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Research Article

Health-related quality of life after Rituximab treatment of patients with antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are severe, socially significant diseases that require a clear understanding of the relationship between the current health status and quality of life of patients. On the one hand, in the scientific literature, there is not enough data to assess the quality of life for the different therapeutic regimens, and no specific tools have been developed to assess functional indicators and health status. On the other hand, with the exception of Rituximab treatment, the available immunosuppressive regimens do not lead to a good clinical response in patients with AAV. The aim of the study is to measure health-related quality of life in a Bulgarian population of patients with systemic vasculitis associated with ANCA undergoing biological treatment with Rituximab by using the generic instrument SF-36 version 2. We conducted a retrospective-prospective, non-interventional, controlled study in two periods in two centers in Bulgaria. Treatment with Rituximab leads to qualitative and quantitative improvement in all components of physical health, including mental and social components. After treatment, all measured parameters were within the normal range for the general population.

Keywords

systemic vasculitis, anti-neutrophil cytoplasmic antibody (ANCA), ANCA-associated vasculitis (AAV), health-related quality of life, SF-36 version 2, rituximab (RTX)

Introduction

Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's granulomatosis) (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome (CSS) associated with circulating anti-neutrophil cytoplasm antibodies (ANCA), are among the most common primary systemic vasculitides in adults (Bloch et al. 1990; Jennette et al. 2013; Hochberg et al. 2019). The presence of common antibod-

ies and the great similarity in clinical features, histological characteristics, treatment, and outcomes are frequently grouped together as ANCA-associated vasculitis (AAV). Earlier recognition of AAV and treatment with Rituximab have significantly reduced mortality (EMA 2009; Hochberg et al. 2019). Patients with AAV are faced with a chronic medical condition, and health-related quality of life (HRQoL), the component of well-being attributed directly to health status, is an increasingly important consideration. Measuring HRQoL has been facilitated in the last 35 years by the development and validation of generic HRQoL instruments such as the Medical Outcomes Survey Short Form 36 (SF-36) (Walsh et al. 2011; Karimi and Brazier 2016). These instruments allow investigators to reliably measure several facets or domains of HRQoL in a multitude of conditions (Asipova et al. 2018). Despite the chronic morbidity observed in patients with AAV (Lane et al. 2005), there is little known about how disease manifestations affect HRQoL (Mukhtyar et al. 2009; Walsh et al. 2011). Small, single-center quality of life studies suggest that multiorgan damage in AAV affects physical components of HRQoL (Koutantji et al. 2003; Newall et al. 2005; Srouji et al. 2006). HRQoL may help focus treatment for patients with AAV and help evaluate newer therapies. The aim of the study is to measure the health-related quality of life (physical, psychological, and social functioning) in a Bulgarian population of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) using the generic instrument SF-36 version 2 undergoing treatment with the biological medicinal product Rituximab (RTX) (EMA 2009). A secondary objective is to evaluate the effectiveness of biological treatment based on the quality of life data obtained. Treatment and disease effects will be measured from the patients' perspective.

