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SYSTEMIC EFFECTS OF IL-17 IN REACTIVE ARTHRITIS

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Abstract
Treatment of patients with reactive arthritis (ReA) remains one of the most difficult problems of modern rheumatology. Its relevance is due to the progressive course of the disease, the severity of the lesion of the musculoskeletal system, the high incidence of lesions in people of working age, the early decline in functional abilities, the loss of professional and social skills, the difficulty of physical and psychological adaptation of patients to impaired motor functions, significant disability, which represent a serious general medical and social problem, leading to huge economic losses.

Introduction

Currently, significant therapeutic progress has been made due to the advent of biological drugs, which have had a huge impact on the effectiveness of therapy and significantly improved the course of autoimmune processes in many patients with rheumatological pathologies. According to the literature, a small number of observations does not yet allow an objective assessment of the use of tumor necrosis factor-α inhibitors in treatment-resistant ReA. But in the clinical case of Tanaka et al., antibodies to the interleukin-6 receptor were used and effectively progressed the improvement of the symptoms of ReA, which does not work on standard protocols. According to a study by Mens et al. treatment of ReA, which was complicated with spondyloarthritis, drugs with IL-17 inhibitors had a positive effect on the course of the disease.

The aim of our study was to investigate the relationship between the G197A polymorphism of the IL 17 A gene and the presence of resistance to secukinumab in ReA patients with spondyloarthritis.

Materials and Research Methods

The study was conducted in the third city clinical hospital №3 in the department of rheumatology of the city of Tashkent. The study was conducted in 76 patients (73 women, 3 men, 24-65 years) of ReA with spondyloarthritis. The control group consisted of 24

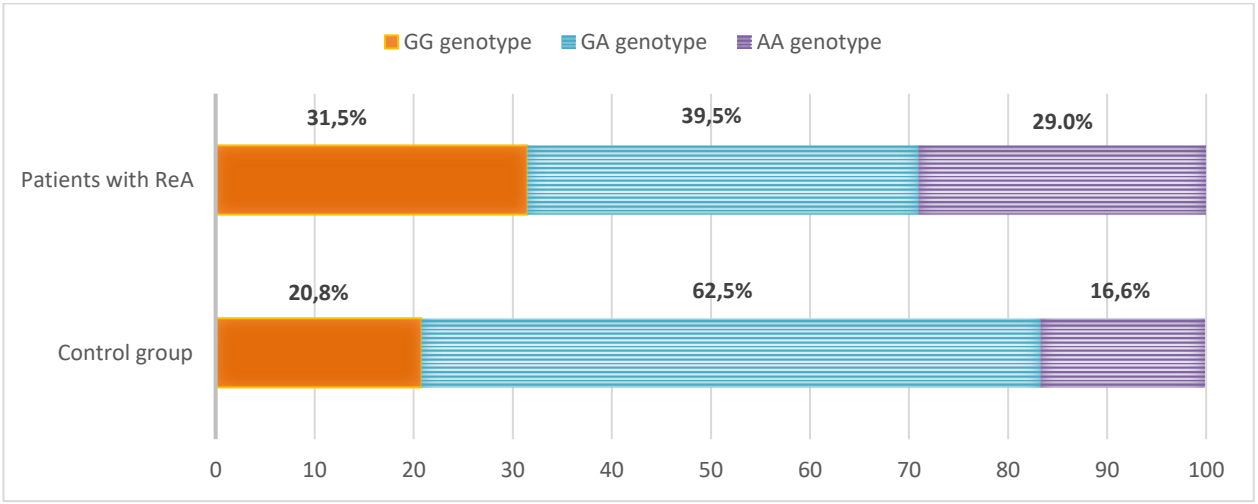
healthy volunteers without a burdened rheumatological history. ReA was diagnosed according to the American College of Rheumatology (ACR) criteria and disease activity was calculated using the DAS28 calculator. All patients who participated in our study were prescribed basic therapy with the IL-17A inhibitor secukinumab (at a dose of 150 mg subcutaneously) and the patients were followed up for 6 months.

Static processing of the data obtained during the study was carried out using the computer program EXCEL and STATISTICA 6.0. To identify the correspondence of genotype distributions to the expected values at Hardy-Weinberg equilibrium and to compare the distributions of genotype and allele frequencies in two subpopulations, the χ2 test (Pearson) was used, where $p<0.05$ was considered statistically significant. The limits of the 95% confidence interval (CI) were calculated by the method of B. Woolf.

Genomic DNA was extracted from whole blood collected in EDTA tubes using the GeneMATRIX Quick Blood DNA Purification Kit (Poland). Identification of all studied polymorphisms in the IL17A gene was performed using the TaqMannSNP genotyping test: 17A (IL-17A G-197A). The reaction was carried out in duplicate using the Fast Real-Time PCR Detection System (Germany).

