QUALITY OF LIFE IN NON-ALLERGIC RHINITIS DEPENDS ON THE PREDOMINANT INFLAMMATORY CELL TYPE

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Three main types of inflammatory Non-Allergic Rhinitis (NAR) have been defined: NAR infiltrated by eosinophils (NARES), by mast cells (NARMA), and by neutrophils (NARNE). In the absence of studies that investigated the Quality of Life (QoL) in NAR, the present work is aimed at evaluating the Quality of Life of patients with NARES, NARMA, and NARNE. One hundred thirty one (131) NAR patients were prospectively and consecutively evaluated: 54 patients with NARES, 38 with NARMA, and 39 with NARNE. Their history, nasal infiltration and rhinomanometry were characterized, and Quality of Life (using 2 instruments) was evaluated, and associated to clinical and histological features. Quality of Life was significantly different in the 3 groups ($p<0.001$); NARES patients had the worst Quality of Life. Nasal resistances were significantly higher in the NARES group. Significant associations were shown in NARES patients between Quality of Life and nasal function. This study provides the first evidence that Quality of Life is impaired in NAR as well as in allergic rhinitis. Furthermore, Quality of Life impairment differs among the various forms of NAR, and there is a correlation with the cellular infiltrating type.

Non-Allergic Rhinitis (NAR), is a heterogeneous disease, which is characterized by nasal hyperreactivity that results in symptoms which include nasal blockage, rhinorrhoea, and sneezing, similar to those of allergic rhinitis. Diagnosis of NAR is established on the basis of persistent symptoms throughout the year after exclusion of infection (as indicated by a clear and watery nasal discharge, as compared with a purulent discharge produced in infectious rhinitis), any anatomical or medical disorder of the nose, and negative skin prick testing for IgE-mediated sensitivity to relevant aeroallergens (1-4).

NAR comprises several forms of rhinitis. The aetiology and/or pathophysiology is established only for some forms of the disease, such as drug-induced rhinitis and non-allergic rhinitis with eosinophilia syndrome (NARES). Other minor forms of rhinitis

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include occupational rhinitis, non-allergic hormonal rhinitis, food-induced rhinitis, emotion-induced rhinitis, physical/chemical irritant-induced rhinitis, and rhinitis of the elderly. In contrast, the aetiology is largely unknown for a majority of about 75–80% of the individuals in whom the disease is classified as being idiopathic or vasomotor rhinitis. This high percentage of idiopathic aetiology is, at least in part, due to the fact that nasal cytology is very rarely performed. Indeed, nasal cytology only recognizes and identifies the NAR types, characterized by an inflammatory cell infiltrate (5-8). In this regard, three main types of NAR characterized by typical inflammatory cell infiltrate has been defined: NAR infiltrated by eosinophils (i.e. NARES), by mast cells (i.e. NARMA), and by neutrophils (i.e. NARNE). These forms of non-allergic rhinitis are characterized by local inflammation that appears to be the main underlying pathological mechanism (9-11). NARES is clinically characterized by perennial nasal symptoms of sneezing paroxysms, profuse watery rhinorrhea, and itching of the nasopharyngeal mucosa in an "on-again-off-again" symptomatic pattern (12). Additionally, these patients had profound nasal eosinophilia (>20% of the granulocytic or mononuclear cells present excluding nasal epithelial cells), which was not associated with allergic disease, as indicated by negative skin-prick testing and no evidence for increased levels of either total or specific IgE in the nasal secretions. In addition, it has been suggested that this condition may be prevalent in up to one third of adults with non-allergic rhinitis, and although it usually occurs as an isolated disorder, in severe cases it may be associated with non-IgE-mediated asthma, aspirin intolerance and nasal polyps (13-16). Eosinophilia in NARES may contribute to nasal mucosal dysfunction, since major basic protein (MBP) and eosinophil cationic protein (ECP) released from the eosinophil granules are capable of damaging the nasal ciliated epithelium and prolonging mucociliary clearance. Prolonged or delayed mucociliary clearance itself may increase the propensity towards infection and predispose the individual to the development of nasal polyps. Nevertheless, the presence of eosinophilia in NARES may be an important predictor for response to treatment with topical anti-inflammatory therapy.