Materials and methods

In our previous studies, which we have already reported (Parvova et al. 2024a; Parvova et al. 2024b), we evaluated epidemiological, health-demographic, and clinical-pharmacological real-world data in patients with systemic vasculitis associated with anti-neutrophil cytoplasmic antibodies in Bulgaria and their quality of life using the EuroQol-5D-5L instrument and the visual analog scale (VAS) before and after treatment with rituximab (RTX). In the present study, we will measure HRQoL using the SF-36 version 2 questionnaire on the same group of patients. The design of the study is identical (Parvova et al. 2024b): retrospective-prospective, observational, non-interventional, controlled study in two periods in two rheumatology centers on the territory of the city of Sofia, Bulgaria. An independent control group was not planned. The selected patient cohort is an "auto" control on its own, as patients self-assess their health status by completing pre- and post-treatment surveys. Survey period: January 2019–September 2020. The main method is to conduct a "direct individual survey" with closed answers. The questionnaire survey was conducted with the SF-36 version 2 generic health status instrument by completing a questionnaire in electronic format from a licensed software product. The original questionnaires are in English and have been validated by the licensee. The working version of the questionnaires was translated into Bulgarian by a licensed translator. The questionnaires are completed independently by the patients, with the opportunity to be assisted by the interviewing researcher where there are ambiguities. Number of patients at stake—not less than 6, not more than 24. Primary endpoints: physical component symmetrical (PCS) and mental component symmetrical (MCS). Secondary endpoints: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH) (Maruish 2011). Inclusion criteria: 1. Signed and dated informed consent; 2. Age over 18 years; 3. Diagnosed AAV; 4. The diagnosis must be established according to the EULAR criteria (Yates et al. 2016); 5. The diagnosis and the decision to conduct treatment must comply with the requirements of the national pharmacotherapeutic guide in rheumatology; 6. The patients have not been treated with a biological or biosimilar medicinal product. 7. Patients must meet criteria for treatment of systemic vasculitis with biologics. Screening visit: familiarization of the participants with the protocol and procedures, signing of the informed consent by the patient, assessment of inclusion and exclusion criteria. Patients were considered screened out if even 1 exclusion criterion was present. Visit 1 takes place before starting the biological treatment. The study participants fill out the SF-36 version 2 questionnaire by answering the questions retrospectively—describing their condition no less than 4 weeks ago. Therapeutic period: includes induction into remission and maintenance treatment. The recommended dose of RTX for induction of remission in 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). After induction into remission with RTX, maintenance treatment should begin no earlier than 16 weeks after the last RTX infusion. Visit 2 takes place 6 months after RTX induction treatment. The study participants fill out the SF-36v2 questionnaire by answering the questions retrospectively—again describing their condition 4 weeks ago. After the set number of participants is reached and/or the set observation period expires, a consolidated report is prepared using the software product. The report will include analysis of primary and secondary endpoints and analysis of the therapeutic effectiveness of biological treatment using health-related quality of life data. In the study are included only people who are: informed in a preliminary conversation with a doctor—a member of the investigation team—about the objectives, risks, and inconveniences of the study and about the conditions under which it will be conducted; are informed of their right to withdraw from the study at any time without negative consequences for them; whether they personally give written informed consent to participate after being aware of the nature, significance, consequences,

and possible risks of their participation. The study was conducted according to the Declaration of Helsinki and subsequent amendments, the Law on Medicinal Products in Human Medicine (LMPHU 2007), the Law of Health (LH 2004), the Personal Data Protection Act (PDPA 2002), and European regulations on clinical trials (EC 2022). The statistical evaluation of the data: 1. The main method will be a descriptive statistical analysis of the obtained study results. 2. The answers obtained will also be tested with various additional statistical methods such as completeness of data, responses within range, consistent responses, estimable scale scores, item internal consistency, discriminant validity, and reliable scales (Clark and Watson 1995). 3. We will use a correlation matrix of the items and factors and calculate a factor of convergence and divergence of the obtained answers and determine the degree of reliability of the obtained results at set normal values for this indicator from 0.00 to 0.40. 4. To assess the reliability and homogeneity of the results, we will use two techniques: inter-rater: different people, same test, and test-retest: same people at different times. Reliability will be measured by factor Chronbach' alpha (Rtt) at norm ≥ 0.70 and average inter-item correlation (Rii) at norm 0.15–0.50. All analyses were performed in accordance with the user's manual for the SF-36v2 Health Survey (3rd ed.), 2011 (Maruish 2011). The SF-36v2 uses norm-based scoring based on a linear T-score transformation method. A mean score of 50 and a standard deviation (SD) of 10, calculated on the basis of the general US population for 2009, is considered a normal score for each of the health domain scales. These norms are considered standard and have been recalculated for all geographic regions of the world. Thus, scores above and below 50 are above and below the mean for the general population, respectively. With a SD of 10, any 1-point difference or change in scores is directly meaningful—1 point is one-tenth of a SD, or an effect size of 10 units.

