Health-related quality of life in severe cryoglobulinaemic vasculitis and improvement after B-cell depleting therapy

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ABSTRACT

Objective. *To study the health-related quality of life (HRQOL) in severe cryoglobulinaemic vasculitis (CV) associated with hepatitis C virus infection (HCV) and to describe the effect of rituximab on HRQOL.*

Methods. *HRQOL was evaluated with the Medical Outcomes Study Short Form 36 (SF-36). Health Survey questionnaire was submitted to 15 patients with severe CV. SF-36 questionnaire was evaluated at baseline and after rituximab.*

Physical Health Composite Summary (PCS) and Mental Health Composite Summary (MCS) scores were calculated according to standard protocols, and normalised to healthy controls. SF-36 summary scores were compared with those of HCV positive patients without CV, and other vasculitis published in the literature. European Quality of Life-5 dimensions (EQ5D) scores were also derived.

Results. *Physical and mental domain scores were all reduced if compared with those of the healthy population, with physical domains being greatly affected. HRQOL of CV was comparable with HRQOL reported for the other small-vessel vasculitis. The development of CV in HCV positive patients worsened PCS rather than MCS score. Birmingham Vasculitis Activity Score (BVAS) did not correlate with HRQOL, while the presence of peripheral neuropathy was associated with a worse HRQOL. Early rituximab treatment improved both PCS and MCS scores, with long-term effects.*

Conclusions. *PCS rather than MCS was affected in HCV positive patients when CV is present. Rituximab improved both physical and mental domains, thus supporting its use before antiviral therapy in severe HCV-related CV. The cost/benefits ratio of a sequential therapy may be supported.*

Introduction

Cryoglobulinaemic vasculitis (CV), is a systemic vasculitis that is primarily mediated by immune complexes and is often associated with hepatitis C virus (HCV) infection and B cell lymphoproliferation (1-5). Development of CV in HCV positive patients further contributes in reduction of quality of life possibly involving fatigue, depression, and cognitive impairment. Antiviral treatments for HCV and other biopsychosocial factors can reduce quality of life and complicate management (6). Also, HCV treatment has a high overall cost that increases when extrahepatic manifestations are considered (7). Published studies have provided preliminary information suggesting that the impact of systemic vasculitis may be significant and far greater than previously anticipated (8-10). Costs for vasculitis-related hospitalisations for polyarteritis nodosa, hypersensitivity vasculitis, Granulomatosis with polyangiitis (Wegener's) (GPA), giant cell arteritis and Takayasu's arteritis in the US amounted to $150 million per year. However, information detailing the impact of the vasculitides on quality of life has been difficult to obtain and in CV, in particular, is absolutely lacking (11). Thus, the goal of this study was to examine the health-related quality of life (HRQOL) in 15 patients with severe manifestations in the course of CV using the Medical Outcomes Study Short Form 36 (SF-36) Health Survey (12). Prospective analyses on the impact of rituximab on HRQOL have been also provided in this cohort.

Methods

This study was approved by the Institutional Review Board of the University of Udine (co-ordinating centre) and by the local ethics committee (13). SF-36 questionnaire was submitted to 15 patients with severe manifestations in the course of CV (*i.e.* active glomeru-

lonephritis, progressive peripheral neuropathy, skin ulcers) enrolled in the recently published randomised, controlled trial on the efficacy of rituximab in CV (13). Details on study design and treatment protocol have been described elsewhere (13). SF-36 questionnaires were evaluated at baseline and in the follow-up after rituximab at month +3, +6, +12 and +24.

Demographic variables are presented in Table I. These included sex, age, duration of the CV, previous treatment with antiviral therapy for HCV, original group of randomisation (conventional treatment or rituximab), baseline Birmingham Vasculitis Activity Score (BVAS), baseline European Quality of Life-5 dimensions (EQ5D), baseline prednisone daily dose.

