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HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH VASCULITES ASSOCIATED WITH ANTINEUTROPHILIC CYTOPLASMIC ANTIBODIES CONDUCTING BIOLOGICAL TREATMENT

ABSTRACT

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The dissertation contains 154 pages and is illustrated with 42 tables, 33 figures and 2 photos. The literature used includes 468 sources.

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The public discussion of the dissertation will take place on 18.03.2022 from 14.00 hours in hall 501 of the Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", Sofia

Contents:

Abbreviations used:

AAV - ANCA-associated vasculitis
ACR - American College of Rheumatology
ADCC - antibody-dependent cellular cytotoxicity
ANCA - Antineutrophil cytoplasmic antibodies
anti - GBM - Anti-glomerular basement membrane disease (Goodpasture syndrome)
ATC - anatomical-therapeutic and chemical classification
AZA - azathioprine
BAFF - The B-activating factor
BASDAI - Bath Ankylosing Spondylitis Disease Activity Index
BP - bodily pain
BVAS - Birmingham Vasculitis Activity Score
BVAS / WG - Birmingham Vasculitis Activity Score for Wegener's Granulomatosis
CDC - complement-dependent cytotoxicity
CHCC - Chapel Hill Consensus Conference
CHMP - Committee for Medicinal Products for Human Use
CSS - Churg-Strauss syndrome
CV - Cryoglobulinemic vasculitis
CYC - cyclophosphamide
DCVAS - Draft criteria for diagnosis and classification of vasculitis
DMARD - Disease-modifying antirheumatic drugs
EGPA - eosinophilic granulomatosis with polyangiitis
EMA - European Medicines Agency
EQ - 5D - EuroQuoL-5D - 5-level EuroQol questionnaire
EULAR - European League Against Rheumatism
EULAR - European League Against Rheumatism
GCA - Giant cell arteritis
GH - general health
GPA - granulomatosis with polyangiitis
HAQ - DI - Health Assessment Questionnaire-Disability Index
HRQoL - health-related quality of life
HUV - Hypocomplementemic urticarial vasculitis
ICD - International Classification of Diseases
IgAV - immunoglobulin A vasculitis
IgG4 - immunoglobulin G4
IIF - indirect immunofluorescence analysis
IL-5 - Interleukin-5
IQR - interquartile range
IVIG - Intravenous immunoglobulins
mAbs - Monoclonal antibodies
MCS - a summary of the mental component
MDE - Minimum detectable effect

MDE - Model-driven Engineering
MedDRA - Medical Dictionary for Regulatory Activities
MH - mental health
MPA - microscopic polyangitis
MPO - myeloperoxidase
MPO - ANCA (pANCA) - associated with myeloperoxidase antineutrophil cytoplasmic antibodies
MTX - methotrexate
MVV - Medium-vessel vasculitis
NETS - Neutrophils extracellular traps
NHIF - National Health Insurance Fund
PAN - Polyarteritis nodosa
PAN - polyarteritis nodosa
PCS - summary of the physical component
PF - physical functioning
PICO - Population, Intervention, Comparison, Outcomes
PICOS - Population, Intervention, Comparison, Outcomes and Study design
PR3 - proteinase 3
PR3-ANCA (cANCA) - proteinase 3 antineutrophil cytoplasmic antibodies
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyzes guidelines
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyzes guidelines
PRO - patient reported outcomes
PVAS - Pediatric Vasculitis Activity Score
QoL - quality of life
QWB - Quality of Well-Being
RE - emotional role
Rii - Average inter-item correlation
RP - physical role
Rtt - Chronbach 'alpha factor
RTX - rituximab
SD - Standard deviation
SF - social functioning
SF - 36 - Medical Outcome Study Short-Form Health Surveys
SIP - Sickness Impact Profile
SOC (MedDRA) - system organ class
SOV - Single-organ vasculitis
SVV - Small-vessel vasculitis
VAS - visual analog scale
VDI - Vasculitis Damage Index
VT - vitality
VVV - Variable vessel vasculitis
UMHAT - University Multidisciplinary Hospital for Active Treatment

WG - Wegener granulomatosis
WHO - World Health Organization

I. INTRODUCTION

A universal and globally acceptable definition of health is given by the World Health Organization (WHO), which states that "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." This broad view of health is fully accepted by the scientific community, and new methods for assessing and treating each disease are entering research and real clinical practice.

Quality of life (Quality of Life - QoL) is a broad theoretical concept that measures people's general perception of their lives. QoL includes both health-related and non-health aspects of human life - economic, political, cultural and others.

Health-related quality of life (Neal- R elated Q uality of Life - HRQoL) is part of the total Qo L of the individual and represents the functional effects of the disease and subsequent therapy as perceived by the patient. In addition to physical functioning, the general concept of health-related quality of life includes other aspects of health called domains, such as psychological and social functioning, that are important to the patient. HRQoL tools can be used to detect undiagnosed or undetected diseases, such as depression.

There are two main types of measures of health status: general tools and disease-specific tools.

The most commonly used common tools in practice are: Medical Outcome Study Short-Form Health Surveys - includes SF-12, SF-36, SF-36 version 2, EuroQuol-5D (EQ-5D), Quality of Well-Being (QWB) Scale, Sickness Impact Profile (SIP) and others.

Specific tools for measuring health status for a specific disease: Benign Prostate Hypertrophy Impact Index (BPH Impact Index), American Urological Association Symptom Index, Living with Asthma Questionnaire Asthma QoL Questionnaire, Diabetes-specific QoL Instrument, etc.

The entry of new therapies in medicine and the biotechnological revolution in the pharmaceutical sector make research on patients' health status an essential part of pre-registration clinical trials, non-interventional and interventional post-registration studies, epidemiological and pharmacoepidemiological studies, etc.

Collecting data on health-related quality of life should be an inherent task for practicing medical professionals in real practice - doctors, pharmacists, health care professionals and others. It is explicitly clear that an illness can worsen the patient's psychosocial status, and conversely, that impaired psychosocial comfort can trigger the onset of an illness or worsen an existing one.

In this dissertation we will investigate health-related quality of life in patients with vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) treated with biologics.

We will analyze patients with the following types of vasculitis:
Microscopic polyangiitis: Necrotizing vasculitis, with little or no immune deposits, affecting mainly small vessels (ie capillaries, venules or arterioles). Necrotizing glomerulonephritis is very common. Pulmonary capillaritis is also common. No granulomatous inflammation.
Granulomatosis with polyangiitis (Wegener's granulomatosis): Necrotizing granulomatous inflammation, usually involving the upper and lower airways and necrotizing vasculitis,

affecting mainly small to medium vessels (capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.
Eosinophilic granulomatosis with polyangiitis (Cherg-Strauss syndrome): Rich in eosinophils, necrotizing granulomatous inflammation involving the airways and necrotizing vasculitis mainly of small to medium vessels associated with asthma and eosinophilia. ANCA antibodies are more common when glomerulonephritis is present.

We chose and formulated the topic of the dissertation because:

1. Systemic vasculitis is a rare and heterogeneous disease that affects different organs and systems with varying degrees of severity depending on the size, location and importance of the affected vessels. Recognition of manifestations suggestive of vasculitis is important, as delaying the diagnosis can significantly affect the clinical outcome . Due to the multisystemic nature of vasculitis, a multidisciplinary approach is usually required. The course of the disease can range from subacute non-specific complaints to life- threatening impairment.
2. The etiology of primary systemic vasculitis is unknown .
3. The pathogenesis is completely unclear in different types of vasculitis. It is generally accepted that there are different immunological mechanisms that play a role in the pathogenesis of vasculitis, and each of them has its own characteristics. Most commonly, these mechanisms include the deposition of an immune complex on vessel walls, autoantibodies (e.g., anti-endothelial antibodies and ANCA), cellular and molecular immune responses, granuloma formation, and endothelial cell damage.
4. The epidemiology of systemic vasculitis is increasingly being studied. All types of vasculitis fall under the definition of "rare diseases". ANCA-associated vasculitis has a total incidence of 20 cases / 1 million population, with a peak in the age group of 65 to 74 years. Wegener's granulomatosis is more common in northern Europe than microscopic polyangiitis, which is more common in southern Europe.
5. AA B is a disease with significantly high mortality, with almost all patients requiring aggressive immunosuppressive therapy. Without treatment, mortality is> 90% within 5 years.
6. The quality of life in standard treatment of vasculitis does not meet modern requirements.
7. The use of biological medicinal products for the treatment of vasculitis is a therapeutic novelty and is of considerable clinical interest.
8. Biological medicinal products have a relatively short "life" cycle, their efficacy is determined on the basis of a minimum number of patients and their therapeutic efficacy is in the post-registration stage of additional clarifications and studies.
9. Improving the health-related quality of life of patients with AAV would provide additional arguments for justifying biologic treatment, given the relatively high cost of drug therapy. On the other hand, this type of study will enrich the knowledge of medical professionals about the symptoms of AAV due to mental and social factors.
10. Insufficient published data on the quality of life in patients with ABA have been found in the scientific literature.
11. There is no evidence that this type of study was conducted in Bulgaria.

Using modern methods and models for assessing health-related quality of life, we will study the general perceptions of health, mental health, social behavior (functioning), role functioning, physical component and other factors (economic, professional, cultural…) in

treatment with biological medicinal products in the Bulgarian population of patients with vasculitis associated with antineutrophil cytoplasmic antibodies, their practical significance and we will evaluate some aspects of therapeutic practice in Bulgaria.

And I. AIMS AND TASKS

II.1. OBJECTIVE

To evaluate the health-related quality of life (physical, psychological and social functioning) in the Bulgarian population of patients with systemic vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), treated with biological drugs.

II.2. TASKS

The following tasks will be solved:

1. Selection of patients with systemic vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) who will undergo treatment with biological medicinal products.

2. Assessment of the compliance of patients undergoing treatment with a biological medicinal product with the requirements of the National Health Insurance Fund.

3. Selection of general and specific tools for analysis of health-related quality of life in the selected patient population.

4. Conducting a series of interviews with each participant in the selected group of patients, according to a pre-prepared protocol, before and after treatment.

5. Processing of results and statistical analysis.

6. Analysis and evaluation of the effectiveness of biological treatment based on data on health-related quality of life.

And II. MATERIALS AND METHODS

We developed a test report in accordance with the topic of the dissertation. The study protocol and procedures are presented in Table 1.

Table 1. Study protocol

1. JUSTIFICATION
1.1. Scientific evaluation
Injuries from a disease are defined as a set of lasting consequences for the patient diagnosed - in this case systemic vasculitis. The reason for this study is to determine the severity of the disease in patients with systemic vasculitis, which is not limited to the clinical symptoms and syndromes characteristic of the disease, but also includes the effects of drug therapy, toxicity, side effects, comorbidity, functional and mental health. There are currently no disease-specific tools for functional assessment in patients with ANCA-associated vasculitis. Most often, different authors use common tools such as Short Test-36 (SF-36), or EuroQol 5-Level Questionnaire (EQ-5D), to assess general health and ability to perform certain tasks. Management of the disease process in patients with ANCA-associated vasculitis requires a clear understanding of their current general health status. The main goal of the diagnostic and treatment process is to identify quantitative and qualitative parameters for accurate diagnosis, measurement of disease activity, general disabilities, functional disorders, choice of therapeutic approach, treatment effectiveness, etc. It is essential that the process of obtaining this information takes place in a systematic structured way. The process of systematic assessment of patients is the most valuable component in the assessment of the disease. The introduction of biological therapies in the treatment algorithms for systemic vasculitis associated with ANCA and the lack of data in the scientific literature to assess the health-related quality of life of patients in biological treatment, make the choice of topic original in nature, and we expect results to upgrade scientific knowledge in this field.
1.2. Legal basis for conducting the study
What we planned study it is essentially a non-interventional observational prospective study. LMPHM does not provide rules and norms for conducting non-interventional research by academic teams, but only by Marketing Authorization Holders. Thus, the law excludes the study we are planning from the scope of the LMPHM and the rules and procedures described in it should not be applied, although by definition there is a complete coincidence with the definition of non-interventional research. Therefore, no test report was submitted for approval by the Local Ethics Committees at the study centers.

The test does not fall under the provisions of the Health Act, Chapter Seven. Section IV. Medical research on humans. Medical science, as it concerns prospective monitoring of medicinal products under the terms of their Authorization for use in real clinical practice.

2. STUDY CENTER

Patients will be selected in two centers:
Clinic of Rheumatology at UMHAT "SofiaMed" AD, Sofia and
Clinic of Rheumatology at the University Hospital "St. Ivan Rilski" EAD, Sofia.

