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Clinical course of COPD in patients with Arg16Gly (rs1042713) polymorphism of *ADRB2* gene

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Abstract

The *ADBR2* gene has been studied for its possible relationship with the development and clinical course of chronic obstructive pulmonary disease (COPD), including response to beta-2 agonists, with existing data being contentious on the subject. So, the purpose of this study was to look into the potential impact of the arginine-16-glycine (Arg16Gly) polymorphism on the clinical course and drug utilization in COPD patients. Data show that patients with Arg16Arg have a lower number of hospital admissions for exacerbations (p=0.048), but only in the total number of exacerbations, including those treated out-patients (p=0.086). Each glycine (Gly) copy was associated with a higher number of exacerbations (OR: 0.25; 95% CI: 0.00-055; p=0.048). The number of exacerbations after LABA/LAMA treatment was similar across groups, indicating that all *ADRB2* variants responded well to the treatment. Furthermore, there were no statistically significant differences in mMRC and CAT values across all study visits. Interestingly, groups differed in their use of antibiotics (AB) at all visits, with Arg16Arg being associated with the least amount of AB use. There was also a link discovered between clycine copies and increased use of glucocorticoids. As a result, Arg16Gly is involved in the clinical course of COPD as well as the utilization of drug groups. Based on the findings, we can speculate that the cross-talk between the *ADRB2* gene and the corticosteroid receptor is altered in patients with the Gly16Gly genotype.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent preventable and treatable disease, that is characterized by the persistent symptoms and lung function limitation caused by the changes in the airways and/or alveoli, which are usually provoked by the impact of harmful particles on susceptible organism [1]. Data from BOLD (Burden of Obstructive Lung Disease) study showed that COPD affect 10.1% of people worldwide with higher prevalence in men (11.8 %) compared to women (8.5%) [2]. Studies also indicate high COPD prevalence in people who never smoked (3-11%) [2,3]. COPD prevalence in Europe is determined at the level of 12.4% [4]. Recent studies have shown that COPD accounted to more than 3 million deaths annually worldwide [5]. There are also predictions that COPD prevalence will grow over time and reach 5.4 million deaths by the year 2060, which will happen due to the growing prevalence of smoking in developing countries and population ageing in the developed ones [6]. Besides COPD being a severe chronic disease by itself, it also promotes development of other diseases, such as coronary artery disease, strokes, diabetes mellitus type 2, chronic kidney disease, pneumonia and lung cancer [7-10].

As it was mentioned in GOLD recommendations, COPD develops due to the combination of environmental factors on the susceptible organism. Smoking remains a main risk factor for COPD development. But multiple studies indicate an important role of different genes in the regulation of inflammation, fibrosis

and airways responsiveness [11]. One of such genes, that was shown to be related to the COPD development [12] and severity [13], and also response to beta-2 agonists, is beta-2 adrenergic receptor (*ADRB2*) gene [14]. Some studies have shown a different prevalence of ADRB2 gene polymorphism among patients with COPD and healthy matched controls [15]. Some studies have also shown a relation of *ADRB2* gene polymorphism to the response to inhaled corticosteroids [16,17].

So, the aim of our study was to compare clinical course of COPD in patients with different variants of ADRB2 gene.

Materials and Methods

The study was performed at the Department of Propedeutics of Internal Medicine of Vinnytsia National Pirogov Memorial Medical University and Vinnytsia City Clinical Hospital n. 1. Local ethics committee permission was obtained prior to the start of the study. All patients signed informed consent prior to any study-related procedures.

One hundred patients with the diagnosis of COPD were included into the study, average age was 64.09±1.94 years. There were 66 men (66%) and 34 women (34%). There were 68 smokers or ex-smokers (68%) and 32 (32%) never smokers, average smoking experience was 24.44±0.84 pack-years. Average COPD duration was 9.35±2.42 years. There were following inclusion criteria: any relevant disease, laboratory disorder or other relevant history, that can affect patient's safety during participation in the study, inability of the patient to follow study procedures, alcohol or illicit drugs abuse in the medical history or at the inclusion. We performed 3 different visits during the study which comprised the following: visit 1 – baseline visit, visit 2 – study visit in 5±1 weeks, visit 3 – final visit in 52±1 weeks.