HRQOL was evaluated using the SF-36 Health Survey, a generic self-reported health questionnaire administered in the patient's native language. The SF-36 measures HRQOL in 8 domains, 4 physical [physical functioning (PF), role physical (RP), bodily pain (BP), and general health (GH)] and 4 mental [social functioning (SF), role emotional (RE), mental health (MH), and vitality (VT)]. The score for each domain was normalised to Italian population scores (11). In addition, domains are summarised as a physical component summary (PCS) and a mental component summary (MCS), with the US norm population mean±SD of 50±10 for comparison with HCV positive patients without CV at different stages of liver disease and other vasculitis published in the literature (14-18). A 5-point difference in scores is generally regarded as the minimum clinically important difference (MCID) for PCS and MCS (19). EQ5D scores were also calculated from SF-36 questionnaire results, by using a published algorithm (20). Costs of acquisition of rituximab were estimated as € 5350 for one cycle (*i.e.* 1 gram x 2).

Statistical analysis

Categorical variables and frequencies were expressed by percentage, while continuous variables were expressed by mean ± standard deviation (SD) or median (range), as appropriate. T-test or Mann-Whitney test for continuous variables, Pearson's or Fisher's exact test for categorical variables were used, as appropriated, to compare the baseline characteristics of the 15 patients under study and the other 36 patients treated with rituximab in the aforementioned trial (13), for whom SF-36 questionnaires were not available.

One-sample t-test or one-sample median test were used to compare norm-based PCS and MCS values from our series with those of other diseases, as appropriate. When median (range) value was not available in the published references, median value was considered equal to mean, since normality distribution was assumed.

Since retreatment with rituximab started from month +6, if relapse occurred, general linear models for repeated measures were performed to compare PCS scores at baseline, month+3 and month +6. The assumptions that the vector of the measures followed a multivariate normal distribution (Shapiro-Wilk test) and the variance-covariance matrices were circular in form (Mauchly's test) were verified. Friedman test was used to compare MCS and EQ5D scores at baseline, month+3 and month +6.

Explorative analyses with paired *t*-test or Wilcoxon paired test were then performed to compare PCS, MCS and EQ5D scores at month +3 and +6 with baseline values, as appropriate. Further explorative analyses by paired *t*-test or Wilcoxon paired test were also performed to compare results at month +12 and at month +24 with baseline values. No correction for multiple comparisons was applied.

Parametric or non-parametric correlation analyses were used to explore the possible associations between PCS, MCS and EQ5D and the following variables: age, duration of the CV, baseline BVAS, baseline prednisone daily dose, while *t*-test or Mann-Whit-

Table I. Baseline characteristics of the patients in the study.

Patient	Sex	Age	Disease duration (years)	Organ involvement	Original group of randomisation	Previous antiviral TX	PD dose (mg/day)	BVAS	EQ5D
1	F	49	5	Skin ulcer	RTX	N	5	12	0.91
2	F	63	8	Nephritis	Con	Y	12.5	6	0.32
3	F	73	10	Peripheral neuropathy	RTX	Y	10	6	0.28
4	F	66	NA	Nephritis, peripheral neuropathy	Con	Y	12.5	18	0.57
5	F	75	3	Skin ulcers, peripheral neuropathy	RTX	Y	10	12	0.34
6	F	39	12	Peripheral neuropathy	Con	Y	0	6	0.28
7	F	60	5	Nephritis	Con	N	10	12	0.79
8	F	59	10	Peripheral neuropathy	RTX	Y	10	16	0.38
9	F	77	4	Nephritis	Con	Y	25	14	0.89
10	M	52	NA	Peripheral neuropathy	Con	Y	0	6	0.39
11	F	77	2	Peripheral neuropathy	RTX	N	2.5	8	0.3
12	F	65	4	Peripheral neuropathy	RTX	N	7.5	14	0.46
13	F	60	5	Nephritis	RTX	Y	7.5	14	0.29
14	F	63	11	Peripheral neuropathy	RTX	N	12.5	6	0.23
15	F	60	11	Peripheral neuropathy	RTX	Y	0	6	0.43

PD: prednisone; BVAS: Birmingham Vasculitis Activity Score; EQ5D: European Quality of Life-5 dimensions; RTX: rituximab group; Con: conventional treatment group; N: no; Y: yes; NA: not available.

ney test, as appropriate, were used to explore the associations between sex, previous treatment with antiviral therapy for HCV, original group of randomisation (conventional treatment or rituximab).