Results

Only patients diagnosed with granulomatosis with polyangiitis (Wegener's granulomatosis, Wegener's disease) were included in the study. The analyzed group of patients consisted of 12 patients: 10 men (83.33%) and 2 women (16.67%). The frequency for Bulgaria of patients with Wegener's granulomatosis is estimated as newly diagnosed cases between 14.7 and 100.80 with a median of 43.05 (Baleva et al. 1994; Dimitrov 2001). As we have reported in our previous readings and publications, 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 can be found (Parvova et al. 2024a; Delyiski 2023). We consider the presence of no more than 40 to 60 patients with this disease in Bulgaria to be an acceptable assumption, and of these, no more than 20 patients have been diagnosed. According to data published by the NHIF for 2017, it is clear that in the first, second, and third quarters of the same year, the NHIF paid for the treatment of 18, 15, and 12 patients, respectively, or an average of 15 patients per month (NHIF 2020). I.e., in the study we covered no less than 60% of all patients in Bulgaria. The mean age of the tracked 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 average age of the women followed was 55.5 years. The average duration of the disease in the group of patients followed by us varied from 1 to 13 years, with a median of 5 years. The time for making a diagnosis after the appearance of the first symptoms is relatively short, despite the varied and complex clinical symptoms: in 58.3% (7 patients) of the cases the diagnosis was made within 1 month, in 3 of the cases it was up to half a year. In 2 of the cases, there was a serious delay in the diagnostic process: in 1 patient, it took more than 1 year, and in the second, 7 years. BVAS activity was assessed by persistent points (BVAS – Persistent points) from 0 to 33 (Exley et al. 1997; Stone et al. 2001; Suppiah et al. 2010). The minimum number of points of persistent type on BVAS e 6 and the maximum 33, with a median of 17 points. The group analyzed by us was assessed as having a moderately severe level of activity according to BVAS version 3 (Luqmani et al. 1994; MDApp 2020; Delyiski 2023; Parvova et al. 2024a). Data quality was assessed using a series of indicators: completeness of data, responses within a given range, consistency of responses, internal consistency of data, discriminant validity, and reliability of data (Hristov et al. 2015). Data completeness is based on 100% completed 12 tests by 12 patients in all domains: physical component summary (general health, physical functioning, role physical, bodily pain) and mental component summary (vitality, social functioning, role emotional, mental health). The raw data on which the statistical analyses were performed contain answers in 8 domains (total 35), with the acceptable limits, missing answers, and frequency evaluated. In Table 1, we present the data quality assessment indicators.

Table 1. SF-36V2 data quality evaluation report—ANCA vasculitis—before treatment.

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. Consistent Responses	100.0%	YES	90
4. Estimable Scale Scores			
Estimable without MDE	100.0%	YES	90
Estimable with Half-Scale MDE	100.0%		
Estimable with Full MDE	100.0%		
5. Item Internal Consistency. Items that failed internal consistency test: **GH05**	100.0%	YES	90
6. Discriminant Validity. Items that failed discriminant validity test: **PF02 PF03 PF09 RP03 RP04 GH01 GH02 GH03 GH04 GH05 VT01 VT03 SF01 SF02 MH04 MH05**	77.1%	NO	80
7. Reliable Scales. Scales that failed reliability criteria: **GH**	87.5%	NO	100

Definition of data quality indicators: 1. Percentage of completed responses (within range) divided by the total possible number of responses (items*N). This calculation includes the Health Transition (HT) item. 2. Percentage of item responses within the range of response codes printed on the questionnaire. This calculation includes the Health Transition (HT) item. 3. Percentage of subjects with no inconsistent responses on the Response Consistency Index (score = 0). 4. Percentage of subjects for whom all scales are computable with and without application of the SFMDE. 5. Percentage of items that correlate (corrected for overlap) 0.40 or higher with their hypothesized scale. 6. Percentage of items that correlated significantly higher with their hypothesized scale than with competing scales. score. 7. Percentage of scales with Cronbach's alpha coefficients greater than or equal to 0.70. Data quality assessment criteria No. 6. Discriminant validity is below the norm of 80%; there is a deviation of 2.9%. 15 items from the quality indicators did not pass the discriminant validity tests. The greatest variance of responses is within the general health (GH) domain. All responses have been reviewed and validated. We consider these deviations to be within statistical error. Determining the internal and construct validity of the source data is essential. Internal validity is a methodology that allows us to rule out alternative explanations for dependent variables, while construct validity enables an instrument to capture latent variables. Construct validity has three components: convergent, discriminant, and nomological validity. Discriminant validity is understood to mean that items should correlate more highly with each other than they do with other items from other constructs that are theoretically assumed not to correlate (hypothetical correlations). Of the 315 items in the correlation matrix, 38 items (12.5%) had a correlation level below 0.40. The reliability level is 87.5%. (Table 2)

Tests of discriminant validity at the level of items of the SF36v2 questionnaires are measured in numerical value: 1, 2, -1, -2, with low values of the measured relationships between items being found in the general health domain. We subjected the obtained results to reliability and homogeneity assessment. Reliability is measured by Cronbach's alpha factor, an indicator of how well different items complement each other in measuring different aspects of the same variable or quality. Values range between zero and one. Values closer to one indicate higher internal consistency; values closer to zero indicate lower internal consistency. A level above 0.70 is considered acceptable. The results on the items (domains) are considered reliable and homogeneous only when for 100% of the items the Cronbach's alpha factor is above a value of 0.70. And with this indicator, in our research 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 we obtained are reliable and homogeneous. The internal consistency between the items is measured by the average inter-item correlation coefficient, Rii (average inter-item correlation; norm 0.15 ÷ 0.50). The range of inter-item correlations is 0.15 ÷ 0.85. The results are presented in Table 3. The obtained results are reliable and homogeneous in all domains.

