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Rituximab use may indicate impaired quality of life in granulomatosis with polyangiitis

Granülomatöz polianjit hastalarında rituksimab tedavisi bozulmuş yaşam kalitesi göstergesi olabilir

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Abstract

Objective: Granulomatosis with polyangiitis (GPA) is an autoimmune disease among the small vessel vasculitides group. It is characterized by the presence of anti-neutrophil cytoplasmic antibodies and can lead to substantial morbidity and mortality if left untreated. In this study, we aimed to evaluate the deterioration in health-related quality of life (HRQoL) of GPA patients and to identify potential factors that may affect HRQoL.

Methods: Forty patients who met the American College of Rheumatology 1990 criteria for GPA classification were included in the study. A control group with similar age and gender characteristics consisted of healthy volunteers. Demographic information, disease characteristics and treatments of the patients were recorded. To evaluate HRQoL, the Turkish version of the Medical Outcomes Study Short-Form 36 (SF-36) was used. Irreversible organ damage attributable to GPA and/or its treatment was assessed using the vasculitis damage index (VDI).

Results: Compared with the control group, SF-36 was significantly impaired for all SF-36 domains except mental health, which is one of the 8 sub-scale components in GPA patients. There was no significant relationship between different SF-36 scores and total VDI score, affected organ system, disease duration, or total steroid dose. Only one negative correlation was observed between the total dose of rituximab and the overall health and emotional role.

Conclusion: Regardless of the disease activity, significantly decreased HRQoL is observed in patients followed up with GPA. Despite advances in management of GPA, our results suggest impairment of HRQoL is still an issue. Furthermore, rituximab treatment may be indicative of altered HRQoL.

Keywords: Granulomatosis with polyangiitis, quality of life, short-form 36, vasculitis damage index, rituximab

Öz

Amaç: Granülomatozis polianjit (GPA), anti-nötrofil sitoplazmik antikor ile ilişkili küçük damar vaskülitleri grubunda yer alan otoimmün bir hastalıktır ve tedavi edilmediği takdirde önemli morbidite ve mortalite ile ilişkilidir. Bu çalışmada, GPA hastalarının sağlıkla ilişkili yaşam kalitesindeki (HRQoL) bozulmayı değerlendirmeyi ve HRQoL'yi etkileyebilecek olası faktörleri belirlemeyi amaçladık.

Yöntem: American College of Rheumatology 1990 GPA sınıflandırması kriterlerini karşılayan kırk hasta çalışmaya dahil edildi. Sağlıklı gönüllülerden benzer yaş ve cinsiyet özelliklerine sahip kontrol grubu oluşturuldu. Hastaların demografik bilgileri, hastalık özellikleri ve tedavileri kaydedildi. HRQoL'yi değerlendirmek için Medical Outcomes Study Short-Form 36 (SF-36) Türkçe versiyonu kullanıldı. GPA'ya ve/veya tedavisine atfedilebilen geri dönüşümsüz organ hasarı, vaskülit hasar indeksi (VDI) kullanılarak değerlendirildi.

Bulgular: Kontrol grubu ile karşılaştırıldığında, GPA hastalarında SF-36 8 alt ölçek bileşeninden biri olan ruh sağlığı dışındaki tüm SF-36 alanları anlamlı olarak bozulmuştu. Farklı SF-36 puanları ile toplam VDI skoru, etkilenen organ sistemi, hastalık süresi veya total steroid dozu arasında anlamlı bir ilişki yoktu. Toplam rituksimab dozu ile yalnızca genel sağlık ve duygusal rol arasında negatif bir korelasyon gözlendi.

Sonuç: Hastalık aktivitesinden bağımsız olarak, GPA ile izlenen hastalarda HRQoL'de anlamlı azalma gözlenmektedir. GPA yönetimindeki ilerlemelere rağmen, sonuçlarımız HRQoL'deki bozulmanın hala bir sorun olduğunu göstermektedir. Ayrıca, rituksimab tedavisi bozulmuş HRQoL'nin göstergesi olabilir.