Results and Discussion

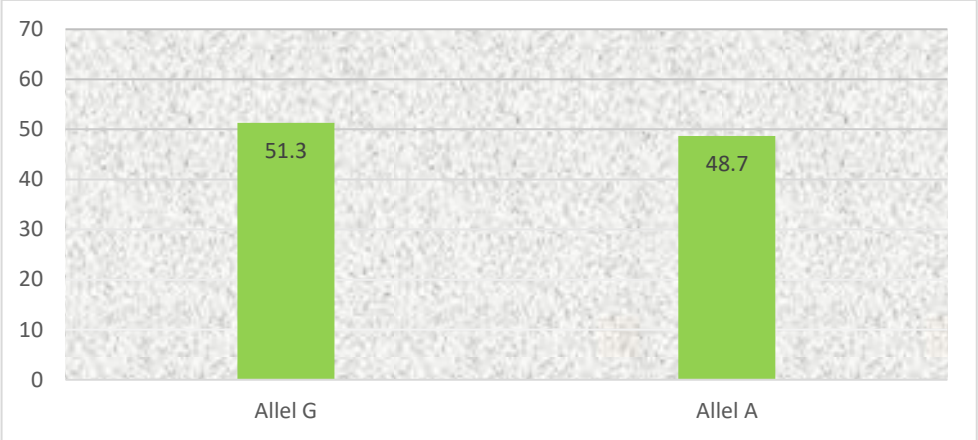
In our study, 76 patients with ReA and 24 healthy volunteers without a rheumatological history were studied. All patients underwent genotyping of the G197A polymorphism of the IL 17A gene. The results of genotyping are shown in Picture №1.



Picture №1 Percentage distribution of genotypes of G197A polymorphism of the IL 17A gene in ReA patients with spondyloarthritis and in the control group

As can be seen from picture №1, the GG genotype of the G197A gene was found in 31.5% of ReA patients, while in the control group it was found in 20.8% of cases. The CT genotype was found in 39.5% of patients, and in the control group it was significantly higher and

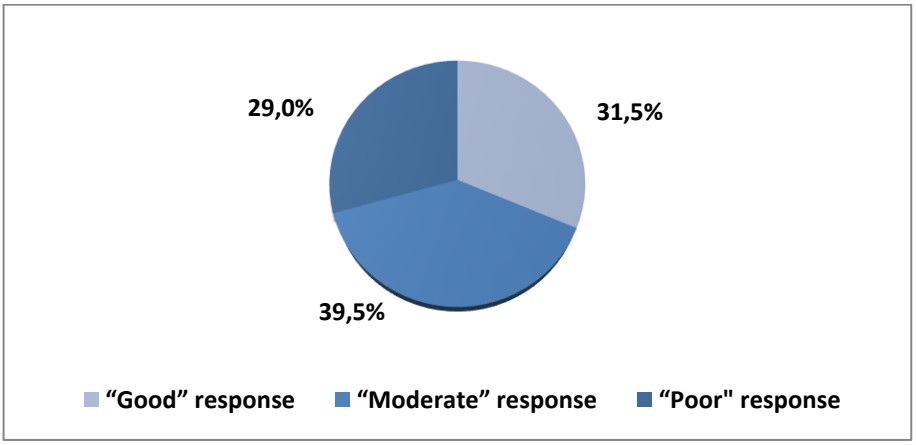
amounted to 62.5% of cases. The frequency of occurrence of the mutant TT genotype was 29.0% and 16.6% in the control group.



Picture №2 Distribution of alleles of polymorphism G197A IL 17A gene

As can be seen from picture **№** 2 the percentages of the G and A alleles were almost the same. The G allele of the G197A isoform was found in 51.3%, the A allele was found in 48.7% of ReA patients. Based on the carriage of three genotypic variants of the G197A IL 17A gene polymorphism, the following associated phenotypic groups were identified depending on the response to secukinumab treatment (Picture №3).

"Good" response to secukinumab (29.5%) carriers of the AA mutant genotype were phenotypically characterized by a good clinical response (DAS<2.6 3-6 months) to secukinumab treatment, as well as low disease activity. "Poor" response to secukinumab (31.5%), carriers of the GG genotype were characterized by high disease activity and clinically poor drug response (DAS>2.6) to secukinumab treatment (Picture № 3). The "moderate" response (39.5%) carriers of the heterozygous GA genotype phenotypically showed an average clinical response (DAS<2.6 less than 3 months) to secukinumab treatment and lower disease activity compared to the "poor response" group.



Picture №3 Percentage distribution of ReA patients by medication response to secukinumab treatment

Despite the large number of studies devoted to the study of polymorphism of the IL 17A gene, the results remain contradictory, which aroused our interest. According to our data, there were no significant differences in the distribution of alleles of the G197A polymorphism of the IL 17A gene in ReA patients and healthy controls. But when comparing genotypic variants, we revealed differences: healthy GG and mutant AA genotypes were more common in patients, while the heterozygous GA genotype was more common in healthy people.

Based on the results of genotyping, we established the relationship between G197A polymorphism of the IL 17A gene and the presence of secukinumab resistance and disease activity. We identified three groups of respondents for treatment with this drug. Patients in the “good” response phenotypic group, those with the AA mutant genotype, showed a good clinical response to secukinumab treatment, as well as low disease activity (DAS28 <2.6). Patients in the "poor" response phenotypic group (patients with the GG genotype) were resistant to secukinumab, even with increasing doses of the drug, clinical remission or low disease activity (DAS28 >5.1) was not achieved. Patients in the "moderate" response group were carriers of the GA genotype G197A polymorphism of the IL 17A gene, which showed a moderate drug response to secukinumab, and disease activity was moderate (DAS28 3.2-5.1).

Conclusion:

Genetic studies of G197A polymorphism of the IL 17A gene in patients with ReA revealed their relationship with resistance to secukinumab, as well as disease activity during treatment with this drug. ReA patients with the GG genotype have a poor response (resistance) to secukinumab treatment, as a result, the disease proceeds with a high degree of disease activity, compared with patients with GA and AA genotypes. Patient genotyping can be used to determine the effectiveness of secukinumab drug therapy and personalized selection of treatment methods for patients with ReA.

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