At the baseline visit all patients signed an informed consent form. We collected relevant medical records and checked inclusion criteria. We recorded data relevant for the study purposes, which included: exacerbations in previous 12 months, which also were separately recorded as in-patient and out-patient exacerbations, smoking status and number of pack-years, COPD duration. Based on the medical records and information provided by the patient we recorded data for the use of the following drug groups: antibiotics (AB), glucocorticoids (GCS) and xanthines. For each of the drug group we recorded the demand of the patient for using them, number of separate courses and total treatment duration in days. All patients completed Modified Medical Research Council (mMRC) scale and COPD Assessment Tool (CAT) questionnaire. Genetic testing was performed at visit 1 with the assessment of Arginine-16-Glycine (Arg16Gly) polymorphism, also known as (+46A>G; rs1042713). For the study purposes all patient were switched to the combination of long-acting muscarinic antagonists (LAMA) and long-acting beta-agonists (LABA). All patients were taught to use new inhaler properly. At visit 2 we collected and intermittent data on mMRC and CAT and reassured proper inhaler use. At 3 visit we collected following information: exacerbations in previous 12 months, which also were separately recorded as in-patient and out-patient exacerbations, use of the AB, GCS and xanthines. For each of the drug group we recorded the demand of the patient for using them, number of separate courses and total treatment duration in days. All patients completed Modified Medical Research Council (mMRC) scale and COPD Assessment Tool (CAT) questionnaire. Genetic testing was performed at the local laboratory of Vinnytsia National Pirogov Memorial Medical University. According to the genetic testing results all patients were divided into 3 groups: Arg16Arg (group 1) – 23 patients (23 %), Arg16Gly (group 2) – 39 patients (39 %), Gly16Gly (group 3) – 38 patients (38 %).

Statistical analysis was performed using SPSS (Version 26.0 for Windows; USA). Descriptive statystics was determined for each interval parameter and is represented by the mean value±standard deviation (SD). We used Kolmogorov Smirnov test for the assessment of data distribution in the sample. Chi-square method was used to compare nominal values. Mann-Whitney U-test and *t*-test were used for the comparison of two independent samples in abnormal and abnormal data distribution correspondingly. Wilcoxon test was used to compare two dependant samples with abnormal data distribution, and *t*-test for paired samples were used to compare data in two dependent samples with normal data distribution. Three and more independent samples were compared where assessed by Kruskal-Wollis test. In correlation analysis we used Spearman correlation coefficient for abnormal data distribution and Pearson correlation coefficient for normal data distribution. Linear regression analysis was used to determine predictors of dependant variables. In regression analysis we only included data that have weak, moderate strong and very strong correlations with dependent variable. Regression analysis results is presented in odds ratio (OR), 95% CI; $p<0.05$ was considered as statistically significant.

Results

In group 1 there were 12 (52.2%) men and 11 (47.8%) women, in group 2 - 29 (74.4%) men and 10 (25.6%) women, in group 3 – 25 (65.8%) men and 13 (34.2%) women. When groups were compared using chi-square methods there was no significant difference between them (p=0.204). Groups also did not differ by the number of smokers (p=0.933) (Table 1). When groups were compared by the number of patients with different clinical COPD groups there was no significant difference (χ^2=6.608, p=0.158). There was no group A patients in all groups (Figure 1). Absence of the group A patients is explained by the use of an in-patient department database, where group A patients were absent. In correlation analysis there was a weak positive correlation of Arg16Arg and GOLD C (r=0.209,

Table 1. Group composition by sex and smoking status. Study groups did not differ by sex (p=0.204) or smoking status (p=0.933).

Group	Arg16Arg (n=23)		Arg16Gly (n=39)		Gly16Gly (n=38)		p
Parameter	n.	%	n	%	n	%	
Men	12	52.2	29	74.4	25	65.8	0.204
Women	11	47.8	10	25.6	13	34.2	0.204
Smokers	16	69.6	27	69.2	25	65.8	0.933