3. STUDY PERIOD

Time to conduct the study January 2019 to September 2020

4. RESEARCH QUESTION AND OBJECTIVES

4.1. Goals

The main aim of the study was to determine the parameters of health-related quality of life in patients with vasculitis associated with antineutrophil cytoplasmic antibodies undergoing biological treatment. The effects of treatment and disease will be measured from the patients' perspective.

4.2. Endpoints

4.2.1. Primary endpoints

The primary endpoints of the study were measurement of physical function, social and behavioral functioning, mental health, and the patient's assessment of his or her general health.

Depending on the general and specific instruments used, the results will be grouped into two main areas - Results obtained through the common instrument SF-36 v ersion 2 and Results obtained through the common instrument EuroQol 5 D

Primary endpoints obtained by SF-36 v ersion 2 - a summary of the physical component (PCS) and a summary of the mental component (MCS) of the entire study population.

Primary endpoints obtained by EuroQol 5 D - mobility; self-service; usual activities; pain and malaise; anxiety and depression.

4.2.2. Secondary endpoints

As secondary endpoints, we will analyze additional parameters, depending on the tools used:

1. **HRQoL:**

- Physical functioning (**PF** - physical functioning)
- Role function (**RP** - role physical)
- Body aches (**BP** - bodily pain)
- General state of health (**GH** - general health)
- Vitality (**VT** - vitality)
- Social functioning (**SF** - social functioning)
- Emotional functioning (**RE** - role emotional)
- Mental health (**MH**)

2. **EuroQol 5D-5L:**

- via visual analog scale

- Visual analogue scale (VAS) - an additional criterion for self-assessment of health status.

5. RESEARCH METHODS

5.1. Study design

Two-center, prospective, observational, non-interventional, controlled study in two periods. There is no separate control group of patients. The selected cohort of patients will be "auto" control, on its own, as patients will complete questionnaires before and after treatment.

5.2. Research methodology

The main method will be conducting of a "direct individual survey" with closed answers. The survey will be conducted with common tools for measuring health status by completing the SF-36 v ersion 2 questionnaire and the EuroQol 5 D questionnaire in electronic format.

We will use licensed software products based on the so-called engineering models (*Model - driven Engineering - MDE)*. MDE is a rapidly evolving new paradigm in software engineering that bases system development on meta-modeling and model transformations and provides methods for building bridges (connections) between similar or different technical spaces and domains.

The original questionnaires are in English and validated by the licensee. The working version of the questionnaires that we will use has been translated into Bulgarian by a licensed translator.

The questionnaires will be completed independently by the patients, and the opportunity will be provided for assistance by the interviewing researcher where there are ambiguities. In this way we will eliminate the possibility of "bias errors" if the interviews are on the principle of " face " to face".

5.3. Conditions for inclusion in the study

A prerequisite for participation in the study is that patients meet the inclusion criteria.

5.3.1. Including criteria

1. Signed and dated informed consent.
2. Age over 18 years.
3. Diagnosed with Granulomatosis with polyangitis (Wegener's).
4. The diagnosis must be made in accordance with EULAR criteria.
5. The diagnosis and decision to conduct treatment must comply with the pharmacotherapeutic guide to rheumatology, approved by the National Council on Prices and Reimbursement of Medicinal Products.
6. Patients should not have been treated with a biological or biosimilar medicinal product.
7. Patients must meet NHIF criteria for the treatment of systemic vasculitis.

5.3.2. Excluding criteria

1. Refusal to sign informed consent.
2. Age under 18 years.
3. Non-compliance with NHIF criteria for treatment of systemic vasculitis.
4. Premature termination of biological treatment.
5. Manifestation of side effects that may compromise the results.

5.3.3. Procedures (scheme) of the study

5.3.3.1. Screening

Screening visit

Introducing the participants to the protocol and procedures.
Signing Informed Consent by the Patient.
Evaluation of inclusion and exclusion criteria.
Patients are considered to have dropped out of screening if there is even 1 exclusion criterion.

5.3.3.2. Visits

Visit 1

It is performed before the start of the biological treatment.
participants in the study filled in two questionnaires - Short Test-36 version 2 (SF-36 version 2) and EuroQol 5-level questionnaire (EQ-5D).

Participants answer the questions retrogradely - describe their condition for 4 weeks ago.

Therapeutic period

Introduction into remission

The recommended dose of MabThera for remission of granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg / m ^{2} body surface area administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Maintenance treatment

After remission with MabThera , maintenance treatment should be started no earlier than 16 weeks after the last MabThera infusion .

Following remission with other standard immunosuppressive therapy, maintenance treatment with MabThera should be initiated during the 4-week period after remission of the disease.

MabThera should be given as two *iv* infusions of 500 mg every two weeks, followed by one *iv* infusion of 500 mg every 6 months thereafter. Patients should be given MabThera for at least 24 months after remission (no clinical signs or symptoms). In patients who may be at higher risk of relapse, physicians should consider a longer duration of maintenance therapy with MabThera, up to 5 years.

Visit 2

It is given 6 months after treatment for remission with Rituximab.
participants in the study filled in two questionnaires - Short Test-36 version 2 (SF-36 version 2) and EuroQol 5-level questionnaire (EQ-5D).
Participants answer the questions retrogradely - describe their condition for 4 weeks ago.

Preparation of a consolidated (aggregated) study report

After reaching the set number of participants in the study, a consolidated report is prepared in two parts, using software products.

The first part of the Report will contain a summary of the physical component (PCS) and a summary of the mental component (MCS) of the whole study group, identified by the two common instruments.

The second part of the Report will contain an analysis of the secondary endpoints - Physical functioning, role functioning, physical pain, general health, vitality, social functioning, emotional functioning and mental health.

Third part - Analysis of the effectiveness of biological treatment based on data on health-related quality of life.

6. ANALYSIS

6.1. Sample size

Planned number of participants in the study:
Expected number of participants - up to 24
Minimum number of participants - not less than 6

6.2. Demographics

The study will include patients over 18 years of age. We will analyze the patients involved by gender, age, disease, time of diagnosis, prior treatment.

6.3. Statistical methods for evaluating the results

We will use statistical methods in three directions:

1. The main method will be to conduct a descriptive statistical analysis of the results of the surveys.

2. The received answers will be tested with various additional statistical methods such as:

1. Completeness of Data;
2. Responses within Range;
3. Consistent Responses;
4. Estimable Scale Scores (Reliability of measured results);
5. Item Internal Consistency;
6. Discriminant Validity;
7. Reliable Scales.

3. We will use a correlation matrix of elements and factors and we will calculate the factor of convergence and divergence of the received answers and we will determine the degree of reliability of the obtained results at given normal values for this indicator from 0.00 to 0.40.

4. To assess the reliability and homogeneity of the results I will use two techniques: inter - rater (internal evaluation): different people, the same test and test - retest (test-retest): the same people at different times.

Reliability will be measured by Chronbach ' alpha factor (Rtt) at ≥ 0.70 and Average inter - item correlation (Rii) at a norm of 0.15-0.50.

6.4. Data management and storage

For each patient a clinical card will be filled in, containing data on age, sex, diagnosis, compliance with inclusive and exclusion criteria, visits, treatment.

6. Protecting patients' rights

physical and mental integrity of the participant in the trial, the right to privacy and the right to protection of his personal data are guaranteed, according to the Personal Data Protection Act.

6.1. Patient information and informed consent

The study will include individuals who are:

1. Informed in a preliminary conversation with a doctor - a member of the research team, about the goals, risks and inconveniences of the test and the conditions under which it will be conducted;
2. Informed of their right to withdraw from the trial at any time without adverse consequences for them;
3. Whether personally written consent to participate, after being aware of the nature, significance, consequences and possible risks of their participation.

6.2. Withdrawal of patients from the study

Patients can withdraw from the study at any time without explanation and without negative consequences for them.

6.3. Ethical norms and standards

The study design and protocol were prepared in accordance with the Declaration of Helsinki and the Guide to Good Clinical Practice. The rights, safety and well-being of the participants in the trial are paramount and take precedence over the interests of science and society.

7. Communication and publication of results

7.1. Publication of the results in scientific journals

The author's team plans to prepare at least two scientific articles with the results of the research. Personal data will not be disclosed, except for summarized health and demographic characteristics.

7.2. Publication of the results of scientific forums - report, poster

The author's team plans to participate with reports in at least three scientific forums. Personal data will not be disclosed, except for summarized health and demographic characteristics.

8. References

Authorization to use Rituximab; Hochberg, Marc C. (ur.). Rheumatology Marc C. Hochberg, Ellen M. Gravallese, Alan J. Silman, Josef S. Smolen, Michael E. Weinblatt, Michael H. Weisman. Rheumatology (Hochberg) Seventh edition.Rhiladelphia, PA: Elsevier, Inc., [2019]; Declaration of Helsinki; The Clinical Good Practice Guide; Raskati K, Dimitrova Z, Hristov E, Parvova-Hristova I. Fundamentals of pharmacoeconomics. 1st edition, Wolters Kluwer, Bulgaria, 2016, ISBN 978-619-90672-0-8

9. Applications

7.1. Appendix 1 - Questionnaire SF -36 version 2 in Bulgarian

7.2. Appendix 2 - Questionnaire EuroQol 5 D -5L in Bulgarian

7.3. Appendix 3 - Clinical Patient Card - BVAS version 3

IV. RESULTS OF OWN STUDIES AND ANALYSIS

IV .1. Representativeness of the sample and demographic characteristics of the analyzed cohort.

Only patients diagnosed with granulomatosis with polyangiitis (Wegener's granulomatosis, Wegener's disease) were included in our study. The analyzed group includes 12 patients - table 2.

Table 2. Distribution of patients by sex

Patients with Wegener's granulomatosis (n /%)	Men (n /%)	Women (n /%)
12 (100)	10 (83.33)	2 (16.67)

We analyzed the size of the examined cohort as part of the total number of patients in Bulgaria in order to determine the representativeness of our study.

Epidemiological data show that newly diagnosed cases (incidence rates) with GPA, MPA and EGPA are 2.1-14.4, 2.4-10.1 and 0.5-3.7 per million population in Europe, respectively, and the prevalence of all AAV cases is of AAV) is estimated at 46-184 per million population. All three diseases meet the definition of "Rare Disease" (Orphan disease).

The incidence for Bulgaria of patients with Wegener's granulomatosis is estimated as newly diagnosed cases between 14.7 - 100.80 with a median of 43.05. No literature and official data from the national statistics on the actual total number of patients with Wegener's Granulomatosis for the period 2018-2021 are found. We consider the presence of no more than 40 to 60 patients with this disease in Bulgaria to be acceptable, and those diagnosed are not more than 20 or as a relative share not more than 30% of the total. The latest published data from the National Health Insurance Fund for 2017 give us grounds for such an assumption, which shows that in the first, second and third quarters of the same year the National Health Insurance Fund paid for treatment of 18, 15 and 12 patients or an average of 15 patients per month.

In the 12 patients included in the study, we can assume that the analyzed population represents 81.6% of the total number of patients as newly diagnosed cases with regression to 11.9% of the maximum frequency. The size of the population analyzed by us, calculated in the total number of patients with the above acceptable assumptions, is not less than 60% of all patients in Bulgaria. Table 3 presents an analysis of the demographic indicators of the patients included in the study. The mean age of follow-up men with Wegener's granulomatosis was 52.4 years, the median was 53 years, and the most common age was 51 years with a standard deviation of 13.54 years.

The mean age of the women followed in the Wegener Granulomatosis Registry was 55.5 years, the median and most common age could not be calculated, as there were only two women in the study and they were not sufficient to extract statistical results (standard deviation 4.95 years).

Table 3. Demographic indicators

Age	Men	Women	Total
18-45	2 (16.66%)	0 (0%)	2 (16.66%)
46-65	7 (58.33%)	2 (16.66%)	9 (75.0%)
Over 65	1 (8.33%)	0 (0%)	1 (8.33%)
Number	10 (83.33%)	2 (16.67%)	12 (100.0%)
Average	52.4	55.5	4
Median	53	-	2
Moda	51	-	-
Standard deviation (SD)	13.54	4.95	4.36

IV .2. Clinical characteristics of the studied group of patients.

We analyzed a series of non-clinical and clinical characteristics of the studied group of patients.

We performed a retrospective analysis of the evolution of the disease in all patients by stratification as follows: mean duration of the disease, time from onset of the first symptoms of the disease to final diagnosis, time to initiation of treatment after diagnosis, duration of conventional treatment and switching to biological treatment (Table 4). The average duration of the disease in the group of patients we followed ranged from 1 to 13 years with a median of 5 years. The time for diagnosis after the onset of the first symptoms is relatively short, despite the diverse and complex clinical symptoms: in 58.3% (7 patients) of cases the diagnosis was made within 1 month, in 3 cases up to half a year. In our sample there are 2 cases with severe delay in the diagnostic process: in 1 patient it took more than 1 year, and in the second case it took 7 years (patient №8) - it was considered that the patient has a primary immune renal disease. Despite the drastic deviation in both patients, the median and fashion according to this criteria are equal to 1 month.