NARMA was initially described by Connell and is characterized by a predominant infiltrate by mast cells (17-20). Mast cells are an important source of mediators, including histamine and leukotrienes, causing profound symptoms, and for pro-inflammatory cytokines, inducing inflammatory cascade.

NARNE is characterized by predominant neutrophilic infiltration without infection. Aetiology is multi-factorial, including cystic fibrosis, antro-choanal polyp, pollution, tobacco smoke (21-24). Infiltrating neutrophils release enzymes, mainly elastase, which produce free radicals that cause mucosal damage. On the other hand, the Quality of Life (QoL) has been widely evaluated in allergic rhinitis (3), but there is no study that deeply investigated QoL in NAR, therefore, the aim of this study is to evaluate QoL in patients with NARES, NARMA, and NARNE.

MATERIALS AND METHODS

Study design

This prospective study was conducted including patients with NAR consecutively visited at the ENT Clinic of Bari (Italy). Subjects with acute upper respiratory infections, anatomic nasal defects (i.e. septum deviation), asthma and/or bronchial hyperreactivity who were using nasal or oral corticosteroids, nasal or oral decongestants, antileukotrienes, and antihistamines during the previous 4 weeks were excluded.

The diagnosis of NAR was made on the basis of a history of nasal symptoms (including sneezing, rhinorrhea, and nasal obstruction typically dependent on exposure to triggers such as odors, irritants, weather changes), presence of inflammatory cells on nasal smears, and negative skin prick test according to validated criteria (2-3).

Skin prick tests, nasal cytology and endoscopy, rhinomanometry, and QoL evaluation by questionnaire were carried out on all subjects. The study was approved by the Institutional Review Board of the University of Bari, and an informed consent was obtained from all patients.

Skin prick test

Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens by carrying out a skin prick test as stated by the European Academy of Allergy and Clinical Immunology: sensitization was considered when the wheal diameter was equal or greater than 3 mm (25). The allergen panel consisted of the

Table I. *QoL evaluation by using the HRQL-RS questionnaire.*

Dimension	NARES (n=54)		NARMA (n=38)		NARNE (n=39)		TEST Kruskal-Wallis P value
	Mean Score	Σ	Mean Score	Σ	Mean Score	Σ	
Social Problems	2.75	0.53	1.62	0.50	1.59	0.33	<0.001
Sleep	2.40	0.84	1.55	0.63	1.60	0.44	<0.001
Non-nasal symptoms	2.30	0.67	1.30	0.41	1.65	0.40	<0.001
Nasal Symptoms	2.62	0.45	1.56	0.34	1.69	0.33	<0.001
QoL – VAS	3.54	1.578	5.37	1.076	6.64	0.723	<0.001

NAR types	Mann-Whitney p-value				
	Social Problems	Sleep	Non Nasal symptoms	Nasal symptoms	QoL – VAS
NARNE vs NARES	<0.01	<0.01	<0.01	<0.01	<0.01
NARMA vs NARES	<0.01	<0.01	<0.01	<0.01	<0.01
NARNE vs NARMA	0.3	0.25	<0.01	0.04	<0.01

A significant difference among groups (p<0.001) was evident. Patients with nonallergic rhinitis with eosinophilia syndrome (NARES) showed the worst score for all dimensions.

following: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria judaica*, birch, hazel tree, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix; the concentration of allergen extracts was 100 I.R./mL (Stallergenes, Milan, Italy).

Nasal cytology

Cytological samples were obtained by scraping with a Rhino-Probe™. The samples were collected from the medial portion of the inferior middle turbinate. After fixing with absolute alcohol for 3 minutes and drying, the samples were stained using the May-Grünwald-Giemsa (Carlo Erba, Milan, Italy) method, then mounted on covered slides and examined under microscopy (Nikon E600, Nikon Italy). Cell count was performed on 10 microscopic samples at high-power magnification (x1000) in immersion (15). Samples were examined blindly by two different readers.

NARES was diagnosed if nasal eosinophils were >20% of total cells recovered from nasal scraping, including both inflammatory and epithelial cells; NARMA was diagnosed if nasal mast cells were >10% of total cells; and NARNE was diagnosed if nasal neutrophils were >50% of total cells (26).

