purulent secretion in group C and runny nose in group A ( $R = -0.466$ ,  $p = 0.014$ ) and a positive correlation between the presence of mucous and purulent secretions in group C ( $R = 0.394$ ,  $p = 0.042$ ). During visit 2, positive correlations occurred in group A between the severity of the disease process on the VAS scale and the following parameters: nasal block, runny nose, the feeling of bursting face and presence of mucous and purulent secretion. There were also positive correlations between runny nose, the feeling of bursting face and presence of mucous and purulent secretion, and between the feeling of bursting face, impaired smell and presence of mucous and purulent secretion; a negative correlation occurred between oedema of the nasal mucosa and the result of the odour identification test. In group C, there were some positive correlations between the severity of the disease process on the VAS scale and all the analysed ailments and symptoms, with the exception of odour identification test result, positive correlations between the nasal block and all the analysed ailments, positive correlations between the runny nose and all the analysed ailments, impaired smell and a negative correlation between runny nose and presence of mucous and purulent discharge, positive correlations between the feeling of bursting face and all the ailments and presence of mucous and purulent secretion, and a positive correlation between presence of mucous and purulent secretion and oedema of the nasal mucosa. In addition, there were negative correlations between nasal block in group C, blocked nose, runny nose and swollen nasal mucosa in group A, between runny nose in group C and severity of the disease process, nasal block and presence of mucous and purulent secretion in group A, and a positive correlation

between the feeling of bursting face in group C and presence of mucous and purulent secretion in group A.

Correlations between individual ailments and symptoms in patients from groups B and D are shown in: table 42 (visit 1) and table 44 (visit 2). During visit 1, positive correlations occurred in group B between the severity of the disease process on the VAS scale and the following parameters: the feeling of bursting face ( $R = 0.486$ ,  $p = 0.010$ ), impaired smell ( $R = 0.400$ ,  $p = 0.039$ ) and presence of mucous and purulent secretion ( $R = 0.433$ ,  $p = 0.024$ ). Positive correlations occurred between nasal block and: the feeling of bursting face ( $R = 0.435$ ,  $p = 0.023$ ) and impaired smell ( $R = 0.459$ ,  $p = 0.014$ ), between the feeling of bursting face and impaired smell ( $R = 0.588$ ,  $p = 0.001$ ) and between presence of mucous and purulent discharge and oedema of the nasal mucosa ( $R = 0.413$ ,  $p = 0.032$ ). There was a negative correlation between the feeling of bursting face and odour identification test result ( $R = -0.396$ ,  $p = 0.041$ ). In group D only a positive correlation was found between presence of mucous and purulent secretion and oedema of nasal mucosa ( $R = 0.537$ ,  $p = 0.032$ ). In addition, a negative correlation was found between the impairment of smell in group D and the severity of the disease process on the VAS scale in group B ( $R = -0.540$ ,  $p = 0.031$ ), as well as a positive correlation between smell impairment in group D and runny nose in group B ( $R = 0.469$ ,  $p = 0.014$ ). During visit 2, a positive correlation occurred in group B between the severity of the disease process on the VAS scale and oedema of nasal mucosa, between runny nose and: the feeling of bursting face and the impairment of smell. There were negative correlations between the result of the odour recognition test and: runny nose and impairment of smell. Correlations occurred in group D between the severity of the disease process on the VAS scale and the following parameters: nasal block, runny nose and impairment of smell, as well as between runny nose and oedema of the nasal mucosa. In addition, there were negative correlations between nasal block in group D and the severity of the disease process in group B, between runny nose in group D and impaired smell in group B, and positive correlations between runny nose in group D and the result of the odour identification test in group B, and between the impairment of smell in group D and a feeling of bursting face in group B.

#### **Evaluation of the frequency of transition from AVR to ANVR in groups A and C during visit 2.**

The frequency of ANVR diagnosis during visit 2 was 0.172 in group A (5 out of 29 cases) and 0.185 in group C (5 out of 27 cases). The differences in the frequency of ANVR diagnosis in these groups during visit 2 were assessed on the basis of the  $\chi^2$  statistic with Yates' correction. The achieved value of the test statistic (0.05) made it possible to conclude that there is no difference in the frequency of diagnosing ANVR between groups A and C ( $p = 0.8224$ ). Conclusion: Nasodren does not affect the frequency of ANVR diagnosis during visit 2.