Table 4. Evolution of the disease in the studied group of patients - stages

Patient	Duration of the disease (years)	Time from first symptoms to diagnosis (months)	Time to the beginning of treatment after placing diagnosis (months)	Conventionally treatment - duration (years)	Rituximab treatment (number of infusions)
1	**11**	**4**	**1**	**5**	**1**
2	**7**	**1**	**1**	**6**	**1**
3	**1**	**2**	**1**	**1**	**1**
4	**2**	**1**	**1**	**2**	**1**
5	**8**	**1**	**1**	**4**	**1**
6	**4**	**1**	**1**	**2**	**1**
7	**4**	**1**	**1**	**3**	**1**
8	**13**	**84**	**1**	**4**	**1**
9	**5**	**6**	**6**	**5**	**1**
10	**5**	**15**	**1**	**5**	**2**
11	**4**	**1**	**2**	**2**	**1**
12	**5**	**1**	**1**	**2**	**2**
Average value	**5.75**	**9.83**	**1.5**	**3.45**	**1.17**
Median	**5**	**1**	**1**	**3.5**	**1**
Moda	**4.5**	**1**	**1**	**2**	**1**
Standard deviation (SD)	**3.49**	**23.70**	**1.44**	**1.62**	**0.38**

The average duration of conventional treatment from the date of diagnosis to the transition to biological treatment is 3 and a half years, with SD = 1.62. Patients received conventional drug treatment as follows: **Immunosuppressants** - INN Cyclophosphamide , Azathioprine , Methotrexate ; **Systemic glucocorticoid therapy** - INN Methylprednisolone , Prednisone , Betamethasone; **Immunoglobulins** - INN Immunoglobulins, normal human . Rituximab treatment included 1 and / or 2 courses of treatment within the study, according to the protocol period. Almost all patients have completed additional courses of Rituximab since the end of the study in September 2020 - between 4 and 6. Unfortunately, they are not included in the quality of life analyzes. We evaluated a series of clinical parameters such as: clinical manifestation of the disease, complications, concomitant diseases, severity of the disease, assessed on the Scale for the activity of vasculitis Birmingham Vasculitis Activity Score - version 3 (BVAS)), conventional treatment - type and duration, presence of progression and / or remission, biological treatment - duration, effect of treatment, etc.

BVAS clinical evaluation card was completed for each patient version 3, containing 9 sections and the 56 elements of the assessment, the maximum achievable points for each section and the total number of points. BVAS activity was assessed by constant points (BVAS - Persistent points) from 0 to 33 (Table 5).

Table 5. Clinical characteristics of the studied group of patients

Patient	Clinical activity of the disease*, measured by the Birmingham Vasculitis Activity Scale (BVAS - Persistent points)**	Complications	Accompanying diseases
1	**12**	Kidney failure	None
2	**19**	Chronic otitis in the right ear Paresis of the right lenticular nerve	None
3	**16**	Kidney failure Arterial hypertension Dyslipidemia	Secondary anemic syndrome
4	**19**	Kidney failure Arterial hypertension DIC syndrome (thrombosis)	Chronic gastritis Secondary anemic syndrome
5	**18**	Kidney failure Infection of the right eye	Dry cough, shortness of breath, pain and tightness in the chest
6	**7**	Dry cough, shortness of breath, pain and tightness in the chest	None
7	**24**	Kidney failure Steroid diabetes	Dry cough, shortness of breath, chest pain and tightness Chronic gastritis Secondary anemic syndrome
8	**33**	Cerebral hemorrhage with subsequent craniotomy Bilateral abscess pneumonia Kidney failure	Secondary anemic syndrome
9	**7**	Pulmonary fibrosis	Osteoporosis Scoliosis
10	**19**	Arterial hypertension	Cushing's syndrome
11	**7**	Arterial hypertension	Generalized osteoporosis with fractures Gallstone disease
12	**6**	None	None

* The clinical manifestation of the disease is determined in accordance with the criteria described in Table 2. Clinical picture of AAV by organs and systems

** Disease manifestations were assessed in the presence of active vasculitis. The results for all manifestations of active (but not new or worsened) vasculitis are evaluated as permanent. Persistent results may range from 0 to 33. New / worse results are evaluated for all manifestations of new or worsening vasculitis. They can range from 0 to 63 [461].

The initial clinical manifestations in the analyzed group of patients are extremely diverse, with symptoms and syndromes from all 9 groups on the rating scale (Table 4, Table 6).

In view of our established average duration of the disease and data collection retrospectively, we will not undertake a detailed description of the initial symptoms - some of them are not described in the medical histories and patients do not remember them clearly.

However, there are definite data on complications and concomitant diseases. The most common complication is the development of renal failure - in 50% of cases, followed by cases of hypertension - 33.3%. Anamnestic 1/3 of patients report as the most common concomitant disease symptoms of the upper respiratory tract - dry cough, shortness of breath, pain and tightness in the chest.

Table 6. Frequency distribution of clinical activity on persistent disease, measured through Rock for activity on vasculitis Birmingham (BVAS - Persistent points)

(Levels)	(Counts)	(% of Total)	(Cumulative %)
6	1	8.3 %	8.3 %
7	3	25.0 %	33.3 %
12	1	8.3 %	41.7 %
16	1	8.3 %	50.0 %
18	1	8.3 %	58.3 %
19	3	25.0 %	83.3 %
24	1	8.3 %	91.7 %
33	1	8.3 %	100.0 %

The minimum number of points of persistent type according to BVAS is 6 and the maximum is 33, with a median of 17 points. The group we analyzed was assessed as moderately severe BVAS activity version 3, not forgetting the fact that all patients received conventional treatment. The descriptive analysis of BVAS activity version 3 is shown in Table 7.

Table 7. Descriptive analysis of BVAS activity version 3

Parameters	

Number (n) / Missing (missing)	**12/0**
Mean	**15.6**
Standard error (mean) / St andart error (mean)	**2.37**
Median	**17.0**
Fashion	**7.00**
Standard deviation	**8.21**
Variance	**67.4**
Range	**27**
Minimum value	**6**
Maximum value	**33**
Skewness	**0.630**
St andart error skewness	**0.637**
Shapiro-Wilk - p	**0.172**

IV .3. Assessment of health status using the tool EuroQol 5 D -5L before conducting biological treatment

present the results of the assessment of health status through the tool EuroQol 5 D -5L on Visit 1, which is conducted before the start of biological treatment. Participants answered the questions retrogradely by describing their condition 4 weeks ago. All analyzes were performed in accordance with EuroQol Research Foundation. EQ -5 D -5 L User Guide, 2019. 5 components are measured - Mobility; Self-service; Usual activities (work, study, housework, family or leisure activities); Pain / Illness and Anxiety / Depression. All patients answered 100% of the questions.

Figure 1 presents the individual data of the patients included in the study according to the 5-dimensional reporting system. A five - digit system is used to determine the individual result number). Perfect health is denoted by five units (11,111) and worst by five fives by 55,555. Each health condition can be transformed into a weighted index score using a country- or region-specific set of values. The values of the EQ-5D index illustrate society's understanding of health and range from -0.590 to 1.0, where negative values correspond to poor health (conditions worse than death), and 1.0 corresponds to perfect health.

1	DT	I have moderate problems in walking about (3)	I have no problems washing or dressing myself (1)	I have moderate problems doing my usual activities (3)	I have moderate pain or discomfort (3)	I am not anxious or depressed (1)
2	CC	I am unable to walk about (5)	I have moderate problems washing or dressing myself (3)	I have moderate problems doing my usual activities (3)	I have extreme pain or discomfort (5)	I am moderately anxious or depressed (3)
3	PT	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have no pain or discomfort (1)	I am not anxious or depressed (1)
4	IG	I am unable to walk about (5)	I am unable to wash or dress myself (5)	I am unable to do my usual activities (5)	I have moderate pain or discomfort (3)	I am extremely anxious or depressed (5)
5	RP	I have moderate problems in walking about (3)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have moderate pain or discomfort (3)	I am moderately anxious or depressed (3)
6	RB	I have moderate problems in walking about (3)	I have no problems washing or dressing myself (1)	I have moderate problems doing my usual activities (3)	I have moderate pain or discomfort (3)	I am not anxious or depressed (1)
7	RS	I have severe problems in walking about (4)	I have moderate problems washing or dressing myself (3)	I have severe problems doing my usual activities (4)	I have extreme pain or discomfort (5)	I am extremely anxious or depressed (5)
8	YS	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have slight pain or discomfort (2)	I am slightly anxious or depressed (2)
9	IS	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have slight problems doing my usual activities (2)	I have no pain or discomfort (1)	I am moderately anxious or depressed (3)
10	VV	I have moderate problems in walking about (3)	I have slight problems washing or dressing myself (2)	I have moderate problems doing my usual activities (3)	I have slight pain or discomfort (2)	I am moderately anxious or depressed (3)
11	MM	I have slight problems in walking about (2)	I have slight problems washing or dressing myself (2)	I have moderate problems doing my usual activities (3)	I have moderate pain or discomfort (3)	I am moderately anxious or depressed (3)
12	SP	I have moderate problems in walking about (3)	I have no problems washing or dressing myself (1)	I have moderate problems doing my usual activities (3)	I have severe pain or discomfort (4)	I am severely anxious or depressed (4)

Photo 1. Five-question health assessment system with EuroQol 5 D -5L instrument

IV .3.1. Comparison of the obtained results for EuroQol 5D -5L index with the data for the general population

comparison was made against standardized standards EuroQol 5 D -5L for the Bulgarian population. The results are presented in Table 8 as relative values. Due to the small number of women, the results are presented for both men and women. The obtained results show that the health-related quality of life in patients diagnosed with granulomatosis with polyangiitis (Wegener's granulomatosis, Wegener's disease) was dramatically worse in all five evaluation domains, and the data obtained were statistically significant - $p<0.05$.

Table 8. Comparison of the results with standardized norms EuroQol 5 D -5L for the Bulgarian population

EQ-5D-5L	Degree of severity	Norms men (n /%)	Women's norms (n /%)	Results n-12 10 men / 2 women
Mobility	No problem	361 (76.0%)	371 (70.0%)	**25.0%**
	Slight problems	72 (15, 2 %)	92 (17.3%)	**8.3%**
	Moderate problems	23 (4.8%)	46 (8, 7 %)	**41.7%**
	Severe problems	17 (3, 6 %)	19 (3.6 %)	**8.3%**
	Impossible	2 (0.4%)	2 (0, 4 %)	**16.7%**
Self-service	No problem	416 (87.5%)	452 (85.3 %)	**58.3%**
	Slight problems	43 (9, 1 %)	54 (10, 2 %)	**16.7%**
	Moderate problems	14 (3.0 %)	23 (4.3%)	**16.7%**
	Severe problems	2 (0.4%)	1 (0, 2 %)	**8.3%**
	Inability	0 (0.0%)	0 (0.0%)	**0.0%**
Usual activities	No problem	388 (81.7 %)	397 (74.9%)	**50.0%**
	Slight problems	69 (14.5%)	103 (19.4%)	**25.0%**
	Moderate problems	5 (1, 1 %)	18 (3.4%)	**8.3%**
	Severe problems	12 (2.5%)	12 (2, 3 %)	**8.3%**
	Impossible	1 (0.2%)	0 (0.0%)	**8.3%**
Pain / Discomfort	No	314 (66, 0 %)	298 (56.2%)	**41.7%**
	Light	109 (2 3.0 %)	152 (28, 7 %)	**16.7%**
	Moderate	38 (8.0%)	61 (11.5%)	**16.7%**
	Heavy	14 (3.0 %)	17 (3.2%)	**16.7%**
	Extreme	0 (0.0%)	2 (0, 4 %)	**8.3%**
Anxiety / Depression	No	343 (72, 1 %)	315 (59.4%)	**41.7%**
	Light	92 (19, 4 %)	136 (25.7 %)	**25%**
	Moderate	24 (5, 1 %)	57 (10, 8 %)	**16.7%**
	Heavy	14 (3.0 %)	16 (3.0%)	**8.3%**
	Extreme	2 (0.4%)	0 (0.0%)	**8.3%**

IV .3.2. EQ VAS - Visual analog scale

It is a self -assessment of the condition of all patients using the Visual Analog Scale. The scale resembles a thermometer and is rated from 0 to 100 points, corresponding to the following questions: **0** = The best health you can imagine and **100** = The worst health you can imagine. EQ VAS data should be presented descriptively, most commonly using a central trend meter

and a variance meter. This can be the mean and standard deviation (SD) or, if the data is skewed, the mean and interquartile range (IQR). The results obtained are presented in Table 9.