Anahtar Kelimeler: Granulomatöz polianjit, yaşam kalitesi, kısa-form 36, vaskülit hasar indeksi, rituksimab

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Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is an anti-neutrophil cytoplasmic antibody associated vasculitis (AAV) which affects various organ systems including upper air ways, lungs, kidneys, peripheral nervous system, gastrointestinal system, joints, eyes and skin, which may lead to mortality and varying degrees of morbidity.[1-3] Mortality can be avoided with early recognition and effective use of immunosuppressants, therefore, assessment of quality of life (QoL) and disease related damage came forth as important aspects well-being in GPA patients.[4-6]

QoL can be defined as an individual's perception of their status in daily life regarding the individual's expectations, aims and standards shaped by own cultural, moral, and social values.[7,8] Several self-reported questionnaires had been developed to quantify health-related quality of life (HRQoL), which is rather subjective and can vary significantly according to the individual's perspective on life. Short-form 36 (SF-36)[9] is a well-established tool to evaluate HRQoL in various patient populations with different conditions and compare with healthy subjects.[1,10-12] Furthermore, SF-36 can also be used to investigate effects of several aspects related to a disease in long-term, such as complications caused by disease itself, treatment agents used for the disease, accompanying comorbidities, patient's demographics and habitual activities.[8,13] SF-36 comprises 36 questions providing composite scores in 8 domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health, with lower scores indicating impaired HRQoL. Accordingly, SF-36 has also been used widespread to evaluate HRQoL in vasculitides patients.[4,14]

The term "disease related organ damage" expresses irreversible deteriorations in functioning of organ systems in varying degrees, caused by any disease related aspect including disease activity and treatment complications, and persists even after the disease is in remission. Irreversible organ damage in vasculitides can be quantified with vasculitis damage index (VDI), which comprises sixty-four domains in eleven organ system-based groups and developed solely for evaluating vasculitis related organ damage.[15,16] Permanent alterations of organ functioning may further hamper HRQoL in GPA patients via complications due to disease activity such as visual and auditory loss, renal and respiratory failure and via treatment associated complications such as malignancies, avascular necrosis and osteoporosis.

Several studies investigated HRQoL in GPA patients; however, there is limited data with contradictory results regarding effects of irreversible organ damage on HRQoL so it is yet to be fully clarified the true impact of hampered organ functions on patient perceived HRQoL.[1,15] Furthermore, earlier studies may not truly reflect effects of recent developments in medical care of GPA patients, therefore, it is intriguing whether impaired HRQoL is still an issue for GPA patients and any new indicators for worse HRQoL emerged. In this study, we aimed to evaluate deteriorations in HRQoL of GPA patients and further investigate potential factors which may impact HRQoL.

Materials and Methods

A cohort was formed from adult patients who had been followed-up in our clinic with a diagnosis of GPA for at least three months. Patients of this cohort were either evaluated during follow-ups or reached via telephone and a visit was arranged. Patients who did not meet the American College of Rheumatology 1990 Classification Criteria for Wegener's Granulomatosis,[17] patients who considered to have active disease at the time of evaluation and patients who did not want to participate were excluded. Patients who had active disease during the evaluation were re-evaluated later when remission achieved. Active disease was decided according to the Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG).[18] Demographics, clinical and laboratory data were recorded.

HRQoL was evaluated with Turkish version of SF-36[19] and disease related permanent damage with VDI. Five factor scale (FFS) scores[20] were calculated to evaluate the disease prognosis at the time of diagnosis. Treatment characteristics and cumulative doses of steroid, cyclophosphamide (CTX) and rituximab (RTX) therapies were recorded. A control group with similar characteristics regarding age and gender were formed from healthy volunteers. Written consent was obtained from all participants.

Demographics and SF-36 scores were compared between GPA patients and healthy controls. Possible correlations between SF-36 scores and demographics, symptom duration, VDI and FFV scores, total doses of steroids, RTX, CTX were investigated in GPA group.

Statistical Analysis

Data was analysed using Statistical Package for the Social Sciences (SPSS) v22.0. Normality of continuous variables was evaluated with Kolmogorov-Smirnov test in addition to visual analyses with plots and histograms. Continuous variables were presented either with median [interquartile range (IQR) or minimum-maximum (min-max)] or mean ± standard deviation (SD) and compared by Mann-Whitney U or Student t-tests according to normality. Categorical

variables are presented with numbers and percentages and compared by x^2 test. Correlations between continuous and ordinal variables were investigated by Spearman's Rho. P values ≤0.05 were considered statistically significant for all comparative analyses. Correlations with a coefficient ≥0.5 and a p-value ≤0.05 considered significant [correlation coefficient (r) between 0.5-0.7 considered moderate, ≤0.7 considered strong and <0.5 considered no correlation].