All statistical tests were two-sided and a $p<0.05$ was considered to be statistically significant. Results are expressed as mean and standard error of the mean (SEM).

Results

Overview

A total of 69 SF-36 Health Survey questionnaires were prospectively collected from 15 patients, 15/15 questionnaires at baseline, +3, +6 and +12 months, 9/15 questionnaires at month +24. All patients were HCV positive, with chronic hepatitis. None suffered from decompensated cirrhosis. All patients were treated with rituximab in a randomised controlled trial, where 51 patients with severe CV were treated with rituximab (10); 9/15 patients belonged to the original "rituximab group" (*i.e.*, rituximab as first-line therapy), while 6/15 patients belonged to the original "conventional treatment group", and they underwent rituximab treatment after failure of the conventional treatment. As stated in the previous work (13), antiviral therapy had to be failed or contraindicated. The original trial enrolled patients suffering from at least one of the following three major clinical involvements: skin ulcers, and/or progressive peripheral neuropathy, and/or active glomerulonephritis. Among the 15 patients herein studied, 2/15 complained skin ulcers, 5/15 had nephritis, and 10/15 suffered from progressive sensory-motor peripheral neuropathy. Retreatment with rituximab was employed in 6/15 patients when relapse occurred, 3/6 within month +12 (end of month +6, month +10, month +10), while in the second year of follow-up in the other 3 patients (end of month +12, month +18, +22).

BVAS significantly decreased in the 24-month follow-up ($p<0.0001$), with significant difference in the score from baseline to month +3 [12 (6-18) *vs*. 6 (0-18), $p=0.03$)], to month +6 [12 (6-18) *vs*. 6 (0-18), $p=0.004$], to month +12 [12 (6-18) *vs*. 6 (0-18), $p=0.003$], and to month +24 [12 (6-18) *vs*. 4 (0-12), $p=0.001$].

No differences between the 15 patients herein studied and the other 36 patients from the original trial (13) were documented as concerns demographic and clinical characteristics (Table II).

Table II. Comparison between the sample of CV with SF-36 questionnaire evaluations and the other CV patients recruited in the original trial (13) and treated with rituximab (rituximab group plus rituximab open label group, n=51).

	SF-36 CV sample (n=15)	Other CV (n=36)	*p*-value
Age (yrs), median (range)	63 (39-77)	65 (37-79)	0.85
Female (%)	1/15 (6.7%)	7/36 (19.4%)	0.41
CV duration (yrs), median (range)	5 (2-12)	6 (0.5-26)	0.44
Organ involvement			
- skin ulcers (%)	2/15 (13.3%)	9/36 (25%)	0.47
- active GN (%)	5/15 (33.3%)	13/36 (36.1%)	0.85
- neuropathy (%)	10/15 (66.7%)	26/36 (72.2%)	0.74
Previous antiviral TX (%)	10/15 (66.7%)	13/33 (39.4%)	0.08
Baseline BVAS, median (range)	12 (6-18)	9 (4-25)	0.90
Baseline PD (mg/day), median (range)	10 (0-25)	5.6 (0-25)	0.56

CV: cryoglobulinaemic vasculitis; GN: glomerulonephritis; TX: treatment; BVAS: Birmingham Vasculitis, Activity Score; PD: prednisone; yrs: years.

Table III. Baseline Medical Outcomes Study Short Form 36 Health Survey scores of CV patients and related mean Z-score.

Domain	Mean Raw score (SEM)	Mean Z-score
PF	34.3 (7.3)	-2.2
RP	20 (10.7)	-1.8
BP	36.7 (8.1)	-1.6
GH	33 (5.5)	-1.9
VT	36.3 (6.3)	-1.2
SF	45.8 (8.5)	-1.7
RE	22.2 (10.6)	-1.8
MH	56.7 (5.1)	-1.0

PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; SF: social functioning; RE: role emotional; MH: mental health; VT: vitality; SEM: standard error of the mean.

Table IV. Physical and mental health summary scores of CV and comparisons with HCV positive patients without CV and patients with other vasculitis.