Table 9. Data from self-assessment of the condition with Visual analog scale

Total Count (N)	Missing*	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
12	0 (0.0%)	10	13	71	39.17	16.04	470	16.85	20.40	28.50	40	50	51.80	60.55

The mode is calculated at 39.17 points with a standard deviation of 16.04 and the median is 40 points. No patient evaluates their condition as very good and / or excellent. One assesses his condition as relatively good, and all the others as bad to bad - the level of self-esteem is 50 or below 50 points. Three of the patients rated themselves below 25 points, which is a sign of a critical condition. Deteriorated self-esteem is mainly due to anxiety / depression, pain / malaise and mobility. The graphical distribution is shown in Figure 1.

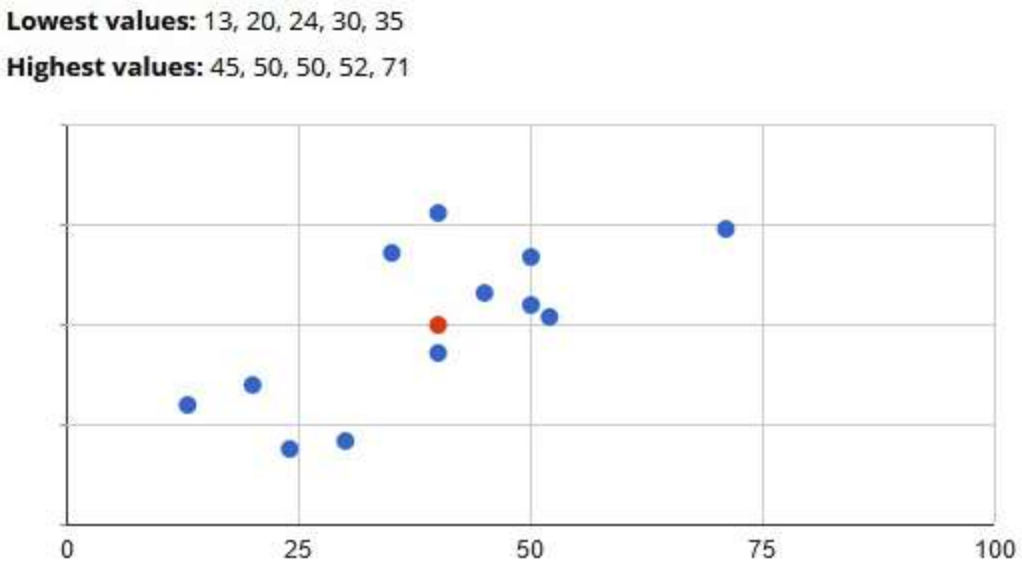

Figure 1. Self-assessment of the condition using Visual analog scale

IV .3.3. EQ VAS comparison with the general population

Standardized **EQ VAS** for the Bulgarian population they average 77.1 for women against 78.7 for men [463]. Our results show a multiple deterioration in health-related quality of life on this parameter in patients with systemic vasculitis associated with ANCA antibodies.

V .4. Assessment of health status using the tool EuroQol 5D -5L after biological treatment with Rituximab

Again, all patients answered 100% of the questions. Figure 2 presents the individual data of the patients included in the study according to the 5 dimensional reporting system. To determine the individual result, a five-digit system was used again number (perfect health - 11,111, worst health - 55,555).

DT	I have no problems in walking about (1)	I have slight problems washing or dressing myself (2)	I have slight problems doing my usual activities (2)	I have moderate pain or discomfort (3)	I am not anxious or depressed (1)
CC	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have slight pain or discomfort (2)	I am not anxious or depressed (1)
PT	I have moderate problems in walking about (3)	I have no problems washing or dressing myself (1)	I have slight problems doing my usual activities (2)	I have moderate pain or discomfort (3)	I am not anxious or depressed (1)
IG	I have moderate problems in walking about (3)	I have slight problems washing or dressing myself (2)	I have slight problems doing my usual activities (2)	I have no pain or discomfort (1)	I am moderately anxious or depressed (3)
RP	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have no pain or discomfort (1)	I am not anxious or depressed (1)
RB	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have slight pain or discomfort (2)	I am not anxious or depressed (1)
RS	I have slight problems in walking about (2)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have slight pain or discomfort (2)	I am not anxious or depressed (1)
YS	I have no problems in walking about (1)	I have slight problems washing or dressing myself (2)	I have no problems doing my usual activities (1)	I have no pain or discomfort (1)	I am not anxious or depressed (1)
IS	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have no pain or discomfort (1)	I am slightly anxious or depressed (2)
VV	I have no problems in walking about (1)	I have no problems washing or dressing myself (1)	I have no problems doing my usual activities (1)	I have slight pain or discomfort (2)	I am not anxious or depressed (1)
MM	I have slight problems in walking about (2)	I have moderate problems washing or dressing myself (3)	I have moderate problems doing my usual activities (3)	I have moderate pain or discomfort (3)	I am slightly anxious or depressed (2)
SP	I have moderate problems in walking about (3)	I have no problems washing or dressing myself (1)	I have slight problems doing my usual activities (2)	I have slight pain or discomfort (2)	I am moderately anxious or depressed (3)

Photo 2. Five-question health assessment system with EuroQol 5 D -5L instrument

V .4.1. Comparison of the results obtained for EuroQol 5 D -5L index after treatment with a biological medicinal product with the data for the general population

comparison was again made against standardized standards EuroQol 5 D -5L for the Bulgarian population. The results are presented in Table 10 as relative values. Due to the small number of women, the results are presented for both men and women.

The results show that the health-related quality of life in patients diagnosed with granulomatosis with polyangiitis (Wegener's granulomatosis, Wegener's disease) treated with the biological drug Rituximab improved significantly, both compared to the baseline visit in this study and also in comparison with the indicators of the Bulgarian population in general. In none of the domains is there a severe or extreme degree of complaints. The obtained data are statistically significant - $p<0.05$.

Table 10. Comparison of the results with standardized norms EuroQol 5D -5L for the Bulgarian population

EQ-5D-5L	Degree of severity	Norms men (n /%)	Women's norms (n /%)	Results n-12 10 men / 2 women
Mobility	No problem	361 (76.0%)	371 (70.0%)	**58.3%**
	Slight problems	72 (15, 2 %)	92 (17.3%)	**25.0%**
	Moderate problems	23 (4.8%)	46 (8, 7 %)	**16.7%**
	Severe problems	17 (3, 6 %)	19 (3.6 %)	**0 (0.0%)**
	Impossible	2 (0.4%)	2 (0, 4 %)	**0 (0.0%)**
Self-service	No problem	416 (87.5%)	452 (85.3 %)	**66.7%**
	Slight problems	43 (9, 1 %)	54 (10, 2 %)	**25.0%**
	Moderate problems	14 (3.0 %)	23 (4.3%)	**8.3%**
	Severe problems	2 (0.4%)	1 (0, 2 %)	**0 (0.0%)**
	Inability	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Usual activities	No problem	388 (81.7 %)	397 (74.9%)	**59.3%**
	Slight problems	69 (14.5%)	103 (19.4%)	**33.3%**
	Moderate problems	5 (1, 1 %)	18 (3.4%)	**8.3%**
	Severe problems	12 (2.5%)	12 (2, 3 %)	**0 (0.0%)**
	Impossible	1 (0.2%)	0 (0.0%)	**0 (0.0%)**
Pain / Discomfort	No	314 (66, 0 %)	298 (56.2%)	**41.7%**
	Light	109 (2 3.0 %)	152 (28, 7 %)	**33.3%**
	Moderate	38 (8.0%)	61 (11.5%)	**25.0%**
	Heavy	14 (3.0 %)	17 (3.2%)	**0 (0.0%)**
	Extreme	0 (0.0%)	2 (0, 4 %)	**0 (0.0%)**
Anxiety / Depression	No	343 (72, 1 %)	315 (59.4%)	**66.7%**
	Light	92 (19, 4 %)	136 (25.7 %)	**16.7%**
	Moderate	24 (5, 1 %)	57 (10, 8 %)	**16.7%**
	Heavy	14 (3.0 %)	16 (3.0%)	**0 (0.0%)**
	Extreme	2 (0.4%)	0 (0.0%)	**0 (0.0%)**

IV.4.2. EQ VAS - Visual analog scale

Table 11. Data from the self-assessment of the condition with Visual analog scale

Total Count (N)	Missing*	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
12	0 (0.0%)	9	40	100	70.08	15.63	841	48.80	56.10	62.25	70	80	84.50	91.75

The mode is calculated at 70.08 points with a standard deviation of 15.63, and the median is 70 points. Almost all patients rate their condition as very good and / or excellent. Only one assesses his condition as bad - the level of self-esteem is 40 points. All patients reported a level above 56 points. The graphical distribution is shown in Figure 2.

Lowest values: 40, 56, 57, 64, 64

Highest values: 75, 80, 80, 85, 100

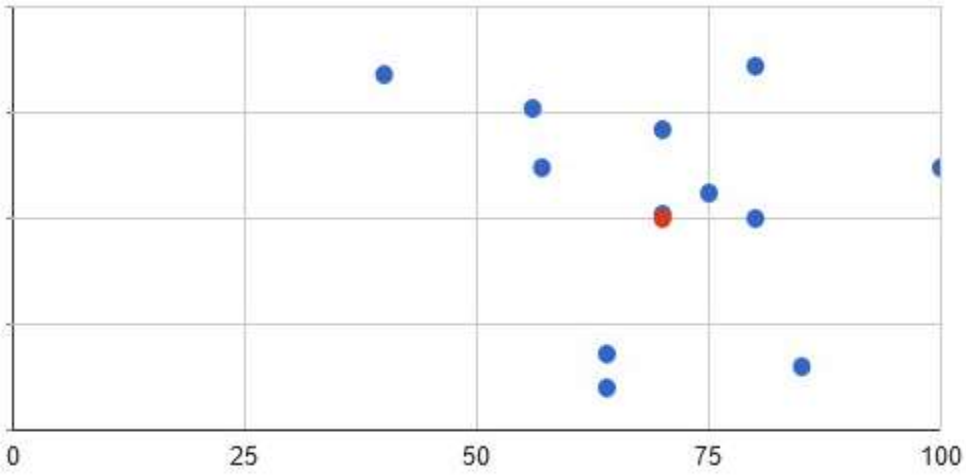

Figure 2. Self-assessment of the condition using Visual analog scale

IV .4.3. EQ VAS with the general population

Standardized **EQ VAS** for the Bulgarian population they average 77.1 for women against 78.7 for men. The results obtained by us are close to the norm for the general population.

present comparative data for EuroQol 5D -5L index between Visit 1 and Visit 2 - before biological treatment and after biological treatment and achieving remission - Table 12.

Table 12. Comparison of the results with standardized norms EuroQol 5D -5L for the Bulgarian population

EQ-5D-5L	Degree of severity	First visit	Visit after treatment	p-value (t-test)
Mobility	No problem	**25.0%**	**58.3%**	
	Slight problems	**8.3%**	**25.0%**	
	Moderate problems	**41.7%**	**16.7%**	**0.008**
	Severe problems	**8.3%**	**0 (0.0%)**	
	Impossible	**16.7%**	**0 (0.0%)**	
Self-service	No problem	**58.3%**	**66.7%**	
	Slight problems	**16.7%**	**25.0%**	
	Moderate problems	**16.7%**	**8.3%**	**0.027**
	Severe problems	**8.3%**	**0 (0.0%)**	
	Inability	**0.0%**	**0 (0.0%)**	
Usual activities	No problem	**50.0%**	**59.3%**	
	Slight problems	**25.0%**	**33.3%**	
	Moderate problems	**8.3%**	**8.3%**	**0.015**
	Severe problems	**8.3%**	**0 (0.0%)**	
	Impossible	**8.3%**	**0 (0.0%)**	
Pain / Discomfort	No	**41.7%**	**41.7%**	
	Light	**16.7%**	**33.3%**	
	Moderate	**16.7%**	**25.0%**	**0.003**
	Heavy	**16.7%**	**0 (0.0%)**	
	Extreme	**8.3%**	**0 (0.0%)**	
Anxiety / Depression	No	**41.7%**	**66.7%**	
	Light	**25%**	**16.7%**	
	Moderate	**16.7%**	**16.7%**	**0.013**
	Heavy	**8.3%**	**0 (0.0%)**	
	Extreme	**8.3%**	**0 (0.0%)**	

We made a comparative analysis of the results of the self-assessment of the situation with the Visual Analogue Scale between Visit 1 and Visit 2. The comparison is shown in Table 13.