Ethics approval (E2-21-792) was obtained by Ankara City Hospital Ethics Committee and the study was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Results

The GPA cohort was consisted of total 81 patients. Twenty-nine patients were either lost to follow-up or could not be reached, 9 were not alive and 3 were not fulfilling American College of Rheumatology 1990 Classification Criteria for Wegener's Granulomatosis.[17] A total of 40 patients were included in the study. Characteristics of the patients were presented in Table 1. Mean ± SD age was 50.4±13.2 years and 42.5% of the patients were male. Seventy percent of the patients had at least one comorbid condition and the most common comorbidities were hypertension (35%), chronic kidney disease (CKD) (15%), osteoporosis (15%) and diabetes mellitus (10%). Median (min-max) FFS score at the time of diagnosis was 0 (0.0-2.0). Median (min-max) VDI score at the time of evaluation was 1.0 (0.0-4.0). When organ system-based subgroups of VDI were investigated, ear nose throat (ENT) damage was the most common (47.5%) followed by renal (25.0%), neuropsychiatric (12.5%) and musculoskeletal (10.0%) damage.

Seventy-two percent of the patients had ever received CTX, 32.5% RTX, 55.0% azathioprine, 20.0% mycophenolate mofetil and 20.0% methotrexate. All patients had been administered glucocorticoids with a median (IQR) total dose of 10120.0 (9460.0) mg. Data regarding treatment agents were presented in Table 1.

Control group comprised 40 healthy volunteers. Age and gender characteristics were similar between patients and controls. All domains of SF-36 were significantly impaired in GPA patients except for mental health (Table 2).

Correlations between the 8 domains of SF-36 and age, body mass index, symptom duration, VDI and FFS scores, total dose of steroids, RTX and CTX treatments were presented in Table 3. Significant correlations were observed only between total RTX dose and general health (r=-0.549, p=0.034) and role emotional (r=-0.513, p=0.050) indicating a moderate negative correlation between total RTX dose and these two SF-36 domains (Table 3).

Table 1. Demographics and clinical characteristics of granulomatosis with polyangiitis patients

	n=40
Age, years, mean ± SD	50.4±13.2
Gender, male, number (%)	17 (42.5)
BMI, mean ± SD	26.7±5.4
Patients with ≥1 comorbidities, number (%)	28 (70.0)
Comorbidities, number (%)	
Hypertension	14 (35.0)
Chronic kidney disease	6 (15.0)
Osteoporosis	6 (15.0)
Diabetes	4 (10.0)
Cataract	3 (7.5)
Avascular necrosis	2 (5.0)
Malignancies	2 (5.0)
Coronary artery disease	1 (2.5)
Congestive heart failure	1 (2.5)
Other	13 (32.5)
Active smokers, number (%)	5 (12.5)
Time from symptom onset, months, median (min-max)	48.0 (4.0-157.0)
Time from diagnosis, months, median (min-max)	42.0 (3.0-156.0)
cANCA positivity in IFA, number (%)	29 (72.5)
PR3 positivity in ELISA, number (%)*	29 (74.4)
VDI score, median (min-max)	1.0 (0.0-4.0)
Patients with involvement in VDI domains, number (%)	
Musculoskeletal	4 (10.0)
Skin/mucous membranes	1 (2.5)
Ocular	1 (2.5)
ENT	19 (47.5)
Pulmonary	0 (0.0)
Cardiovascular	2 (5.0)
Peripheral vascular disease	1 (2.5)
Gastrointestinal	0 (0.0)
Renal	10 (25.0)
Neuropsychiatric	5 (12.5)
Other	4 (10.0)
FFS at baseline, median (min-max)	0 (0.0-2.0)
Treatments	
CTX ever users, number (%)	29 (72.5)
RTX ever users, number (%)	13 (32.5)
Mycophenolate mofetil ever users, number (%)	6 (15.0)
Azathioprine ever users, number (%)	22 (55.0)
Methotrexate ever users, number (%)	8 (20.0)
Cumulative steroid dose, mg, median (IQR)	10120.0 (9460.0)
Cumulative CTX dose, mg, median (IQR)	6000.0 (5000.0)
Number of RTX cycles, median (IQR)	2.0 (4.0)

**Evaluated over 39 patients in whom PR3ELISA had been worked-up, ANCA: Anti-neutrophil cytoplasmic antibody, BMI: Body mass index, CTX: Cyclophosphamide, ELISA: Enzyme linked immunosorbent assay, ENT: Ear nose throat, FFS: Five factor scale, PR3: Proteinase 3, IFA: Immunofluorescent assay, IQR: Interquartile range, RTX: Rituximab, SD: Standard deviation, VDI: Vasculitis damage index*