Table 2. Multitrait/multi-item correlation matrix—before treatment.

Items	PF	RP	BP	GH	VT	SF	RE	MH
Scale = 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
Scale = 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
Scale = 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
Scale = 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
Scale = 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
Scale = 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
Scale = 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
Scale = 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***

* Position adjusted due to potential 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 hypothesized value.

[2] We have poor discriminant validity when items correlate significantly higher with competing scores or scales than with their hypothesized value.

Table 3. Scale reliability and homogeneity estimates for different domains.

Rock	K *	Rtt **	Rii ***
PF - Physical Functioning	10	0.970	0.766
RP - Role Physical	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 - Role Emotional	3	0.976	0.931
MH - Mental Health	5	0.849	0.529

* k = Number of Items;
** Rtt (reactions to tests scale) = Cronbach's alpha;
*** Rii (average inter-item correlation).

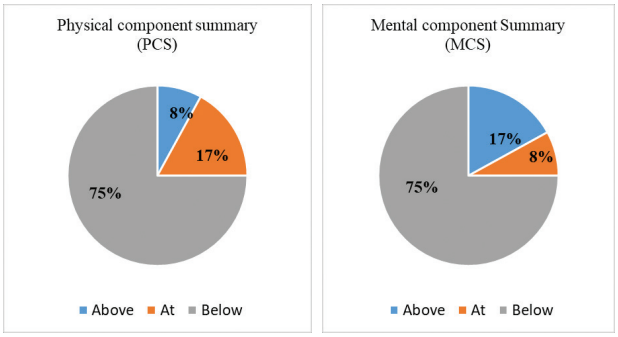

Figure 1. PCS: physical component symmetry and MCS: mental component symmetry.

The summary results for health-related quality of life for the two main domains—physical and mental components—are presented in Figs 1, 2. The measured quality of life across the two criteria in 75% of respondents (patients with ANCA-associated vasculitis) was below the norms for the general population.

An impression of a problematic characterization of general health by the respondents is confirmed—only 1 patient (8.3%) declared a feeling of normal general health, while all the remaining 11 declared deteriorated general health. The presence of bodily pains was found in 7 patients (59%). Respectively, 7 and 8 patients declared deteriorated, below the norms for the general population, physical, and role functioning. 75% of the patients declared a very poor health status.

In Fig. 3, we present generalized results for the mental component by its four elements: vitality, social functioning, emotional functioning, and mental health. Vitality: the relative share of those declaring normal and better than normal vitality is 42%, while 58% of the relative share do not feel alive. 50% of patients define themselves as socially excluded, and 75% as having lost and/or severely deteriorated their emotionality. 50% of respondents rated their mental health as worse than normal.

A general comparative analysis of the results of the physical and mental component and the elements forming them in absolute and relative values is presented in Fig. 4. Obviously, a conclusion is necessary that according to none of the elements forming the health-related quality of life, the respondents are not defined as normal and/or good health and do not fall into the healthy group of the general population. The worst results are in physical functioning, emotional state, and feeling of general health, and in general health, we must not forget that we are conducting the analyses despite the low reliability and discriminant validity results.

The data for the assessment of depression in our group of patients are presented in Fig. 5. 66% of the patients were definitely in a depressed state.