Table 13. Status Self-Assessment with Visual Analog Scale - Comparison between Visit 1 and Visit 2

Visits	Total Count (N)	Missing *	Unique	Min	Max	Mean	StDev	Sum	Percentile						
									0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
visit 1	12	0 (0.0%)	10	13	71	**39.17**	16.04	470	16.85	20.40	28.50	**40**	50	51.80	60.55
visit 2	12	0 (0.0%)	9	40	100	**70.08**	15.63	841	48.80	56.10	62.25	**70**	80	84.50	91.75

IV .5. Assessment of health status using the tool SF-36v2 Health Survey before conducting biological treatment

We present the results of health status assessment using the tool SF -36 v 2 Health Survey of Visit 1, which takes place before the start of biological treatment.

Participants answered the questions retrogradely by describing their condition 4 weeks ago. All analyzes are made in accordance with User 's manual for the SF -36 in 2 Health Survey (3 rd ed .) , 2011.

SF -36 v 2 uses norm-based estimation based on a linear T-score transformation method. A normal result for each of the scales of the respective health domain is considered to be a mean of 50 and a standard deviation (SD) of 10, calculated on the basis of the total US population for 2009.

These standards are considered standard and have been recalculated for all geographical regions of the world. Thus, estimates above and below 50 are above and below the average for the general population, respectively. With a standard deviation of 10, any difference of 1 point or change in the results has a direct meaning - 1 point is one tenth of the standard deviation or the size of the effect is 10 units.

Data quality is assessed through a series of indicators: completeness of data; answers within a given range; sequence of answers; internal consistency of data; discriminatory validity and reliability of data.

Data quality indicators are defined as follows:

1. Percentage of completed responses (within range) divided by the total possible number of responses (* N items).
2. Percentage of answers to the questions in the range of answer codes printed in the questionnaire.
3. Percentage of subjects without conflicting responses in the response sequence index (score = 0).

4. Percentage of subjects for whom all scales are computable.
5. Percentage of elements for which the correlation level (adjusted for overlap) is 0.40 or higher on their hypothetical scale.
6. Percentage of elements that correlate significantly higher with their hypothetical scale than with competing scales.
7. Percentage of scales with Cronbach's alpha coefficients greater than or equal to 0.70.

Table 14. Evaluation of the quality of pre-biological questionnaire data in patients with ANCA vasculitis

Data quality indicators:	**Satisfactory norms**		
1. Completeness of data Items with 5% or more missing values: **None**	**100.0%**	**YES**	**90%**
2. Responses within Range Items with 5% or more out-of-range values: **None**	**100.0%**	**YES**	**100%**
3. Sequence of answers	**100.0%**	**YES**	**90%**
4. Estimable Scale Scores Estimable without MDE Estimable with Half-Scale MDE Estimable with Full MDE	**100.0%** **100.0%** **100.0%**	**YES**	**90%**
5. Item Internal Consistency Items that failed internal consistency test: **GH05**	**97.1%**	**YES**	**90%**
6. Discriminant validity Items that failed discriminant validity test: **3 - PF02 PF03 PF09** **2 - RP03 RP04** **5 - GH01 GH02 GH03 GH04 GH05** **2 - VT01 VT03** **2 - SF01 SF02** **2 - MH04 MH05**	**77.1%**	**NO**	**80%**
7. Reliable Scales Element that does not meet the criteria for data reliability: **GH**	**87.5%**	**NO**	**100%**

The criterion for assessing the quality of the data № 6. Discriminant validity is below the norm of 80% - there is a deviation of 2.9%. 15 elements of the quality indicators do not cover the tests for discriminant validity - 3 - PF02 PF03 PF09; 2 - RP03 RP04; 5 - GH01 GH02 GH03 GH04 GH05; 2 - VT01 VT03; 2 - SF01 SF02 and 2 - MH04 MH05.
The greatest dispersion of responses is within the General Health (GH) domain. All responses were reviewed and validated. We believe that these deviations can be considered a deviation within the statistical error.

It is essential to determine the internal and constructive validity of the source data. It is important to distinguish between and constructive validity. Internal validity is a methodology

that allows us to exclude alternative explanations for dependent variables, while the validity of the design allows the tool to capture latent variables. Constructive validity has three components: convergent, discriminant and nomological validity.

Discriminatory validity is understood and assumed that the elements must correlate higher with each other than they correlate with other elements of other constructions that are theoretically assumed not to correlate (hypothetical correlations).

Out of 315 elements in the correlation matrix, in 38 elements (12.5%) the level of correlation is below 0.40. The level of reliability is 87.5%.

Table 15. Multifunctional / multi-item correlation matrix

Domain	PF	RP	BP	GH	VT	SF	RE	MH
PF - Physical functioning								
PF01	**0.76 ***	0.65	0.47	0.52	0.67	0.67	0.68	0.47
PF02	**0.87 ***	0.73	**0.38**	0.68	0.78	0.80	0.89	0.58
PF03	**0.90 ***	0.92	0.56	0.67	0.94	0.82	0.96	0.77
PF04	**0.76 ***	0.57	0.40	0.39	0.54	0.63	0.63	0.37
PF05	**0.85 ***	0.73	0.53	0.70	0.82	0.81	0.68	0.74
PF06	**0.89 ***	0.71	0.42	0.52	0.66	0.81	0.81	0.49
PF07	**0.95 ***	0.90	0.65	0.63	0.92	0.81	0.91	0.73
PF08	**0.93 ***	0.81	0.43	0.74	0.81	0.89	0.84	0.73
PF09	**0.92 ***	0.76	**0.39**	0.79	0.82	0.93	0.80	0.72
PF10	**0.84 ***	0.79	**0.34**	0.67	0.82	0.77	0.74	0.78
RP - Role Physical								
RP01	0.59	**0.82 ***	0.46	**0.22**	0.70	0.59	0.63	0.48
RP02	0.57	**0.76 ***	0.59	**0.09**	0.64	0.47	0.55	0.40
RP03	0.94	**0.70 ***	0.45	0.69	0.84	0.89	0.95	0.66
RP04	0.89	**0.86 ***	0.63	0.69	0.98	0.77	0.92	0.82
BP - Bodily pain								
BP01	0.50	0.66	**0.94 ***	**0.25**	0.60	0.50	0.69	0.38
BP02	0.49	0.52	**0.94 ***	**0.27**	0.53	0.43	0.58	0.34
GH - General health								
GH01	0.54	**0.22**	**0.01**	**0.49 ***	**0.35**	0.62	**0.36**	**0.31**
GH02	**0.22**	**0.13**	**-0.04**	**0.45 ***	**0.31**	**0.31**	**0.24**	0.65
GH03	**0.20**	**0.05**	**0.11**	**0.48 ***	**0.17**	**0.28**	**0.17**	0.52
GH04	0.77	0.63	0.44	**0.52 ***	0.84	0.70	0.76	0.71
GH05	0.72	0.53	**0.39**	**0.35 ***	0.62	0.65	0.58	0.41

VT - Vitality								
VT01	0.77	0.89	**0.37**	0.40	**0.64 ***	0.73	0.77	0.52
VT02	0.74	0.77	0.56	0.72	**0.85 ***	0.67	0.75	0.77
VT03	0.79	0.74	0.49	0.74	**0.79 ***	0.63	0.80	0.90
VT04	0.78	0.76	0.64	0.62	**0.87 ***	0.65	0.83	0.69
SF - Social Functioning								
SF01	0.88	0.69	**0.29**	0.78	0.77	**0.68 ***	0.77	0.65
SF02	0.75	0.74	0.61	0.55	0.59	**0.68 ***	0.74	0.38
RE - Role Emotional								
RE01	0.87	0.87	0.63	0.63	0.89	0.79	**0.97 ***	0.67
RE02	0.87	0.88	0.70	0.64	0.93	0.81	**0.95 ***	0.71
RE03	0.88	0.80	0.56	0.61	0.81	0.82	**0.93 ***	0.56
MH - Mental Health								
MH01	0.55	0.48	**0.37**	0.59	0.62	**0.36**	0.42	**0.76 ***
MH02	0.49	0.51	**0.12**	0.58	0.63	**0.29**	**0.41**	**0.70 ***
MH03	**0.15**	**0.14**	**0.12**	0.44	**0.34**	**-0.03**	**0.18**	**0.55 ***
MH04	0.93	0.79	0.52	0.83	0.88	0.92	0.89	**0.67 ***
MH05	0.72	0.69	**0.30**	0.78	0.79	0.77	0.71	**0.66 ***

Notes:
* The position has been adjusted due to the possibility of overlap. Positions marked with an asterisk have the highest degree of correlation.
1. Convergent validity is defined as poor when the correlation level is below 0.40 or higher than the corresponding hypothetical value.
2. We have poor discriminant validity when the elements correlate significantly higher with competing scores / scales than with their hypothetical value.

The software product evaluates the results for reliability and homogeneity. Reliability is measured by Cronbach's Alpha factor. This factor is an indicator of how well the different elements complement each other in their measurement of different aspects of the same variable or quality.

Values vary between zero and one. Values closer to one show higher internal consistency, values close to zero show lower internal consistency. A level above 0.70 is considered acceptable. The results on the elements (domains) are considered reliable and homogeneous only when for 100% of the elements the Cronbach's Alpha factor is above the value of 0.70.
And with this indicator, in our study we find that in the General Health domain the result is below the norm - 0.678 or 0.022 units below the norm. We accept that this result is insignificant in terms of statistical significance, and the results obtained by us are reliable and homogeneous.
The internal consistency between the elements is measured by the coefficient for average correlation between the elements - Rii (Average inter-item correlation). The norms for the methods are presented in Table 16 and the results in Table 17. The results obtained are reliable and homogeneous in all domains.

Table 16. Reliability standards

Reliability	Criteria for good evaluation
Cronbach's Alpha	**≥ 0, 70**
Range of inter-item correlations	**0, 15 ÷ 0, 85**
Average inter-item correlation	**0, 15 ÷ 0, 50**
Cronbach alpha's scope if the item is removed	**Removing an element reduces Cronbach's alpha level below 0.70**
Range of corrected item - scale correlations	**≥ 0 50**

Table 17. Scale Reliability and Homogeneity Estimates for different domains

Scale	K *	Rtt **	Rii ***
PF - Physical Functioning	10	0.970	0.766
RP - Physical Role	4	0.902	0.696
BP - Bodily Pain	2	0.952	0.908
GH - General Health	5	**0.678**	0.297
VT - Vitality	4	0.898	0.688
SF - Social Functioning	2	0.789	0.651
RE - Emotional Role	3	0.976	0.931
MH - Mental Health	5	0.849	0.529

* k = number of positions

** Rtt (Reactions to tests Scale) = Cronbach's Alpha Factor; *** Rii (Average inter-item correlation)

The summarized results for the health-related quality of life in the two main domains - physical and mental components are presented in Figure 3. The quality of life measured by both criteria in 75% of respondents (patients with ANCA-associated vasculitis) is below the norm for the general population.

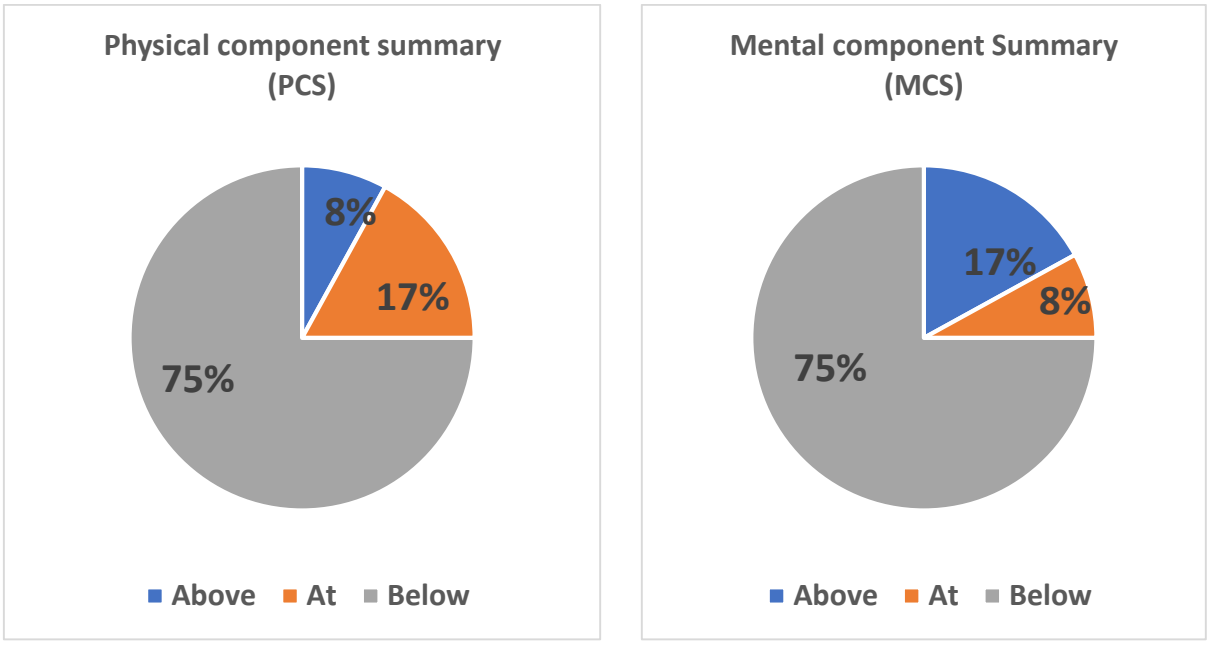

Figure 3. Summary results for the physical and mental component of the health condition

A summary comparative analysis of the results of the physical and mental component and their constituent elements in absolute and relative quantities is presented in Figure 4.