Table 2. Demographics and SF-36 scores in GPA patients and healthy controls

	GPA patients n=40	Healthy controls n=40	p
Age, years, mean ± SD	50.4±13.2	48.4±12.3	0.246
Gender, male, number (%)	17 (42.5)	17 (42.5)	1.000
SF-36 scores, median (IQR)			
Physical functioning	85.0 (25.0)	95.0 (10.0)	**<0.001**
Role physical	50.0 (100.0)	100.0 (50.0)	**<0.001**
Bodily pain	57.5 (22.5)	85.0 (30.0)	**<0.001**
General health	45.0 (25)	70.0 (35.0)	**<0.001**
Vitality	50.0 (30)	65.0 (25.0)	**0.001**
Social functioning	62.5 (25)	100.0 (37.5)	**<0.001**
Role emotional	33.3 (100.0)	100.0 (66.7)	**0.007**
Mental health	68.0 (24.0)	72.0 (16.0)	0.114

GPA: Granulomatosis with polyangiitis, IQR: Interquartile range, SD: Standard deviation, SF-36: Short-form 36

Table 3. Correlations between SF-36 scores and demographics, symptom duration, total dose of treatment agents, VDI scores, baseline FFS scores

SF-36 domains		Age	BMI	Symptom duration	VDI	FFS	Total CTX dose	Total RTX dose	Total steroid dose
Physical functioning	r	-0.077	0.214	0.008	0.075	-0.099	0.000	-0.339	-0.275
	p	0.643	0.197	0.961	0.652	0.547	0.999	0.217	0.090
Role physical	r	0.198	0.147	-0.052	0.218	0.144	-0.026	-0.388	-0.097
	p	0.227	0.379	0.753	0.182	0.383	0.903	0.152	0.558
Bodily pain	r	-0.032	0.003	0.073	0.039	-0.185	-0.125	-0.248	0.034
	p	0.846	0.986	0.660	0.812	0.259	0.553	0.373	0.837
General health	r	0.016	-0.005	0.022	0.222	-0.082	-0.089	**-0.549**	-0.178
	p	0.925	0.975	0.892	0.175	0.619	0.671	**0.034**	0.278
Vitality	r	-0.117	-0.014	-0.060	0.333	0.203	-0.172	0.205	0.055
	p	0.478	0.933	0.716	0.038	0.214	0.411	0.464	0.738
Social functioning	r	0.208	0.173	0.159	0.251	0.020	-0.043	-0.274	0.045
	p	0.203	0.299	0.335	0.124	0.902	0.840	0.323	0.785
Role emotional	r	0.243	0.147	-0.233	0.104	0.166	-0.083	**-0.513**	-0.232
	p	0.136	0.380	0.154	0.528	0.314	0.695	**0.050**	0.155
Mental health	cc	-0.006	0.102	-0.110	0.111	-0,032	-0.180	0.075	-0.090
	p	0.972	0.544	0.505	0.502	0.844	0.390	0.790	0.584

BMI: Body mass index, CTX: Cyclophosphamide, FFS: Five factor scale, r: Correlation coefficent, RTX: Rituximab, SF-36: Short form 36, VDI: Vasculitis damage index

Discussion

Our results demonstrated impaired HRQoL measured by SF-36 in GPA patients, even in remission defined by BVAS/WG, with deteriorations in all domains of SF-36 except for mental health. We did not observe any significant correlations between SF-36 domains and age, symptom duration, body mass index, irreversible organ damage quantified by VDI and FFS scores at the time of diagnosis. Total dose RTX dose significantly correlated with worse general health and emotional role scores. Such relation was not observed with total CTX and steroid doses.

GPA is a one of the most debilitating rheumatic conditions with frequent organ/life threatening manifestations, long disease duration and recurrent flares, leading to devastating effects of an individual's overall well-being. With intensive monitoring and immunosuppressive treatment, mortality can be evaded in most cases, yet irreversible organ damage caused by the disease and complications due to intensive immunosuppressive treatment comprising steroids and various immunosuppressants may lead to morbidity and impaired HRQoL. Several studies indicated impaired HRQoL in vasculitides.[1,4,14,21-23]

In a cross-sectional study evaluating employment, work disability and QoL in patients with AAV, 189 patients with AAV were evaluated.[24] Specific and non-specific questionnaires, including SF-36, were sent to the patients, and clinical-biological data and determinants that could affect QoL were analyzed.[24] In this study, it was shown

that the QoL was significantly impaired in AAV patients compared to the general population.[24]

A systematic literature review reviewed relevant articles on HRQoL and fatigue, as well as on AAV-related comorbidities.[25] A significant decrease in HRQoL and an increase in fatigue and anxiety were reported in the AAV in this review. Also, in this review, decreased physical component score and mental component score were associated with fatigue, mood disorders, sleep disturbance, and/or unemployment. A cross-sectional comparative study which was conducted to describe aspects of HRQoL in Mexican patients with AAV evaluated patients with AAV and compared them to groups of patients with rheumatoid arthritis, CKD, and healthy volunteers. In this study, significant differences were shown only in the section of bodily pain of SF-36.[26] In a study evaluating the effect of sinonasal morbidity on QoL in AAVs, patients with and without ENT involvement were compared, and it was shown that the QoL, especially in the presence of ENT involvement, was significantly reduced.[27] Studies evaluating HRQoL according to specific involvement patterns are not sufficient.