Rhinomanometry

Nasal airflow resistance was measured by active anterior electronic rhinomanometry. Patients wore a tight-fitting face mask, and breathed through one nostril with their mouth closed. A sensor, placed in the controlateral nostril, recorded data on pre- and post-nasal pressures via airflow and pressure transducers. The instrument (Rhinomanometer Menfis, Amplifon Italy) was connected to a personal computer. The signals of transnasal airflow and pressure were amplified, digitalized, and saved for statistical analysis.

Nasal resistance is measured as Pa/mL/sec as the sum of the recorded airflow in milliliter per second through the right and left nostrils at a pressure difference of 150 Pa across the nasal passage.

Four or more airflow measurements were performed

Table II. *QoL evaluation by using the RQLQ questionnaire.*

Dimension	NARES (n=54)		NARMA (n=38)		NARNE (n=39)		TEST Kruskal-Wallis P value
	Mean Score	Σ	Mean Score	Σ	Mean Score	Σ	
Social Problems	2.75	0.53	1.62	0.50	1.59	0.33	<0.001
Sleep	2.40	0.84	1.55	0.63	1.60	0.44	<0.001
Non-nasal symptoms	2.30	0.67	1.30	0.41	1.65	0.40	<0.001
Nasal Symptoms	2.62	0.45	1.56	0.34	1.69	0.33	<0.001
QoL – VAS	3.54	1.578	5.37	1.076	6.64	0.723	<0.001

NAR types	Mann-Whitney p-value				
	Social Problems	Sleep	Non Nasal symptoms	Nasal symptoms	QoL – VAS
NARNE vs NARES	<0.01	<0.01	<0.01	<0.01	<0.01
NARMA vs NARES	<0.01	<0.01	<0.01	<0.01	<0.01
NARNE vs NARMA	0.3	0.25	<0.01	0.04	<0.01

A significant difference among groups (p<0.001) was evident. Patients with nonallergic rhinitis with eosinophilia syndrome (NARES) showed the worst score for all dimensions. NARMA=nonallergic rhinitis with mast cells; NARNA= nonallergic rhinitis with neutrophils

for each patient and the mean value was recorded when reproducible values were achieved. Normal values are < 0.50 Pa/mL/sec (27).

Quality of Life

Health-Related Quality of Life (HRQL) assessment included two disease-specific instruments. The first was the Health-Related Quality of Life in Rhino Surgery (HRQL-RS), validated (28) and adapted for the use in the Italian population. This specific health profile HRQL-RS questionnaire consists of 25 items summarized in 6 dimensions: nasal and non-nasal symptoms, sleep, emotional symptoms, headache, and practical problems, these last three dimensions were summarized in a single dimension: social problems. Responses to the items are scored on a 4-point scale, the lower the score, the better the HRQL. Most items are the same used in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) provided by Juniper and colleagues (29). Moreover, a visual analogue scale (from 0=worst QoL to 10=best QoL) was given to measure the patients' general feeling related to their nasal disease.

The second questionnaire was the above-mentioned Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) consisting of 28 items distributed in seven dimensions: sleep problems (3 items), non-hay fever symptoms (7 items), practical problems (3 items), nasal problems (4 items), eye symptoms (4 items), activities (3 items), and emotions (4 items). Responses to the items are scored on a 7-point Likert scale, while dimensions and overall scores are scored on a 0-6 scale (29). In both cases, the lower the score, the better the HRQL.

Statistical analysis

Data were described as mean and standard deviation. Continuous variables and categorical variables were compared by means of the Kruskall Wallis test (non-parametric analysis of variance) and the Mann Whitney