#### **The course of ailments compared between group A and C, and B and D on individual days of self-observation.**

In the analysis, the results of severity of individual ailments were compared between group A and C, and B and D on individual days of self-observation. The results of the severity of the ailments are shown in tables 46-65, while the aggregate results are presented in table 66. The analysis included a 7-day period of self-observation, for which the results of all patients in all groups of patients were available. Comparisons of the results between groups for individual days of self-observation were performed with the use of U Mann-Whitney test.

##### **1) Comparison of the parameters analysed in groups A and C**

There were no statistically significant differences in average results of the severity of the disease process on VAS scale between the groups over the entire 7-day period of self-observation (table 67). Statistically significant differences between the average values of severity of nasal block occurred on day 5, 6 and 7 on self-observation – the average results

obtained in group A were significantly lower (table 68). There were no statistically significant differences in average results of the severity of runny nose over the entire 7-day period of self-observation (table 69). Statistically significant differences between the average values of severity of the feeling of bursting face occurred only on the first day of self-observation – the average result was significantly lower in group C (table 70), while statistically significant differences were observed between the average results of severity of impairment of smell on self-observation days 4 to 7 – average results were significantly lower in group A (table 71).

## 2) Comparison of the parameters analysed between groups B and D

There were no statistically significant differences in average results of severity of individual ailments in the 7-day observation period between group B and D (tables 72-76).

The interpretation of the results of the analysis of differences between the results obtained in the 7-day observation period is as follows:

- 1) Groups A and C. Despite significant differences previously detected in the Mann-Whitney test between the decrease in the disease process severity on the VAS scale in groups A and C in the entire 7-day treatment period analysed, the differences between the results for individual days of self-observation were not statistically significant (the observed improvement in the group of patients receiving Nasodren was visible only after taking into account the entire period of self-observation). It could have resulted from the wide discrepancy of results from individual days of self-observation around the central values. Statistically significant differences were observed between the severity of nasal block results in groups A and C on days 5-7, which leads to the conclusion that between day 4 and 5 of self-observation in the group of patients receiving Nasodren, a significantly greater decrease in the severity of nasal block occurred than in patients in the control group (C) despite the lack of significant difference found in the 7-day period of therapy. The previously observed lack of changes in the entire 7-day period of self-observation may have been the result of comparing the impact of earlier days on the final result and/or a wide discrepancy of results around central values. The lack of significant differences in the average results of severity of a runny nose on individual days of self-observation corresponded with the lack of differences between the average decreases in the severity of this ailment in groups A and C. The average result of the severity of the feeling of bursting face in group C was lower than that in group A only on the first day of self-observation; on the following days, there were no such differences. Thus it can be concluded that between day 1 and 2, a significantly larger decrease in the severity of this symptom occurred in group A than in group C. This result corresponds with the statistically significant difference between the differences in average results of the severity of the feeling of bursting face over the entire 7-day period of self-observation. The average results of the severity of smell impairment on days 4-7 in group A were significantly lower than in group C, from which it can be concluded that between day 3 and 4 in group A there occurred a significantly greater decrease in the severity of this symptom. This result does not correspond with the lack of statistically significant differences between the average results in differences in the severity of this symptom in groups A and C over the 7-day period of self-observation; it may be connected with the wide discrepancy in the results of differences around the central values. Nasodren significantly influences the dynamics of changes in nasal block, the feeling of bursting face and the impairment of smell over the 7-day period of self-observation in the AVR patient group.
- 2) Group B and D. In groups B and D there were no statistically significant differences between any results analysed on individual days of self-observation. This corresponds with the previously obtained result of the Mann-Whitney test for comparing the

remission of individual ailments between groups B and D. Nasodren does not significantly affect the dynamics of the ailments analysed over the 7-day period of self-observation in the group of patients with ANVR.