Disease	n.	PCS (SEM)	MCS (SEM)§
Severe HCV-CV	15	29.7 (2.6)	35.8 (26.7- 62.8)°
CHC (ref. 14)	158	49 (0.8)*	43 (0.9)
Comp. Cirrh. HCV (ref. 14)	76	44 (1.2)*	43 (1.5)
Decomp. Cirrh. HCV (ref. 14)	53	37 (1.5)****	36 (1.9)
AAV (ref. 16)	346	27.6 (0.7)	40.4 (0.6)
GPA (ref. 15)	180	33.5 (0.7)	44.2 (0.9)
Takayasu's arteritis (ref. 17)	158	39.2 (1.0)***	44.5 (1.0)

PCS: physical component summary; MCS: mental component summary; HCV: hepatitis C virus; CV: cryoglobulinaemic vasculitis; Comp. Cirrh.: compensated cirrhosis; Decom. Cirrh.: decompensated cirrhosis; AAV: ANCA-associated vasculitis; GPA: Granulomatosis with polyangiitis (Wegener's). SEM: standard error of the mean.
°median (range).
*$p<0.0001$ by t-test. **$p<0.001$ by t-test. ***$p<0.01$ by *t*-test. ****$p<0.05$ by t-test.
§when median (range) value was not available in the published references, median value was considered equal than mean, since normality distribution was assumed.

Quality of life in severe CV

Baseline SF 36 Health Survey scores for each domain are presented in Table III, along with Z-score normalised to healthy, Italian controls using data from the 1998 US Survey of Functional Health Status, as stated. PF was the domain which was

most affected by CV (Table III). Overall, both physical and mental domains were affected in CV, with deeper involvement of the physical domains (Table III). Notably, patients complaining peripheral neuropathy showed lower VT and MH scores than patients without (p=0.002, and p=0.03, respectively). In patients with neuropathy, both PCS and MCS scores were more affected than in patients without neuropathy (p=0.17, and p=0.05, respectively) (data not shown).
Age, randomised group, previous antiviral therapy, CV duration, baseline BVAS, baseline daily prednisone dose did not correlate with PCS or MCS.
Mean EQ5D score was 0.46±0.23, by using a published algorithm (20), and it was slightly correlated only with baseline BVAS score (p=0.049).

Comparisons between CV and HCV patients without CV or patients with other vasculitis

Both PCS and MCS scores did not significantly differ from GPA population (p=0.16 and p=0.1, respectively), as well as from ANCA-associated vasculitis (AAV) patients (p=0.43 and p=0.68) (Table IV).
The PCS score of CV patients, but not MCS score, was significantly lower than that provided by the patients suffering from a large-vessel arteritis, as represented by Takayasu's arteritis (Table IV). PCS score resulted significantly lower than that of HCV positive patients without CV, even if decompensated cirrhosis was present (Table IV). On the other hand, MCS score of CV patients resulted as affected as in all subgroups of HCV positive patients (*i.e.* CHC, compensated or decompensated cirrhosis), as well as patients affecting by other vasculitis (Table IV).

Efficacy of rituximab on quality of life in the short-term follow-up

Both PCS and MCS scores were significantly improved by rituximab (p=0.002, and p=0.041) (Fig. 1). The improvement was observed early at month +3, and it was maintained at month +6 for both summary scores (p=0.69 for PCS month +3 *vs.* PCS month +6; p=0.91 for MCS month +3 *vs.* MCS month +6). The same result was obtained in the EQ5D score (p=0.015) (Fig. 2), with no differences between month +3 and month +6 (p=0.7).
No correlation between BVAS and PCS or MCS score was demonstrated at each time points of follow-up (data not shown).

Efficacy of rituximab on quality of life in the long-term follow-up and related costs

Evaluation of quality of life at month +12 and at +24 was available for 15/15 and 9/15 patients, respectively.