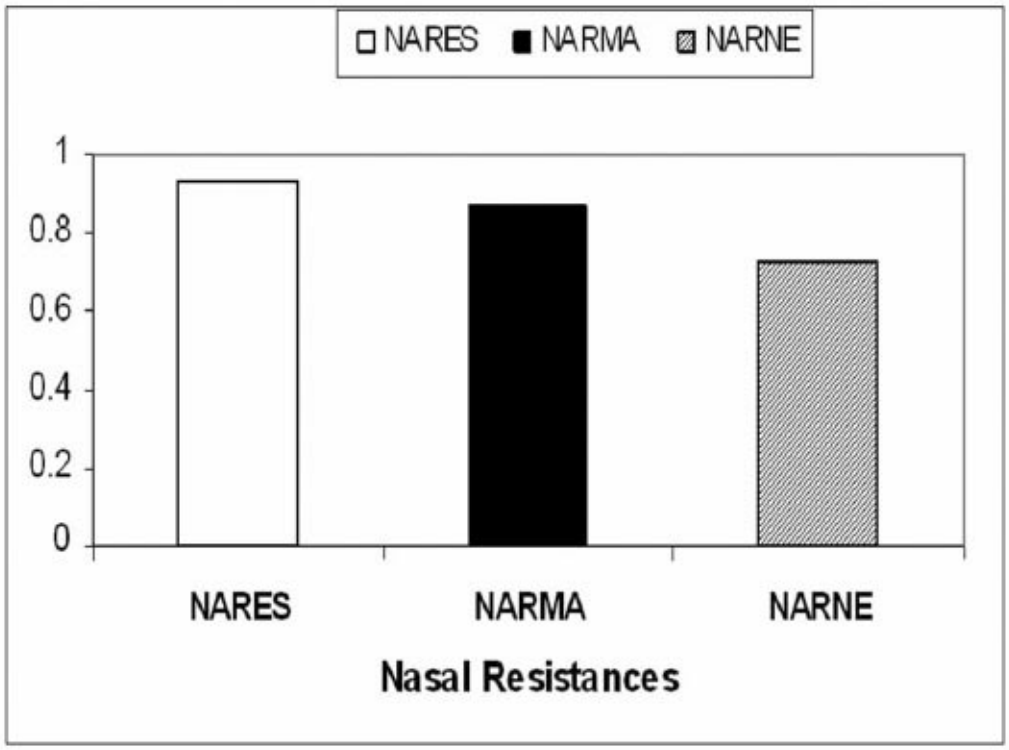

Fig. 1. *Nasal resistances, expressed as Pa/mL/sec in patients with non-allergic rhinitis with eosinophilia syndrome (NARES), non-allergic rhinitis with mastcells (NARMA) and with Neutrophils (NARNA). There were significant differences between NARES and NARNE (*) (p<0.001), NARES and NARMA (**) (p=0.005), and NARNE and NARMA (***) (p=0.001).*

U test for post-hoc comparisons. The Kolmogorov-Smirnov test was used to compare nasal resistance values. Correlations were evaluated by the Spearman test. Q^2 and G^2 tests were used to compare the frequency and onset age of polyps to NAR subsets. SPSS software was used for computation. A 2-sided p-value<0.05 was considered statistically significant.

RESULTS

Patients

131 patients with NAR were prospectively and consecutively evaluated: 75 males and 56 females, mean age 40.6 ± 4.4 years. All of them were negative to the skin prick test. They were grouped according to diagnosis, such as the type of infiltrating inflammatory cells: 54 patients with NARES, 38 with NARMA, and 39 with NARNE.

Quality of Life

i) HRQL-RS questionnaire: globally there was a significant difference among groups (p<0.001). In particular, NARES patients showed the worst score for all dimensions: social problems (p<0.01), sleep (p<0.01), non-nasal symptoms (p<0.01), nasal symptoms (p<0.01), and personal perception of QoL by VAS (p<0.01) in comparison with the other two groups. NARNE patients had worse QoL concerning nasal symptoms (p=0.04), non-nasal symptoms (p<0.01), and QoL perception by VAS (p<0.01) in comparison to NARMA patients (Table I). For sleep NARNE patients had worse snoring and nocturnal awakening, as reported in Fig. 1;

ii) RQLQ questionnaire: globally there was a significant difference among groups (p<0.001). In particular, NARES patients showed the worst score for all dimensions: practical problems (p<0.01), sleep problems (p<0.05), non-hay fever symptoms (p<0.01), nasal problems (p<0.01), and emotional problems (p<0.01) in comparison with the other two groups. NARNE patients had worse QoL concerning non-hay fever symptoms (p<0.01), and emotional problems (p<0.05) in comparison to NARMA