The results of the health status assessment using the SF-36v2 health instrument survey of Visit 2, which takes place after starting the biological treatment, are based on

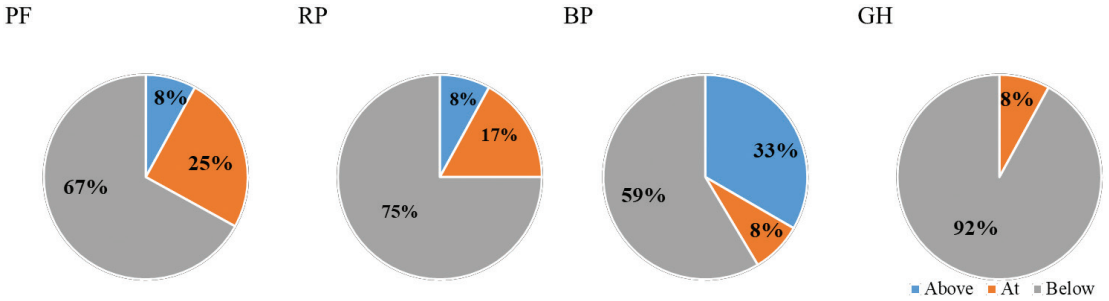

Figure 2. PCS: physical component summary scale scores.

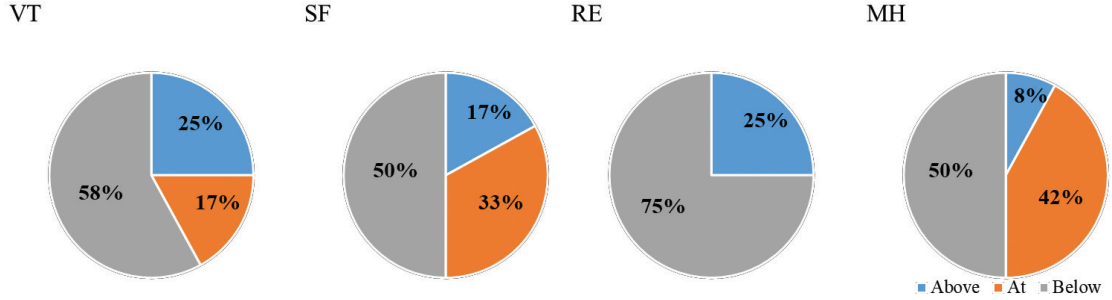

Figure 3. MCS: mental component summary scale scores.

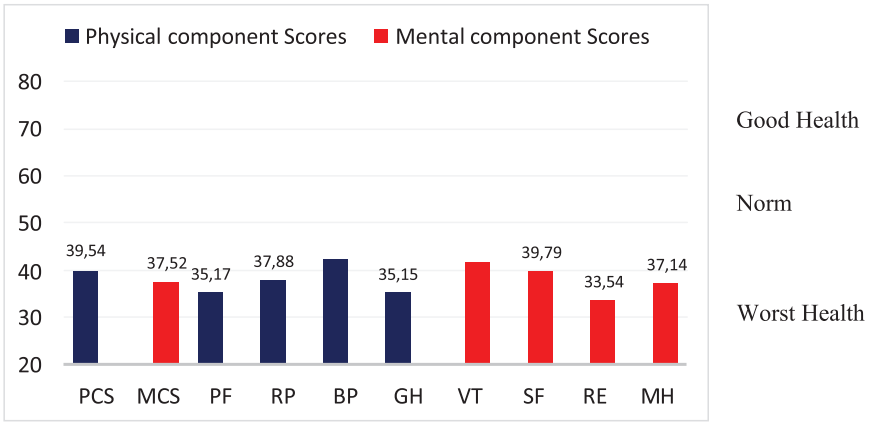

Figure 4. Total sample by elements—before treatment.

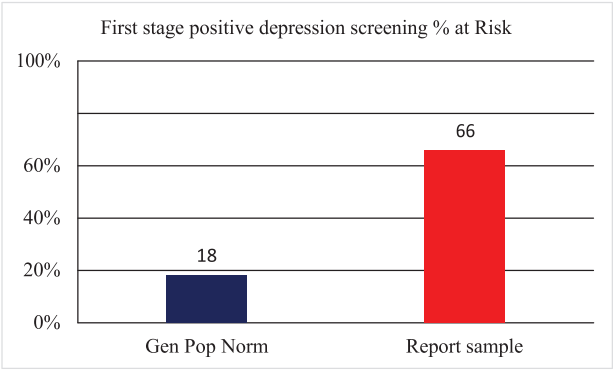

Figure 5. SF36v2 as a screening for depression—before treatment.

100% completeness of the data—all 12 subjects answered the questions retrogradely, describing their condition for the past period of time—6 months. The evaluation of the indicators is presented in Table 4.

Table 4. SF-36V2 Data Quality Evaluation Report—ANCA vasculitis—after treatment.