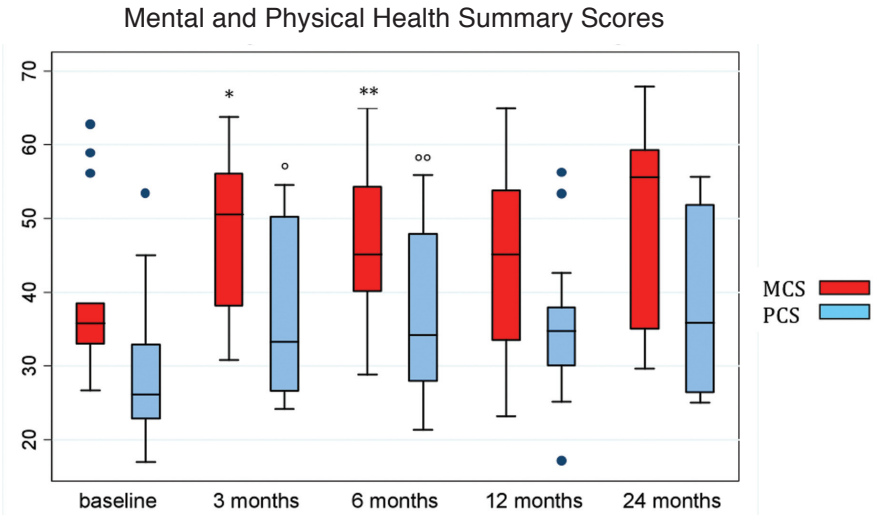

Fig. 1. MCS and PCS score at baseline and in the follow-up after rituximab in CV summarised in boxplot graphs.
*p=0.02 (*vs.* baseline). **p=0.01 (*vs.* baseline). °p=0.001 (*vs.* baseline). °°p=0.02 (*vs.* baseline).

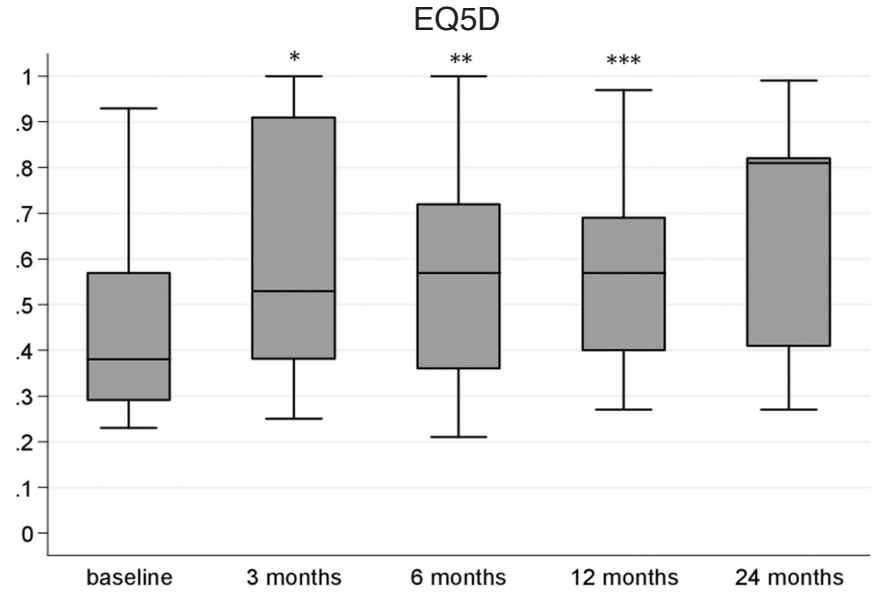

Fig. 2. EQ5D score at baseline and in the follow-up after rituximab in CV summarised in boxplot graphs.
*p=0.006 (*vs.* baseline). **p=0.03 (*vs.* baseline). ***p=0.03 (*vs.* baseline).

Both PCS and MCS scores were maintained higher than the baseline values, though not significantly (Fig. 1). Also, EQ5D remained higher than baseline value at month +12, but not at month +24 (Fig. 2).
No correlation between BVAS and PCS or MCS score was demonstrated at month +12 and +24, as well as for EQ5D at the same cut points (data not shown).
The improvement in EQ5D score provided a total amount of 1,48 Quality Adjusted Life Years (QALY) gain at month +12. If a cost of 5350 EU for

one rituximab cycle (*i.e.* 1 g x 2, day 1 and day 15) was assumed, the cost/QALY was 68,297.90 euros.