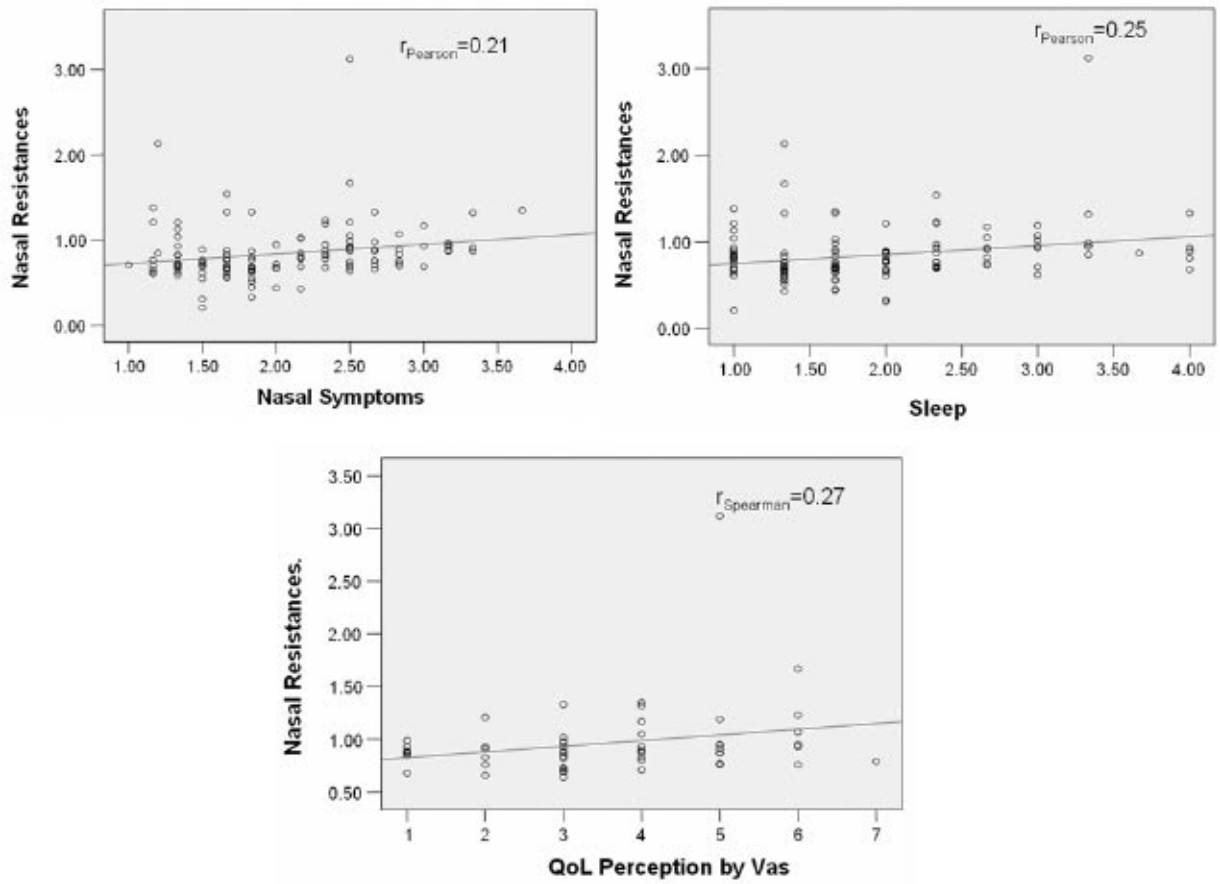

Fig. 2. *Relationships between (a) nasal resistance, expressed as Pa/mL/sec, and sleep (p=0.001), (b) nasal symptoms (p=0.001), and (c) QoL perception by VAS (p=0.045) in patients with non-allergic rhinitis with eosinophilia syndrome (NARES).*

patients (Table II).

Rhinomanometry

Nasal resistances were increased in all groups with difference among groups (p<0.001). There were significant differences between NARES and NARNE (p<0.001), NARES and NARMA (p=0.005), and NARNE and NARMA (p=0.001) as reported in Fig. 1.

Relationship between QoL and rhinomanometry

A significant association was reported for the relationship between nasal obstruction and dry throat (p<0.001), nasal obstruction and snoring (p<0.001) in all groups, nasal resistance and QoL perception by VAS in NARES patients (p=0.045) as reported in Fig. 2.