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. Consistent Responses	100.0%	YES	90
4. Estimable Scale Scores			
Estimable without MDE	100.0%	YES	90
Estimable with Half-Scale MDE	100.0%		
Estimable with Full MDE	100.0%		
5. Item Internal Consistency. Items that failed internal consistency test: **GH01 GH04**	94.3%	YES	90
6. Discriminant Validity. Items that failed the discriminant validity test: **PF01 PF03 PF05 PF06 PF07 PF10 RP01 RP04 GH01 GH02 GH03 GH04 GH05 VT01 VT03 SF02 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 are defined and evaluated in a similar manner as described before treatment. In criterion #6, discriminant validity is again below the norm of 80%—there is a deviation of 6.1%. 21 items from the quality indicators did not pass the discriminant validity tests. The greatest dispersion of responses is found within the physical functioning (PF), mental health (MH), and general health (GH) domains. All responses have been reviewed and validated. The reliability level of the data in the Vitality and General Health domains is 25% below the norm. We believe that this is due to the wide range of given answers—in the vitality group, the range is from 1 to 6, and in general health, from 1 to 5. On the one hand, this is due to the extremely varied clinical picture in patients with systemic vasculitis, and on the other hand, the small number of 12 patients gives a high relative weight to the differences in responses. Of the 315 items in the correlation matrix, 76 items (25%) had a correlation level below 0.40 (Table 5). The reliability level is 75%; we assume that the low reliability is due to the low degree of correlation of the Vitality and General Health items. Deviations are due to dynamics in clinical symptoms and subjective feelings in different patients.

Tests of item-level discriminant validity again found low values of measured item relationships in the general health domain—correlating with reliability scores. The mental health scores are borderline for the most part—there is more of a hypothesized relationship than a measured one with the other components of the assessment. Reliability data are presented in Table 6. In the general health domain, the score is below the norm—0.604 or 0.096 units below the norm, with a normal mean correlation coefficient between items (Rii = 0.234). Compared to pre-treatment tests, we found a low level of reliability through Cronbach's alpha factor for the bodily pain component (0.497), with a normal average correlation coefficient between items (Rii = 0.331).

The physical and mental component and item structure are presented in Figs 6, 7. The measured quality of life across the two 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 within the general population norms.

The qualitative and quantitative improvement of all components of the physical health domain is confirmed—for all indicators, patients enter the norms for the population in relative shares above 60%, with an average

Table 5. Multitrait/Multi-Item Correlation Matrix—after treatment.

Domain	PF	RP	BP	GH	VT	SF	RE	MH
Scale = 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
Scale = 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
Scale = BP - Bodily 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**
Scale = 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
Scale = 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
Scale = 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
Scale = 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
Scale = 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***

Table 6. Scale reliability and homogeneity estimates.

Scale	K *	Rtt **	Rii ***
PF - Physical Functioning	**10**	**0.893**	**0.456**
RP - Role Physical	**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 - Role Emotional	**3**	**0.960**	**0.889**
MH - Mental Health	**5**	**0.769**	**0.399**

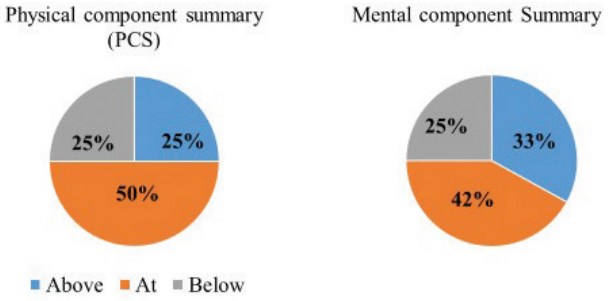

Figure 6. Physical and mental component summary after treatment with rituximab.

value of 70.5%. In Fig. 8, we present generalized results for the mental component by its four elements: vitality, social functioning, emotional functioning, and mental health. Vitality: the relative share of those declaring normal and better than normal vitality was 83% (before treatment with Rituximab, 42%). A total of 75% of patients defined themselves as fully socialized, and 75% defined themselves as emotionally stable—before treatment, 75% defined themselves as having lost and/or severely deteriorated their emotionality. 83% of respondents rated their mental health as normal and better than normal for the general population.

A general comparative analysis of the results of the physical and mental component and the elements forming them in absolute and relative values is presented in Fig. 9. In almost all of the elements forming the health-related quality of life, the respondents are defined as in normal and/or good health and fall into the healthy group from the general population. Only in four components are the results below the norm of 50: physical functioning (49.41); physical role (45.56); social functioning (49.4); and emotionality (47.17).