Obviously, it must be concluded that according to none of the elements that form the health-related quality of life, the respondents are not defined in normal and / or good health and do not fall into the group of healthy people from the general population.

The worst results are in physical functioning, emotional state and the feeling of general health, and in general health we must not forget that we conduct the analyzes despite the low results for reliability and discriminatory validity.

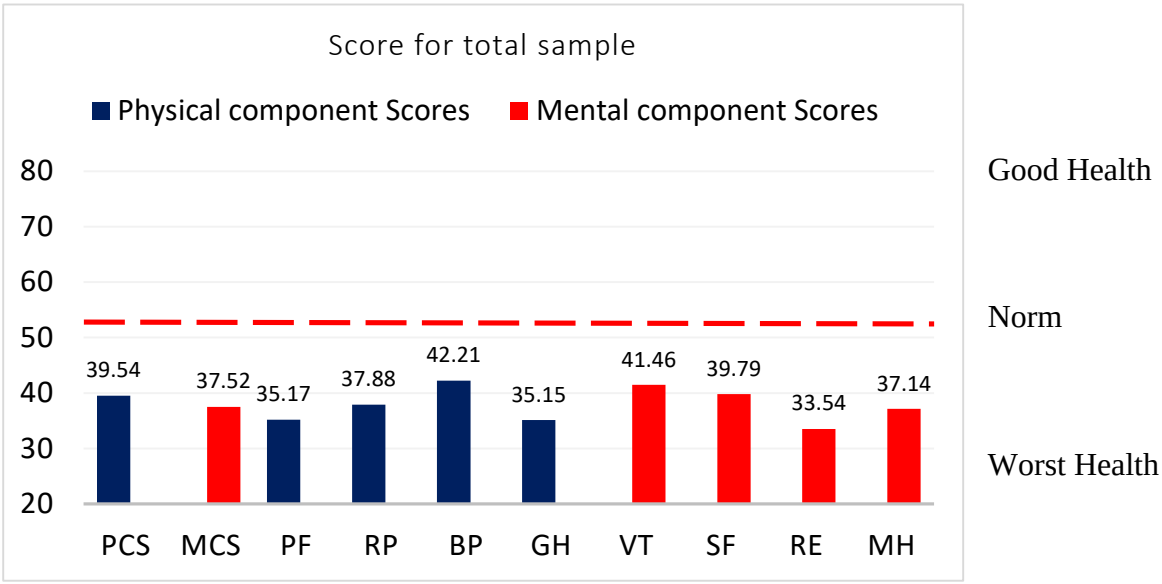

Figure 4. Total sample by elements

SF36v2 questionnaire is often used as a screening test for depression. The data for assessing depression in our group of patients are presented in Figure 5. 66% of patients are definitely depressed.

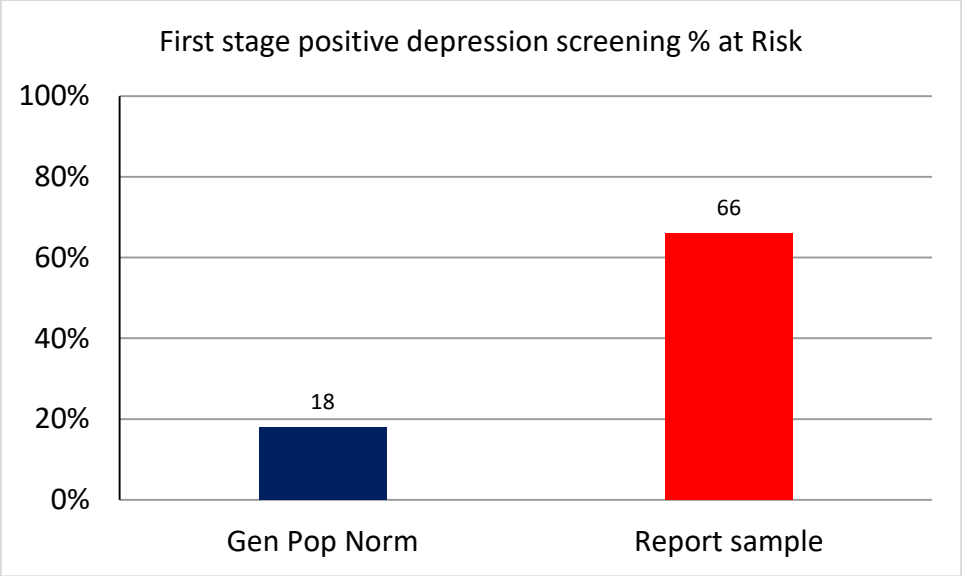

Figure 5. SF36v2 as a screening for depression

In Table 18 we present the metric conversion of health status data into absolute values - so norm-based results scores). The mean values correspond to the data in Figure 4. The population norm for the arithmetic mean and median is 50, with a standard deviation of 10.

Table 18. SF-36 v 2 - Summary analysis of measurements and their results based on norms for the general population

	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Mean	**36.17**	**37.88**	**42.21**	**35.16**	**41.46**	**39.79**	**33.54**	**37.13**	**39.53**	**37.52**
25th Percentile	21.18	24.60	28.53	29.65	28.83	29.77	16.13	24.71	31.24	26.39
50th Percentile (Median)	**38.40**	**39.19**	**40.43**	**35.59**	**40.72**	**42.30**	**31.80**	**41.71**	**41.36**	**39.61**
75th Percentile	47.97	47.05	62.00	42.01	52.60	52.33	49.20	46.94	44.81	45.94
Standard Deviation	**14.37**	**12.72**	**16.41**	**8.81**	**13.94**	**14.58**	**16.89**	**13.58**	**10.49**	**13.73**
Min	19.26	21.23	21.68	18.95	22.89	17.23	14.39	16.86	22.53	17.74
Max	57.54	57.16	62.00	49.86	67.45	57.34	56.17	56.10	55.78	58.82
N	12	12	12	12	12	12	12	12	12	12

Nowadays, the results are based on norms scores) are denoted as T Score. T score is a linear transformation of the results of the summary summaries of the two main SF domains of health status and constituent components, which allows us to more easily interpret the results obtained

relative to the general population data. Using the T scale transforms data metrically from 0–100 with mean (mean) 50 and standard deviation (SD) 10.

Table 19. SF-36v2 - Scale of results, transformed data 0-100 (T Scores)

	PF	RP	BP	GH	VT	SF	RE	MH
Mean	**44.17**	**46.35**	**50.92**	**34.08**	**39.06**	**56.25**	**45.83**	**48.75**
25th Percentile	5.00	9.38	17.00	22.50	12.50	31.25	4.17	25.00
50th Percentile (Median)	**50.00**	**50.00**	**46.50**	**35.00**	**37.50**	**62.50**	**41.67**	**57.50**
75th Percentile	75.00	71.88	100.00	48.50	62.50	87.50	83.33	67.50
Standard Deviation	**37.53**	**35.40**	**40.69**	**18.52**	**29.33**	**36.35**	**40.44**	**25.95**
Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	10.00
Max	100.00	100.0	100.00	65.00	93.75	100.00	100.0	85.00
N	12	12	12	12	12	12	12	12

IV .6. Assessment of health status using the tool SF -36 v 2 Health Survey after biological treatment

We present the results of health status assessment using the tool SF -36 v 2 Health Survey of Visit 2, which takes place after the biological treatment. The participants answered the questions retrogradely, describing their condition for the past period of time - 6 months. All analyzes are made in accordance with User 's manual for the SF -36 in 2 Health Survey (3 rd ed.), 2011. The quality of the data and the results obtained are presented by analogy with the study before biological treatment.

Table 20. Evaluation of the quality of pre-biological questionnaire data in patients with ANCA vasculitis

Data quality indicators:	**Standard norms**		
1. Completeness of data Items with 5% or more missing values: **None**	**100.0%**	**YES**	**90%**
2. Responses within Range Items with 5% or more of out of range values: **None**	**100.0%**	**YES**	**100%**
3. Consistent Responses	**100.0%**	**YES**	**90%**
4. Estimable Scale Scores Estimable without MDE Estimable with Half-Scale MDE Estimable with Full MDE	**100.0%** **100.0%** **100.0%**	**YES**	**90%**
5. Item Internal Consistency Items that failed internal consistency test: **GH01 GH04**	**94.3%**	**YES**	**90%**
6. Discriminatory validity Items that failed discriminant validity test: **6 - PF01 PF03 PF05 PF06 PF07 PF10** **2 - RP01 RP04** **5 -GH01 GH02 GH03 GH04 GH05** **2 -VT01 VT03** **1 - SF02** **5 - MH01 MH02 MH03 MH04 MH05**	**73.9%**	**NO**	**80%**
7. Reliable Scales Scales that failed reliability criteria: **BP, GH**	**75.0%**	**NO**	**100%**

Data quality indicators shall be defined and assessed in a similar manner as described in Section IV .5. The criterion for assessing the quality of the data № 6. Discriminant validity is below the norm of 80% - there is a deviation of 6.1%. 21 elements of the quality indicators do not cover the tests for discriminant validity - 6 - PF01 PF03 PF05 PF06 PF07 PF10; 2 - RP01 RP04; 5 - GH01 GH02 GH03 GH04 GH05; 2 -VT01 VT03; 1 - SF02; 5 - MH01 MH02 MH03 MH04 MH05.

The largest dispersion of responses is within the domains Physical Functioning (PF), Mental Health (MH) and General Health (GH). All responses were reviewed and validated.

The level of reliability of the data in the domains Vitality and General Health is 25% below the norm. We believe that this is due to the wide range of answers given - in the group Vitality the range is from 1 to 6, and in General Health - from 1 to 5. On the one hand there is an extremely diverse clinical picture in patients with systemic vasculitis, and on the other country, the small number of 12 patients gives a high relative weight to the differences in responses.

Of the 315 elements in the correlation matrix, 76 elements (25%) had a correlation level below 0.40 (Table 21). The level of reliability is 75%, as indicated in Table 20. The low reliability is due to the low degree of correlation of the elements Vitality and General Health. The deviations are due to the dynamics of clinical symptoms and the subjective feeling in different patients.