p=0.037) and negative with GOLD D (r=-0.242, p=0.015). In ANOVA analysis there was no significant difference in the age (p=0.173), COPD duration (p=0.469) and number of pack-years (p=0.903) between study groups. There was a tendency towards a difference in amount of exacerbation between the study groups (p=0.086). There was a significant difference in amount of hospital admissions between study groups in 1 year prior to the study (p=0.048). There was no significant difference in the number of out-patient exacerbations (p=0.418). There was a weak negative correlation between the Arg16Arg genotype and amount of exacerbations (r=-0.220, p=0.028) and hospital admissions (r=-0.210, p=0.036), and a weak positive correlation of Arg16Gly genotype and number of hospitalizations (r=0.208, p=0.038). In regression analysis we found an increased risk of exacerbations in patients with Arg16Gly genotype (OR: 0.482; 95% CI: 0.066–0.898; p=0.024), also each Gly copy in genotype was associated with an increased risk of exacerbations (OR: 0.25; 95% CI: 0.00 – 055; p=0.048) (Table 2). After the year of treatment there was no significant difference in the number of exacerbations between the groups (p=0.143), hospital admissions (p=0.835) and number of out-patient exacerbations (p=0.21) (Table 3). So, Arg16Arg is associated with the smaller number of exacerbations and hospital admissions and each Gly copy increases this risk. Administration of tiotropium/olodaterol combination led to the significant decrease of the number of exacerbations (p=0.001) and hospitalizations (p=0.01) in Arg16Arg group, but there was significant improvement in the amount of out-patient exacerbations (p=0.218). Arg16Gly also significantly improved in terms of exacerbations (p<0.001) and hospital admissions (p<0.001), but not the number of out-patient exacerbations (p=0.199). Similar dynamics was also observed in Gly16Gly, where we observed significant improvement of the amount of exacerbations (p<0.001) and hospitalizations (p<0.001), but not out-patient exacerbations (p=0.144). Study groups did not differ significantly by values of mMRC and CAT at any of the study visits. So, mMRC at visit 1 was 2.26±0.14 in Arg16Arg group, 2.44±0.11 in Arg16Gly group and 2.55±0.11 in Gly16Gly group (p=0.261). But at the level of a tendency each Gly copy increase mMRC value by 0.15 [OR: 0.15; 95 % CI: -0.05 – 0.3; p=0.102]. CAT values at visit 1 was 21.91±1.70 in Arg16Arg group, 24.46±1.3 in Arg16Gly group and 25.03±1.26 in Gly16Gly group (p=0.318).

At visit 2 mMRC was 2.13±0.13 in Arg16Arg group, 2.21±0.09 in Arg16Gly group and 2.32±0.1 in Gly16Gly group (p=0.493), CAT value was – 21.91±1.70 in Arg16Arg group, 19.47±1.21 in Arg16Gly group and 20.58±1.13 in Gly16Gly group (p=0.383).

At visit 3 mMRC was 1.83±0.16 in Arg16Arg group, 1.97±0.11 in Arg16Gly group Arg16Gly and 2.08±0.11 in Gly16Gly group (p=0.395), CAT was 17.91±1.54 in Arg16Arg group, 19.47±1.21 in Arg16Gly group and 20.58±1.13 in Gly16Gly group (p=0.341).

After using MANOVA method for the comparison of more then 2 related samples we found that Arg16Arg group significantly improved values of mMRC (χ^2=15.8, p<0.001) and CAT (χ^2=29.727, p<0.001) during the study. Same dynamics was observed for the Arg16Gly group - mMRC (χ^2=27.000, p<0.001) and CAT (χ^2=45.622, p<0.001); and Gly16Gly group - mMRC (χ^2=24.582, p<0.001) and CAT (χ^2=64.781, p<0.001). So, study groups had similar values of mMRC and CAT during the study indicating similar symptoms burden throughout the study. LABA/LAMA combination was effective in improving the symptoms in all variants of *ADRB2* gene.

When comparing the amount of antibiotic (AB) courses there was a significant difference in the amount of antibiotics use between the study groups. Using Tukey's method there was a significant difference between Arg16Arg and Arg16Gly groups (p=0.018) and Arg16Arg and Glt16Gly groups (p=0.015). There

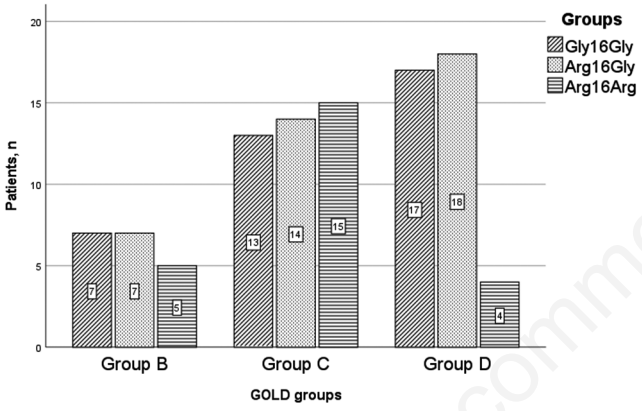

Figure 1. Prevalence of different COPD GOLD groups in the study groups. Study groups did not differ by the distribution of clinical COPD groups (p=0.158). So, ADRB2 polymorphism does not affect the severity of COPD in the studied population.