Notably, no differences were noticed in the baseline characteristics of the 9 patients with 24 months of follow-up when compared with the remaining 6 patients (data not shown).

Discussion

Preliminary studies suggested that the impact of systemic vasculitis on HRQOL and costs may be significant. Although there are over 15 types of primary vasculitis, HRQOL has been reported for only six different vasculitis types: AAV, Takayasu's arteritis, giant cell arteritis, and Behçet's disease (9, 10, 15-17, 21-23). Because recruiting patients with a rare illness is often costly and logistically difficult, researchers' ability to describe HRQOL is limited, especially with rarer forms of vasculitis, including CV.

This work provided the first evaluation of HRQOL in severe HCV-related CV patients, (*i.e.* patients with at least one of the following major manifestations: active nephritis, progressive neuropathy, or active skin ulcers), and the effect on HRQOL of B-cell depleting therapy in this disease, even if in a limited number of cases.

Differently from the other vasculitis, CV is often associated with HCV infection, thus a combination effect of an autoimmune disease and an infectious disease should be taken in account when HRQOL is considered in this kind of patients. In fact, patients chronically infected with HCV have a decreased HRQOL compared to the general population (24, 25). The impact of the disorder is comparable with other stressful life events and chronic diseases, like diabetes (26). Also, although treatment of chronic HCV with (peg)interferon-alpha and ribavirin has been associated with an improvement on (almost) all different dimensions of the SF-36, it could further diminish HRQOL, mainly in women, due to its side effects, thus impairing subscale physical functioning (27).

In our study, the presence of major cryoglobulinaemic manifestations in HCV-positive patients greatly affected physical rather than mental components, if compared with HCV-positive patients without CV. This observation is consistent with the results observed in other small-vessel and large-vessel vasculitis, where PCS is more impaired than MCS as respect to general healthy population (15-17).

However, CV patients showed the same impairment in PCS and MCS as observed in GPA or AAV in general, while there was a much more pronounced involvement of physical components than in large-vessel vasculitis, probably due to a deeper impairment of PF and RP domains. HRQOL appeared more impaired by peripheral nerve involvement in CV, and this finding is consistent to the same observation in AAV patients (16). Even if the comparison of HRQOL ought to involve patients coming from the same Hospital Units, the use of literature data could be acceptable, in particular in such rare diseases, although this point represents a limitation of our study.

Interestingly, early rituximab therapy ameliorated both PCS and MCS scores, with sustained results up to 12 months. Notably, MCS score showed the most important improvement, with a score about 50, which was maintained over time up to 24 months. This observation points out the possible advantage on HRQOL of rituximab administration before antiviral therapy in severe CV. Starting from month +12, a reduction of PCS and MCS scores was observed, consistently with a clinical relapse also observed in the original trial, where retreatment with rituximab was generally employed in the second year of follow-up. The possible delay between the time of retreatment and the time of clinical relapse could in part explain the slightly lower degree of response in PCS and MCS at 24 months. Thus, in selected cases, planning a retreatment with rituximab within month +12, may avoid such delay and possible progression in irreversible disability.

HRQOL was incompletely explained by disease activity in CV, as measured by BVAS score, because the disease per se could decrease HRQOL, irrespectively from the disease activity (9). This finding reinforces that HRQOL cannot be reduced to biological effects of the disease and that accounting for many other factors is important. In particular in CV, chronic HCV infection may play a crucial role.

Finally, cost/QALY gain in the first year of treatment was about 70,000 euros. Since the majority of patients showed a prolonged clinical response to a single cycle of rituximab (13), this cost may be largely acceptable in a lifetime scenario.

In conclusion, CV has a profound physical and mental impact on HCV positive patients, as well as reported for other primary systemic vasculitis. Rituximab improved both physical and mental domains over time. Differently from antiviral therapy, rituximab may produce a very good effect on mental health components both in the short and long term, thus supporting its use before antiviral therapy in severe HCV-related CV. Costs of rituximab in severe CV appeared affordable, and the possible benefits on HRQOL of a subsequent antiviral therapy may be increased by previous B-cell depleting therapies.

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