Table 21. Multitrait / multi-item correlation matrix

Domain	PF	RP	BP	GH	VT	SF	RE	MH
PF - Physical functioning								
PF01	**0.52 ***	0.70	**-0.23**	0.71	0.70	0.71	0.65	0.75
PF02	**0.75 ***	0.44	**-0.18**	**0.29**	0.50	0.62	0.67	0.38
PF03	**0.74 ***	0.47	**-0.02**	0.48	0.53	0.55	0.80	0.59
PF04	**0.84 ***	0.59	**-0.33**	0.57	0.62	0.65	0.75	0.72
PF05	**0.48 ***	0.71	**0.33**	0.56	0.78	0.51	0.43	0.54
PF06	**0.55 ***	**0.20**	**-0.20**	**0.30**	**0.35**	**0.28**	0.60	**0.31**
PF07	**0.60 ***	0.67	0.44	**0.36**	0.68	**0.39**	0.60	0.48
PF08	**0.78 ***	**0.39**	**-0.05**	**0.36**	0.42	0.55	0.59	0.47
PF09	**0.76 ***	**0.35**	**-0.10**	0.50	0.43	0.72	0.65	0.49
PF10	**0.66 ***	0.49	**-0.39**	**0.11**	0.42	0.69	0.56	0.28
RP - Role Physical								
RP01	0.63	**0.89 ***	**0.27**	0.53	0.92	0.63	0.64	0.61
RP02	0.61	**0.97 ***	**0.29**	0.48	0.90	0.66	0.60	0.56
RP03	0.61	**0.97 ***	**0.29**	0.48	0.90	0.66	0.60	0.56
RP04	0.78	**0.62 ***	**0.04**	0.49	0.72	0.83	0.80	0.53
BP - Physical pain								
BP01	**0.09**	**0.34**	**0.48 ***	**0.35**	0.44	**0.02**	**0.04**	**0.32**
BP02	**-0.19**	**0.12**	**0.48 ***	**-0.14**	**0.09**	**-0.21**	**-0.13**	**-0.15**
GH - General health								
GH01	0.76	0.69	0.50	**0.29 ***	0.80	0.55	0.65	0.62
GH02	0.48	0.74	**0.34**	**0.57 ***	0.80	0.44	0.55	0.78
GH03	**0.37**	**0.25**	**-0.12**	**0.56 ***	**0.28**	0.62	0.45	0.69

GH04	**-0.01**	**-0.06**	**-0.46**	**-0.31 ***	**0.02**	**0.01**	**0.17**	**-0.19**
GH05	**0.25**	**-0.01**	**-0.14**	**0.61 ***	**0.18**	**0.33**	0.52	0.70
VT - Vitality								
VT01	0.57	0.87	**0.19**	0.68	**0.82 ***	0.61	0.76	0.72
VT02	0.75	0.74	**0.37**	0.74	**0.77 ***	0.55	0.72	0.69
VT03	0.82	0.91	**0.06**	0.47	**0.82 ***	0.82	0.75	0.55
VT04	0.66	0.88	**0.36**	0.56	**0.90 ***	0.56	0.66	0.63
SF - Social Functioning								
SF01	0.48	0.67	**-0.10**	0.56	0.59	**0.71 ***	0.62	0.49
SF02	0.89	0.71	**-0.14**	0.66	0.69	**0.71 ***	0.83	0.73
RE - Role Emotional								
RE01	0.78	0.70	**-0.10**	0.70	0.79	0.67	**0.93 ***	0.81
RE02	0.91	0.67	**-0.11**	0.72	0.77	0.79	**0.95 ***	0.80
RE03	0.79	0.71	**0.02**	0.83	0.78	0.85	**0.91 ***	0.82
MH - Mental Health								
MH01	**0.25**	**0.12**	**-0.22**	0.50	**0.05**	0.48	0.41	**0.47 ***
MH02	0.84	0.68	**0.21**	0.51	0.73	0.55	0.57	**0.48 ***
MH03	**0.37**	0.47	**0.17**	0.80	0.56	**0.36**	0.58	**0.67 ***
MH04	0.64	**0.32**	**-0.20**	0.64	0.45	0.50	0.81	**0.60 ***
MH05	0.77	0.68	**0.09**	0.88	0.82	0.75	0.81	**0.73 ***

The levels of connection between the elements are measured in numerical value: 1, 2, -1, -2. Again, in the General Health domain, low values of the measured relationships between the elements are found - there is a correlation with the results for reliability. Mental health outcomes are marginal for the most part - there is more of a hypothetical relationship than measured with other components of assessment.

Reliability data are presented in Table 22. In the General Health domain, the result is below the norm - 0.604 or 0.096 units below the norm, with a normal coefficient of average correlation between the elements - Rii = 0.234.

Compared to pre-treatment tests, we found a low level of reliability through Cronbach's Alpha Factor for the Physical Pain component - 0.497, with a normal mean correlation coefficient between the elements - Rii = 0.331.

Table 22 . Reliability and homogeneity ratings for different domains

Scale	K *	Rtt **	Rii ***
PF - Physical Functioning	**10**	**0.893**	**0.456**
RP - Physical Role	**4**	**0.940**	**0.797**
BP - Bodily Pain	**2**	**0.497**	**0.331**
GH - General Health	**5**	**0.604**	**0.234**
VT - Vitality	**4**	**0.925**	**0.754**
SF - Social Functioning	**2**	**0.817**	**0.691**
RE - Emotional Role	**3**	**0.960**	**0.889**
MH - Mental Health	**5**	**0.769**	**0.399**

The summarized results for the health-related quality of life in the two main domains - physical and mental components are presented in Figure 6. The quality of life measured by both criteria in 75% of respondents (patients with ANCA-associated vasculitis) was above the norms for the general population, in contrast to the data for both components before treatment, where 75% of respondents were according to the norms for the general population.

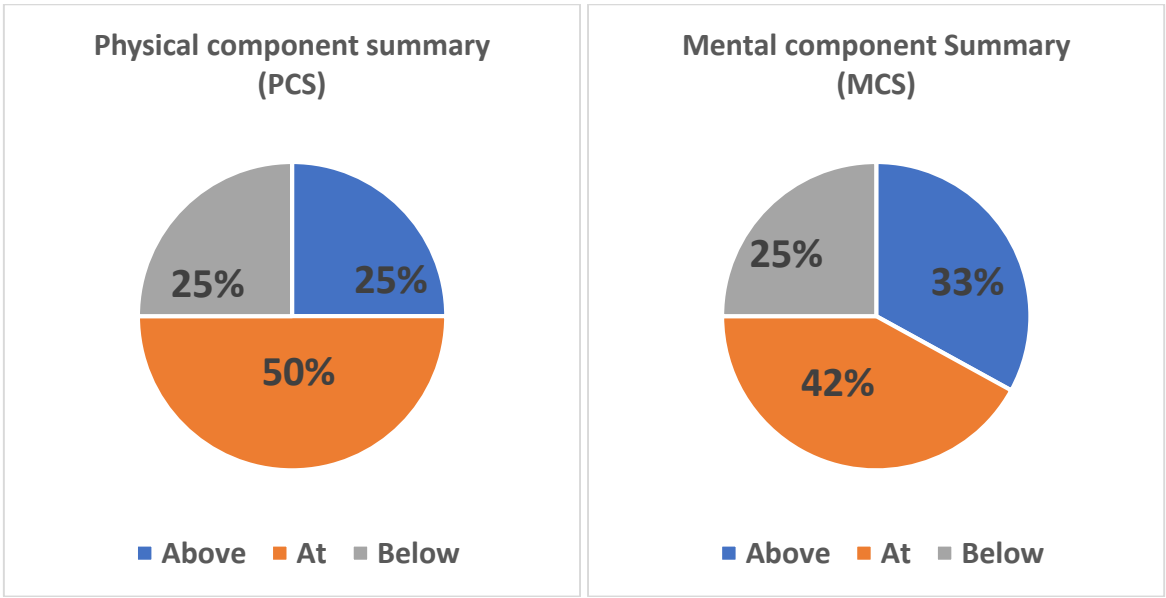

Figure 6. Summarized results for the physical and mental component of the health condition

A summary comparative analysis of the results of the physical and mental component and their constituent elements in absolute and relative quantities is presented in Figure 7.

Obviously, it must be concluded that in almost all of the elements that form the health-related quality of life, the respondents are defined in normal and / or good health and fall into the group of healthy people from the general population.

Only in four components the results are below the norm of 50 - physical functioning 49.41; physical role - 45.56; social functioning - 49.4 and emotionality - 47.17. Physical and social functioning are within the statistical error.

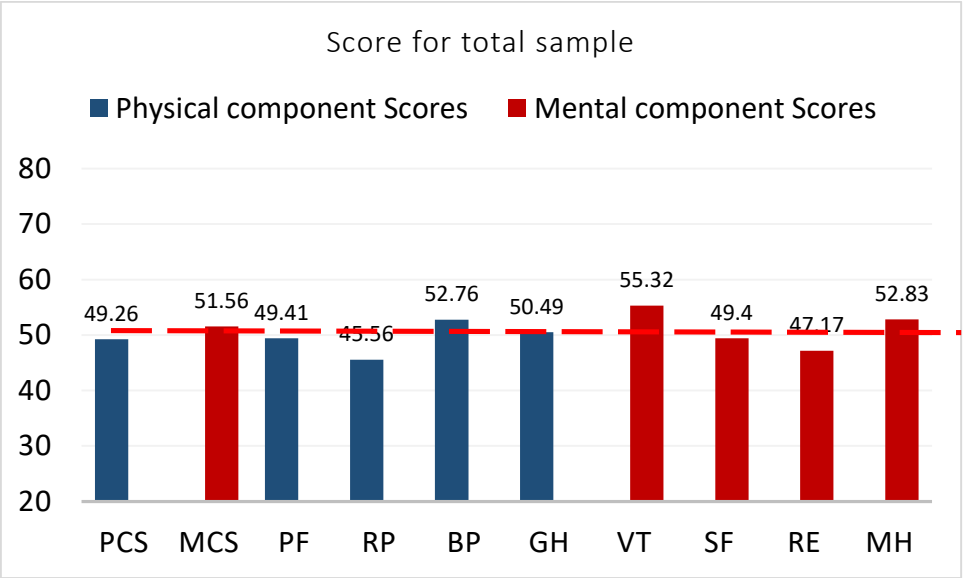

Figure 7. Total sample by elements

As already mentioned in the general section, the SF 36 v 2 questionnaire can be used as a test for screening for depression.

The data for the assessment of depression in our group of patients after treatment are the limits of the norm for the general population. Only 16% of patients are depressed with a population norm of 18%.

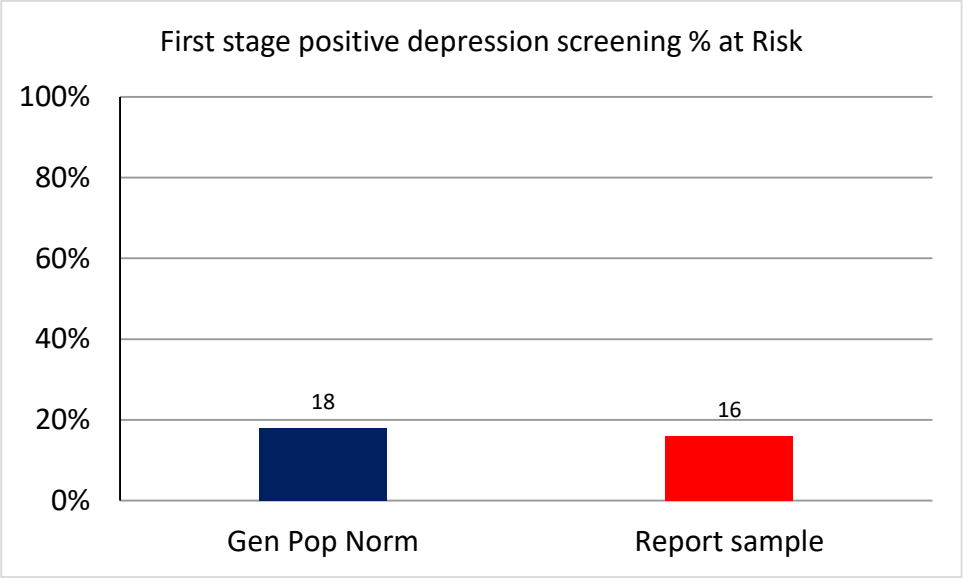

Figure 8. SF 36 v 2 as a screening for depression

Table 23 presents the metric conversion of health status data into absolute values – norm-based-scores).

mean values correspond to the data in Figure 37. The population norm for the arithmetic mean and median is 50, with a standard deviation of 10.

Table 23. SF36v2 - Summary analysis of measurements and their results based on norms for the general population

	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Mean	**49.41**	**45.55**	**52.76**	**50.49**	**55.32**	**49.40**	**47.17**	**52.83**	**49.26**	**51.65**
25th Percentile	45.10	40.31	46.68	43.20	48.14	44.81	42.24	45.64	45.02	44.05
50th Percentile (Median)	**51.80**	**47.05**	**51.51**	**52.00**	**55.57**	**49.82**	**45.72**	**53.48**	**49.12**	**52.00**
75th Percentile	55.63	53.79	62.00	57.94	65.96	57.34	56.17	60.02	54.91	60.45
Standard Deviation	**7.57**	**9.90**	**7.50**	**8.40**	**11.00**	**7.84**	**8.59**	**8.13**	**6.02**	**8.76**
Min	32.66	27.96	42.24	35.59	34.77	32.27	31.80	43.02	37.68	38.33
Max	57.54	57.16	62.00	62.70	67.45	57.34	56.17	63.95	58.04	63.93
N	12	12	12	12	12	12	12	12	12	12

Table 24 presents transformed data **(T Scores)** from 0–100 with mean (mean) 50 and standard deviation (SD) 10.