Table 2. Clinical parameters in study groups. Study groups had no difference in age, COPD duration and number of pack-years. A tendency was found for the total amount of exacerbation in 1st year (p=0.086) and a significant difference in hospital admissions (p=0.048), proving a possible relation of *ADRB2* gene polymorphism with the clinical course of COPD. No difference were found after LABA/LAMA treatment between all study groups, showing efficacy of this combination in all variants of *ADRB2* gene.

Group Parameter	Arg16Arg (n=23)	Arg16Gly (n=39)	Gly16Gly (n=38)	p
Age, years	63.7±2.18	62.15±1.7	66.32±1.34	0.173
COPD duration, years	12.0±2.77	11.92±1.31	9.71±0.88	0.469
Pack-years	25.35±5.57	23.05±3.5	25.32±4.22	0.903
Exacerbation 1st year, n	2.13±0.21	2.97±0.27	2.87±0.25	0.086
Hospitalizations 1st year, n	0.83±0.19	1.49±0,16	1.18±0.17	0.048
Out-patient 1st years, n	1.30±0.15	1.51±0.21	1.68±0.16	0.418
Exacerbations 2nd years, n	1.35±0.18	1.62±0.12	1.89±0.22	0.143
Hospitalizations 2nd year, n	0.30±0.12	0.38±0.1	0.39±0.1	0.835
Out-patient 2nd year, n	1.09±0.17	1.23±0.11	1.50±0.2	0.210

also was a significant difference in the duration of treatment with antibiotics, which was 8.61±1.55 days in Arg16Arg group; 13.64±1.24 days in Arg16Gly group, 13.0±1.26 days in Gly16Gly (p=0.037). In correlation analysis there was a weak negative correlation between Arg16Arg genotype with the amount of antibiotic courses (r=-0.301, p=0.002) and duration of treatment with antibiotics (r=-0.253, p=0.011). Each Gly copy had a weak correlation with the amount of antibiotic courses (r=0.252, p=0.011). In regression analysis it was found that each Gly copy increase the amount of antibiotic courses by 0.35 (OR: 0.35; 95 % CI: 0.01-0.6; p=0.006) and duration of treatment with antibiotics by 2.2 days (OR: 2.2; 95 % CI: 0.2-4.2; p=0.033). There was no significant difference between the groups in the amount of corticosteroids (GCS) (p=0.825) and xanthines (p=0.804), and duration of treatment with GCS (p=0.249) and xanthines (p=0.680) (Table 3).

At the end of the study there was a significant difference in the amount of AB courses between the study groups (p=0.036). In correlation analysis there was a weak correlation between the Gly copy and amount of antibiotics courses (r=0.245, p=0.014). There was no significant difference in the duration of treatment with antibiotics (p=0.229). There was no significant difference in the amount of GCS courses (p=0.333) and GCS treatment duration (p=0.126). But there was a weak correlation between Gly copies and the duration of the treatment with GCS (r=0.200, p=0.045), and it was shown regression analysis at the level of tendency, that each Gly copy increase he duration of treatment with antibiotics by 1.2 days (OR: 1.2; 95 % CI: -0.05–2.5; p=0.057). There was no significant difference in the amount of xanthines courses (p=0.542) and duration of treatment with xanthines (p=0.607) (Table 4).

In Arg16Arg there was a tendency towards a decrease of the amount of AB courses (p=0.052) and duration of AB treatment (p=0.058) after the year of participation in the study. There was a significant improvement in the amount of GCS courses (p=0.026) and duration of GCS treatment (p=0.028). There was no improvement in the amount of xanthines courses (p=0.160) and duration of zanthines treatment (p=0.108). In Arg16Gly group there was a significant improvement in the use of all medication groups: AB courses (p<0.001), AB duration (p<0.001), GCS courses (p=0.001), GCS duration (p=0.001), xanthines courses (p=0.019) and duration (p=0.025). Gly16Gly group had improvement only in the AB use: number of courses (p=0.004) and duration of treatment (p<0.001), but not in GCS courses (p=0.416) and GCS treatment duration (p=0.341) as well as xanthines courses (p=0.684) and duration (p=0.248).

Discussion

The prevalence of different genotypes in our study is similar to the data in the study of Katsarou *et al*. where prevalence of different genotypes was the following: Gly16Gly – 36.93%, Arg16Gly – 49.36%, Arg16Arg – 13.71% [18]. In our study we have slightly lower (39 %) heterozygous patients and a higher part of patients with Arg16Arg genotype (23%). Our study had only 100 patients included, which have potentially not indicated other potential differences between different populations, so study with higher number of patients should be conducted.