There have been a few studies specifically evaluating HRQoL of patients with GPA. Faurschou et al.[1] demonstrated worse scores in all domains of SF-36 in GPA patients with inactive disease. Walsh et al.[4] reported altered physical domains of SF-36 even at the time of diagnosis in AAV (58.5% of the patients with GPA), particularly with older age and neurologic involvement. Tomasson et al.[15] reported improvements in SF-36 scores with effective treatment in GPA patients in comparison to baseline SF-36 values and significant correlation with disease activity. We observed marked alterations in HRQoL in GPA patients under remission similar to the results of Faurshcou et al.[1] Remarkably, our results demonstrated sparing of mental health.

Disease related permanent organ damage should presumably be a major aspect regarding HRQoL in GPA. However, previous reports have been contradictory. Furthermore, impact of different organ systems on HRQoL may vary. Faurschou et al.[1] did not report any significant relationship between VDI scores and HRQoL except for a weak correlation with pulmonary domain. Tomasson et al.[15] evaluated patients from two different cohorts and demonstrated an inverse relationship with physical component summary score of VDI only in patients from one cohort. In our study we did not find out a significant inverse correlation between any domain of SF-36 and VDI.

Effects of several other factors on HQoL in GPA had also been evaluated. Walsh et al.[4] reported older age as a factor related with impaired SF-36 scores. Faurschou et al.[1] revealed number of GPA flares and disease duration do not affect SF-36 scores. Our results demonstrated no significant relationship between age, body mass index, symptom duration and SF-36 scores. In addition, we also did not observe any effect of FFS score at the onset of diagnosis, a major prognostic parameter for vasculitides, on SF-36 scores.

Effective immunosuppressive treatment is the cornerstone in management of GPA. Patients with severe manifestations and refractory/recurrent disease usually receive potent treatment agents such as CTX and high dose steroids, including pulse administrations, which increase overall disease burden with addition of treatment related complications. In addition to these conventional agents, RTX, a CD20 B lymphocyte inhibitor, emerged as a highly effective treatment agent in GPA. Although RTX has initially been used for patients who do not respond to conventional agents or could not adhere to other treatments, lately RTX has been considered as principal induction agent particularly in severe disease.[28] Faurschou et al.[1] reported in 2010 that adhering to maintenance therapy with conventional agents was related with impaired physical component summary scores when compared to patients who were off treatment. In our study, we evaluated correlations between total dose of ever administered RTX, CTX, steroids and SF-36 domains, and observed that total RTX dose had significant inverse correlation with general health and role emotional. As aforementioned, RTX was traditionally used in refractory and resistant patients, which was also valid for our cohort. Therefore, increased RTX use may imply refractory and recurrent disease which may be related to the alterations in SF-36 domains.

To our best knowledge, for the first time such relation with RTX is demonstrated. The small sample size was the major limitation for our study which avoided advanced statistical analyses to be executed to better demonstrate possible effectors of HRQoL. Secondly, cross-sectional nature of the study avoided detection of temporal changes. Furthermore, due to the small sample size we could not evaluate whether subdomains of VDI had any effect on SF-36 scores. Lastly, since this is a single-center study, general assumptions should be made carefully based on our results.

Conclusion

GPA has multiple aspects, aside from disease related manifestations alone, which may impact the overall well-being. HRQoL provides a perspective to patients

regarding their condition, therefore, assessment of HRQoL may act as an extract to evaluate overall success of the clinicians medical approach contributing to other outcome measures. Despite advances in management of GPA, our results suggest impairment of HRQoL is still an issue. Furthermore, RTX treatment may be indicative of altered HRQoL. Larger studies evaluating GPA patients comprehensively may further clarify the major confounders affecting HRQoL.

Ethics

Ethics Committee Approval: Ethics approval (E2-21-792) was obtained by Ankara City Hospital Ethics Committee and the study was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: Written consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.E., O.K., A.O., Design: S.C.G., A.E., B.A., O.K., A.O., Data Collection or Processing: P.A.D., M.A.E., Analysis or Interpretation: P.A.D., S.C.G., A.E., B.A., O.K., A.O., Literature Search: P.A.D., S.C.G., A.E., M.A.E., Writing: P.A.D.

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