Table 24. SF-36v2 - Scale of Results, Transformed Data 0-100 (T Scores)

	PF	RP	BP	GH	VT	SF	RE	MH
Mean	**78.75**	**67.71**	**77.08**	**66.33**	**68.23**	**80.21**	**78.47**	**78.75**
25th Percentile	67.50	53.13	62.00	51.00	53.13	68.75	66.67	65.00
50th Percentile (Median)	**85.00**	**71.88**	**74.00**	**69.50**	**68.75**	**81.25**	**75.00**	**80.00**
75th Percentile	95.00	90.63	100.00	82.00	90.63	100.00	100.00	92.50
Standard Deviation	**19.78**	**27.55**	**18.60**	**17.66**	**23.15**	**19.55**	**20.55**	**15.54**
Min	35.00	18.75	51.00	35.00	25.00	37.50	41.67	60.00
Max	100.00	100.00	100.00	92.00	93.75	100.00	100.00	100.00
N	12	12	12	12	12	12	12	12

V. DISCUSSION

The frequency of newly diagnosed patients in Bulgaria with Wegener's granulomatosis is estimated between 14.7 - 100.80 with a median of 43.05. No literature and official data from the national statistics on the actual total number of patients with Wegener's Granulomatosis for the period 2018-2021 are found. We consider the presence of no more than 40 to 60 patients with this disease in Bulgaria to be acceptable, and those diagnosed are not more than 20 or as a relative share not more than 30% of the total.

In the 12 patients included in the study, we can assume that the analyzed population represents 81.6% of the total number of patients as newly diagnosed cases with regression to 11.9% of the maximum frequency. The size of the population analyzed by us, calculated through the total number of patients with the above acceptable assumptions, is not less than 60% of all patients in Bulgaria.

mean age of the monitored men was 52.4 years, the median was 53 years, with SD 13.54 years. The mean age of the women followed was 55.5 years - there were only two women in the study.

The average duration of the disease is from 1 to 13 years with a median of 5 years. The time for diagnosis - in 58.3% (7 patients) up to 1 month, in 3 cases is up to half a year, in 1 patient - 1 year, and in the second case - 7 years.

BVAS activity was assessed by constant points (BVAS - Persistent points) from 0 to 33. The minimum number of points of persistent type according to BVAS is 6 and the maximum is 33, with a median of 17 points. The group we analyzed was assessed as moderately severe BVAS activity version 3, not forgetting the fact that all patients received conventional treatment.

Assessment of health status using the tool EuroQol 5D -5L before conducting biological treatment

The values of the EQ-5D index illustrate society's understanding of health and range from -0.590 to 1.0, where negative values correspond to poor health (conditions worse than death), and 1.0 corresponds to perfect health. The health-related quality of life in patients diagnosed with granulomatosis with polyangiitis was worsened in all five evaluation domains, and the data were statistically significant.

Self-assessment of the condition with Visual analog scale.
Standardized EQ standards YOU for the Bulgarian population are average 77.1 for women, 78.7 average for men. Our results - mode 39.17, standard deviation 16.04 and median 40 points show a multiple deterioration in health-related quality of life on this parameter in patients with systemic vasculitis associated with ANCA antibodies.

No patient evaluates their condition as very good and / or excellent. One assesses his condition as relatively good, and all the others as bad to bad - the level of self-esteem is 50 or below 50 points. Three of the patients rated themselves below 25 points, which is a sign of a critical condition. Deteriorated self-esteem is mainly due to anxiety / depression, pain / malaise and mobility.

comparison was again made against standardized standards EuroQol 5D -5L for the Bulgarian population. The results show that the health-related quality of life in patients diagnosed with granulomatosis with polyangiitis treated with the biological drug Rituximab is significantly improved, both compared to the baseline visit in this study and compared to the indicators of the Bulgarian population. at all. In none of the domains is there a severe or extreme degree of complaints. The mode is calculated at 70.08 points with a standard deviation of 15.63, and the median is 70 points. Almost all patients rate their condition as very good and / or excellent. Only one assesses his condition as bad - the level of self-esteem is 40 points. All patients reported a level above 56 points.

Self-assessment of the condition with Visual Analog Scale at Visit 2 after treatment with Rituximab shows results close to the norm for the general population.

Assessment of health status using the tool SF-36v2 Health Survey before conducting biological treatment

The impression of problematic characterization of the general health by the respondents is confirmed - only 1 patient (8.3%) declares a feeling of normal general health, while all the other 11 declare deteriorated general health. The presence of physical pain was found in 7 patients (59%). Respectively, 7 and 8 patients report worsened, below the norms for the general population, physical and role functioning. On a weighted average of all four elements, 75% of patients reported severely deteriorating health status.

The elements forming the mental component - vitality, social functioning, emotional functioning and mental health are as follows: vitality - the relative share of those declaring normal and better than normal vitality are 42%, while 58% do not feel vital; 50% of patients describe themselves as socially excluded, and 75% as lost and / or severely deteriorating their emotionality; 50% of respondents rate their mental health as worse than normal.

According to none of the elements that form the health-related quality of life, the respondents are not defined in normal and / or good health and do not fall into the group of healthy people from the general population. The worst results are in physical functioning, emotional state and the feeling of general health.

Depression assessment data show that 66% of patients are definitely depressed at a population rate of 18%.

Assessment of health status using the tool SF-36v2 Health Survey after biological treatment

The summarized results for health-related quality of life in the two main domains - physical and mental components show that the measured quality of life in both criteria in 75% of patients is above normal for the general population, in contrast to data for both components before treatment. where 75% of the respondents were according to the norms for the general population.

Qualitative and quantitative improvement of all components of the physical health domain is established - according to all indicators the patients enter the norms for the population in relative shares over 60%, with an average value of 70.5%.

The elements forming the mental component - vitality, social functioning, emotional functioning and mental health are as follows: vitality - the relative share of those declaring normal and better than normal vitality are 83%; 75% of patients identify themselves as fully socialized; again, 75% are defined as emotionally stable; 83% of respondents describe their mental health as normal and better than normal for the general population.

Respondents are defined in normal and / or good health in almost all of the elements that form the health-related quality of life and fall into the group of healthy people from the general population. Only in four components the results are below the norm of 50 - physical functioning 49.41; physical role - 45.56; social functioning - 49.4 and emotionality - 47.17. Physical and social functioning are within the statistical error.

Only 16% of patients are depressed, with a population norm of 18%.

VI. MAIN CONCLUSIONS FROM THE DISSERTATION

CONCLUSIONS

1. We found that the time from onset of symptoms to diagnosis is relatively short, however, the diagnosis is made at an advanced stage of the disease - the measured activity of the disease in the Bulgarian population is moderately severe according to BVAS version 3.

2. Conducting only conventional treatment does not change the physical function, emotional state and general health of patients. According to none of the elements that form the health-related quality of life, patients are not defined in normal and / or good health and do not fall into the group of healthy people from the general population.

3. The health-related quality of life of patients without treatment and standard treatment of vasculitis is very poor compared to the general population and does not meet modern requirements. 2/3 of the patients are severely depressed.

4. The use of biological medicinal products for the treatment of vasculitis is a therapeutic novelty and with the timely initiation of treatment with biological medicinal products (Rituximab) leads to rapid control of clinical symptoms and entry into longterm remission.

5. Rituximab biologic treatment resulted in a significant improvement in health-related quality of life in over 75% of patients in the two main domains, physical and mental health, compared to conventional patients, where 75% of patients did not identify as healthy.

6. Biological treatment leads to qualitative and quantitative improvement of all components of physical health - according to all indicators, patients are within the norms of the population.

7. The elements that form the mental component - vitality, social functioning, emotional functioning and mental health after biological treatment are within the norm for a healthy population. The level of depression after treatment with a biological product is within the norm for the general population.

8. Improving health-related quality of life in patients with AAV provides additional arguments to justify biological treatment as an alternative, despite the relatively high cost of drug therapy.

9. The study enriches the knowledge of medical professionals about the symptoms of AAV due to mental, physical and social factors.

10. Measurement of health-related quality of life in patients with AAV can be used for routine analysis of health before and after treatment.

11. Our study shows that Rituximab treatment is the best therapeutic alternative in current rheumatological practice for the treatment of AAV.

RECOMMENDATIONS

1. Unfortunately, in Bulgarian conditions, treatment with Rituximab is reimbursed only in patients with Wegener's granulomatosis. Treatment with biological products of the other two diseases - Microscopic polyangiitis and Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) are not reimbursed by the NHIF and patients with these diseases do not receive the necessary treatment. We consider it necessary to make the necessary scientific, regulatory and legislative changes so that these patients also have access to Rituximab treatment.

VII. CONTRIBUTIONS

CONTRIBUTIONS OF SCIENTIFIC AND THEORETICAL NATURE AND ORIGINALITY OF THE PhD THESIS

1. For the first time in Bulgaria a systematic study of patients with vasculitis, associated with antineutrophil cytoplasmic antibodies performing biological treatment.

2. For the first time in Bulgaria a retrospective analysis of the evolution of the disease in patients with vasculitis associated with antineutrophils cytoplasmic antibodies by stratification and evaluation of clinical activity measured by the vasculitis activity scale BVAS - Persistent points.

3. For the first time in Bulgaria, health-related quality of life is measured in patients with vasculitis associated with antineutrophil cytoplasmic antibodies, before and after biological treatment using common instruments.

METHODICAL CONTRIBUTIONS

1. An original protocol and design of a non-interventional, observational, prospective / retrospective study to measure health-related quality of life in the Bulgarian population of vasculitis patients associated with antineutrophil cytoplasmic antibodies before and after biological treatment was developed.

2. Measurement of health-related quality of life in patients with AAV can be used for routine analysis of health before and after treatment.

CONTRIBUTIONS OF SCIENTIFIC AND APPLIED NATURE

1. The study enriches the knowledge of medical professionals about the symptoms of AAV due to mental, physical and social factors.

CONFIRMATIVE CONTRIBUTIONS

1. Improving health-related quality of life in patients with AAV provides additional arguments to justify biological treatment as an alternative, despite the relatively high cost of drug therapy.

2. Our study confirms pre-registration efficacy data that Rituximab treatment is the best therapeutic alternative in current rheumatological practice for the treatment of AAV.

VIII. SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION

1. Asipova N, Hristov E, **Delyiski Tz,** Parvova I, Yordanov E, Andreevska K, Ognianov S, Burgazliev H. Health related quality of life - a pilot study in healthy volunteers. (**2018**) Rheumatology (Bulgaria), 26 (4), pp. 18-28. SCOPUS

2. **Delyiski Tzv,** Hristov E , Marinchev L , Parvova I, Dimitrova Zl. Health related quality of life in patients with antineutrophil cytoplasm antibody associated vasculitis conducting biological treatment - a systematic review of scientific publications. The 23rd Balkan Medical Days "The Balkan medicine during COVID-19 pandemic" organized by the Romanian National Section of the Balkan Medical Union. 01-02 October 2021 Arch Balk Med Union. (**2021)** 56 (Supplement 1): S33-34. SCOPUS

3. Asipova N, **Delyiski Tzv,** Hristov E, Yordanov E, Parvova I. A single-center, open-label, longitudinal, prospective study of health-related quality of life in pharmacy students. The 23rd Balkan Medical Days "The Balkan medicine during COVID-19 pandemic" organized by the Romanian National Section of the Balkan Medical Union. 01-02 October 2021 Arch Balk Med Union. (**2021)** 56 (Supplement 1): S58-59. SCOPUS

4. Shopov G, **Delyiski Tzv,** Hristov E, Parvova I. New approaches in the treatment of systemic vasculitis with biological medicinal products. The 23rd Balkan Medical Days "The Balkan medicine during COVID-19 pandemic" organized by the Romanian National Section of the Balkan Medical Union. 01-02 October 2021 Arch Balk Med Union. (**2021)** 56 (Supplement 1): S32. SCOPUS

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6. Asipova N, Hristov E, **Delyiski Tz,** Parvova I, Yordanov E, Andreevska K, Ognianov S, Burgazliev H. Health related quality of life - a pilot study in healthy volunteers. National Student Conference on Pharmaceutical and Chemical Sciences, FHF, Sofia University "Kliment Ohridski", Sofia, Bulgaria, 19-20.04.**2018,** Online: https://pharmconference.com/2018/ , REPORT

7. Asipova N, Hristov E, **Delyiski Tz,** Parvova I, Yordanov E, Andreevska K, Ognianov S, Burgazliev H. Health related quality of life - a pilot study in healthy volunteers. With the seventh Congress of Pharmacy with international participation, November 21-24, **2019**, Rila Hotel, resort Borovets, Bulgaria. REPORT