In our study we showed a tendency towards a difference in the amount of exacerbations between the study groups and what is more

Table 3. Utilization of drugs by the study groups 12 months prior to inclusion. There was a significant difference in the total amount of antibiotics (AB) courses (p=0.01) and AB treatment duration (p=0.037) between study groups, where occurrence of Glycine copy was associated with higher AB use. No significant difference was found in the use of glucocorticoids (GCS) and xanthines.

Group Parameter	Arg16Arg (n=23)	Arg16Gly (n=39)	Gly16Gly (n=38)	p
AB courses, n	1.09±0.2	1.77±0.14	1.79±0.17	0.01
AB duration, n	8.61±1.55	13.64±1.24	13.0±1.26	0.037
GCS courses, n	0.83±0.32	1.0±0.17	1.16±0.47	0.825
GCS duration, n	2.96±0.83	5.28±0.94	4.21±0.88	0.249
Xanthines coruses, n	0.57±0.23	0.79±0.16	0.97±0.58	0.804
Xanthines duration, n	3.30±1.27	4.13±0.87	3.0±0.96	0.680

Table 4. Utilization of drugs by the study groups 12 month after the inclusion. After the treatment with LABA/LAMA there was a significant difference in the total amount of antibiotics (AB) courses (p=0.036), but not and AB treatment duration (p=0.229) between study groups, where occurrence of Glycine copy was associated with higher AB use. No significant difference was found in the use of glucocorticoids (GCS) and xanthines.

Group Parameter	Arg16Arg (n=23)	Arg16Gly (n=39)	Gly16Gly (n=38)	p
AB courses, n	0.78±0.14	0.90±0.12	1.29±0.16	0.036
AB duration, n	5.91±1.24	6.08±0.85	8.16±1.09	0.229
GCS courses, n	0.26±0.11	0.41±0.1	1.58±1.04	0.333
GCS duration, n	1.13±0.49	1.95±0.47	3.58±1.13	0.126
Xanthines courses, n	0.35±0.15	0.41±0.09	1.08±0.79	0.542
Xanthines duration, n	1.22±0.44	2.10±0.46	2.34±1.0	0.607

important a significant difference in the amount of hospital admissions. Existing scientific data is controversial with several studies showing similar results to ours, but some with the opposite conclusions. In the Rotterdam study it was shown, that each Arg16 copy reduced the risk of exacerbation by 30% in patients using long-acting beta-agonists, while Gly16 copies were related to the higher risk of exacerbation [13]. Same data was shown by Rabe *et al*., who concluded that Arg16Arg genotype had lower risk of exacerbations when compared to the Arg16Gly and Gly16Gly in patients treated with salmeterol [19]. But Ingebrigsten *et al.* showed quite different results where patients with Arg16Arg and Arg16Gly had higher risks of severe COPD exacerbation when compared to Arg16Gly [20]. Our study included patients of the Slavic ancestry, so the difference in data can represent some racial differences in the activity of the receptor and should be investigated deeper.

In our study we showed, that a combination of tiotropium/oldaterol was similarly effective in all genotypes in the reduction of exacerbations and hospital admissions. There is a variety of studies, that assessed treatment efficacy with beta-2 agonists in *ADRB2* polymorphism, with most result indicating no effect on the clinical response. Bleecker *et al*. indicated no difference in response to beta-2 agonists in different Arg16Gly polymorphism [21]. Same results were obtained in Korean population with Atg16Gly polymorphism shown no impact on the clinical response to beta-2 agonists [22]. Also there was no difference in the response to indacaterol [23].

We have not identified studies that were looking at the utilization of different drugs used for the treatment of exacerbations such as antibiotics, glucocorticoids and xanthines. This data can be interesting for future research as we can see clearly different utilization of drugs by the different genotype groups. Interestingly, there was a difference in the GCS use by the end of the study, which can indicate an existing cross-talk between *ADRB2* gene and corticosteroid receptor, which has been described for different organs [24].

Conclusions

Arg16Gly polymorphism of *ADRB2* gene affect clinical course of COPD with Cly copies leading to the higher risk of exacerbations and hospitalizations. Polymorphism does not affect clinical response to LABA/LAMA combination in terms of exacerbations, hospitalizations, mMRC and CAT improvement, but, interestingly, can affect the duration of antibiotic and glucocorticosteroids therapy, indicating potential involvement of the receptor in the processes of elimination of infectious agent and also a cross-talk with the receptor of corticosteroids, with potential altering of its function.

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