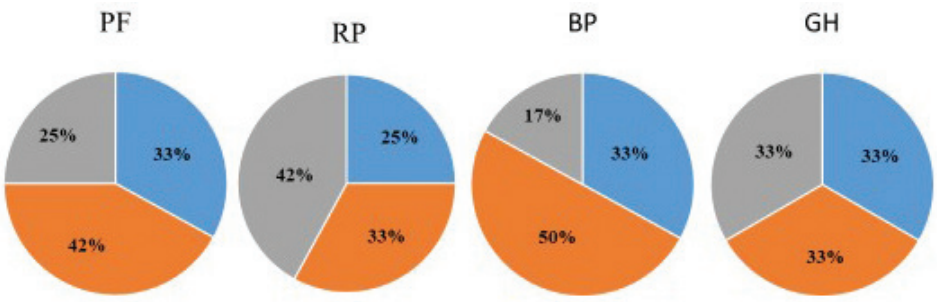

Figure 7. PCS scale scores—after treatment with rituximab.

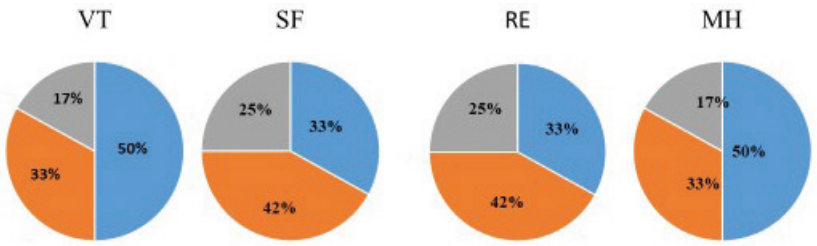

Figure 8. MCS scale scores—after treatment with rituximab.

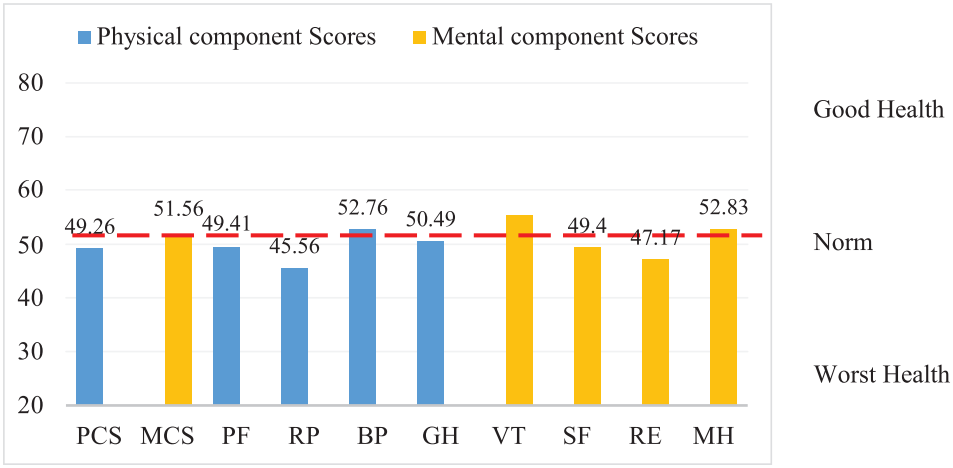

Figure 9. Total sample by elements—after treatment.

The data for the evaluation of depression in our group of patients after treatment are within the limits of the norm for the general population (Fig. 10). Only 16% of patients were depressed compared to a population norm of 18%; the pre-treatment baseline was 66%.

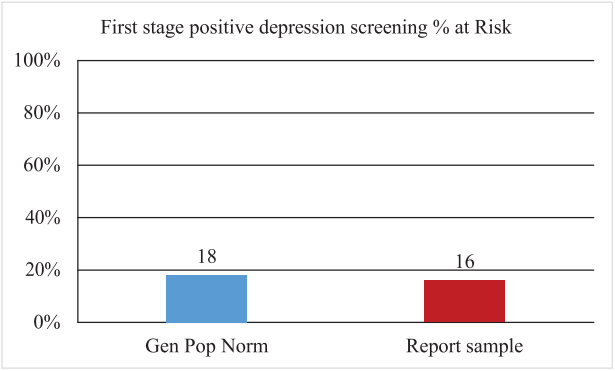

Figure 10. SF36v2 as a screening for depression—after treatment.