Association with nasal polyps

57.5% of NARES patients had nasal polyps, 30.2% of NARMA patients, and 3.3% of NARNE (p<0.0001). In addition, nasal polyps are more frequent in subjects with age >35 years in NARES patients (p<0.001). However, given the number of subscales, patient subgroups, and statistical comparisons, a loss of statistical power inherent in performing multiple statistical comparisons has to be considered.

DISCUSSION

NAR diagnosis is based on two main issues in patients with nasal symptoms consequent to exposure to irritants: negative skin prick test and cytologic assessment. Nasal cytology is a crucial step to manage patients with NAR. Indeed, cytology alone allows to correctly diagnosis the different types of NAR. On the basis of prevalent inflammatory cell type, three main forms of NAR may be considered: NARES, NARNE, and NARMA.

The condition "non-allergic rhinitis with

eosinophilia syndrome" (NARES) was originally characterized on the basis of the presence of greater than 20% eosinophils in nasal smears of symptomatic patients with perennial sneezing attacks, a profuse watery rhinorrhea, nasal pruritis, nasal obstruction and occasional loss of smell (1, 13). In addition to these symptoms, a marked feature of the disease was the lack of evidence of allergy, as indicated by negative skin prick tests and/or absence of serum IgE antibodies to specific allergens. The prevalence of NARES has been shown to range between 13 and 33% in patients with non-allergic rhinitis (31-32). Although the specific etiology of NARES is not clear, in view of the features shared by this syndrome and the ASA triad (nasal polyposis, intrinsic asthma, and intolerance to aspirin) and because NARES patients frequently develop nasal polyps and asthma later on in life, it has been suggested that NARES may be an early expression of the triad (1). Indeed, in about 50% of NARES patients without a history of respiratory symptoms, bronchial responsiveness is associated with an increase in the number of sputum eosinophils, but not with an increase in the number of nasal eosinophils (33-36). Few studies have investigated NARMA; this rhinitis is characterized by a pathophysiologic mechanism and clinical pattern very similar to allergic rhinitis (17, 37-39). NARNE is a chronic inflammation of the nose due to different causative agents that induce damage of the respiratory epithelium.

On the other hand, Health-Related Quality of Life (HRQL) measures the impact of a pathologic condition in the patient's daily life. Besides the disease-related symptoms, it includes a wide spectrum of daily life activities such as physical and social activities, emotional problems, general feeling, and so on. HRQL of patients with nasal diseases is frequently used in clinical studies. A Health-Related Quality of Life in Rhinological Surgery questionnaire has been proposed in patients surgically treated (28). RQLQ is the most used instrument in studies concerning allergic rhinitis (28).

This study provides the first evidence that QoL is impaired in NAR and there is a significant difference between different forms. In particular, NARES is the more severe form of NAR as demonstrated by worst QoL, increased nasal resistance, and frequent association with nasal polyps. It appears evident that eosinophilic infiltration induces severe inflammation that causes the most severe symptoms. Indeed, eosinophils are the best markers of allergic inflammation (40-42). Moreover, eosinophils are the main inflammatory cell infiltrating nasal polyps. Inflammatory edema associated with polyp neoformation contributes to the impairment of nasal airflow. In this regard, nasal obstruction is a crucial symptom that causes several complications (43).

This study demonstrates that there is a relationship between inflammation, nasal obstruction, impaired nasal airflow, and QoL. Moreover, NARES is frequently associated with nasal polyps, thus making this form of NAR the most severe. In addition, there is also a difference between NARNE and NARMA based on the different cellular pattern. In other words, the inflammatory cell type appears to be crucial in determining the severity of nasal symptoms that may be evaluated both by QoL questionnaires and rhinomanometry.

In conclusion, this study provides the first evidence that QoL is also impaired in NAR, as well as in allergic rhinitis, and the QoL impairment is dependent on the type of cellular infiltrate. Moreover, nasal cytology is a crucial diagnostic tool to diagnosis these disorders. Finally, further studies should be addressed to evaluate whether patients with NARES, NARNE, and NARMA may have differential treatment responses.

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