In Table 7, we present a metric conversion of the health status data into absolute values—the so-called results based on norms (norm-based scores). The mean values correspond to the data in Fig. 9, with the same population norms for arithmetic mean and median 50, with a standard deviation of 10.

In Table 8, we present transformed data (T scores) from 0–100 with a mean (mean) of 50 and a standard deviation (SD) of 10.

Discussion and conclusion

As we indicated at the beginning of the article, in studies already reported by us (Parvova et al. 2024a), the frequency of newly diagnosed patients in Bulgaria with Wegener's granulomatosis is estimated between 14.7 and 100.80 with a median of 43.05. There are no literary and official data from the national statistics about the actual total number

Table 7. SF-36 v2 scale and summary measure scores, norm-based scoring.

	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 8. SF-36 v2 scale scores, 0–100 scoring (transformed 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

of patients with Wegener's granulomatosis for the period 2018–2021. As an acceptable assumption, we consider the presence of no more than 40 to 60 patients with this disease in Bulgaria, of which the diagnosed are not more than 20 or, as a relative share, not more than 30% of the total number. With 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 a regression to 11.9% of the maximum frequency. The size of the population analyzed by us, calculated from the total number of patients with the acceptable assumptions made above, is not less than 60% of all patients in Bulgaria. An impression of a problematic characterization of general health by the respondents is confirmed—only 1 patient (8.3%) declared a feeling of normal general health, while all the remaining 11 declared deteriorated general health. The presence of bodily physical pains was found in 7 patients (59%). Respectively, 7 and 8 patients declared deteriorated, below the norms for the general population, physical, and role functioning. 75% of the patients declared a very poor 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 is 42%, while 58% do not feel alive; 50% of patients define themselves as socially excluded, and 75% as having lost and/or severely deteriorated their emotionality; 50% of respondents rated their mental health as worse than normal. For none of the elements forming the health-related quality of life, the respondents do not define themselves in normal and/or good health and do not fall into the group of the healthy of the general population. The worst results are in physical functioning, emotional state, and feeling of general health. Depression score data showed that 66% of patients were definitely depressed, compared to a population norm of 18%.

In the exact opposite direction are the results of the health status assessment using the SF-36v2 Health Survey after biological treatment with Rituximab. The summary results for the health-related quality of life for the two main domains, physical and mental components, showed that the quality of life measured by the two criteria in 75% of the patients was above the norms for the general population, in contrast to the data for the two components before treatment. where 75% of respondents were within the norms for the general population. We found a qualitative and quantitative improvement in all components of the physical health domain—on all indicators, patients entered the norms for the population in relative shares above 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 is 83%; 75% of patients define themselves as fully socialized; again, 75% define themselves as emotionally stable; 83% of respondents rated their mental health as normal and better than normal for the general population. In almost all of the elements forming the health-related quality of life, the respondents are defined as in normal and/or good health and fall into the healthy group of the general population. Only in four components are the results 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 statistical error. Only 16% of patients are depressed, compared to the population norm of 18%.

The health-related quality of life in untreated and standard vasculitis patients is very poor compared to the general population and does not meet current requirements. 2/3 of patients are severely depressed. The application of biological medicinal products for the treatment of vasculitis is a therapeutic novelty, and the timely initiation of treatment with biological medicinal products (Rituximab) leads to rapid control of clinical symptoms and entry into a long remission. Biologic treatment with Rituximab resulted in a significant improvement in health-related quality of life in more than 75% of patients in the two main domains of physical and mental health, compared to patients on conventional treatment, where 75% of patients were not defined as healthy. Biological treatment leads to a qualitative and quantitative improvement of all components of physical health; according to all indicators, patients enter the norms for the population. The elements forming the mental component—vitality, social functioning, emotional functioning, and mental health—after biological treatment are within the limits of the norm for the healthy population. The level of depression after treatment with a biologic product is within the normal range for the general population. The improvement of the health-related quality of life in patients with AAV provides additional arguments to justify biological treatment as an alternative, despite the relatively high costs of drug therapy. The study adds to the knowledge of medical professionals about the symptomatology of AAV

due to mental, physical, and social factors. Measurement of health-related quality of life in patients with AAV can be used for routine analysis of health status before and after treatment. Our study shows that Rituximab treatment is the best therapeutic alternative in current rheumatology practice for the treatment of AAV.

Additional information

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Data availability

All of the data that support the findings of this study are available in the main text.

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