Association of the ANCA-associated vasculitis (AAV) patient-reported outcome (AAV-PRO) questionnaire with established outcome measures in AAV

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with regard to the work. J. Robson is a coinventor of the AAV-PRO which is freely available for use in academic and clinical settings.

Abstract

Objective: The ANCA-associated vasculitis (AAV) patient-reported outcome (AAV-PRO) questionnaire has been developed to capture the impact of AAV and its treatment on the patient perspective. We aimed to explore the association of the patient's domain scoring in the AAV-PRO with disease activity and extent, damage, depression, health-related quality of life and treatment.

Methods: In a prospective longitudinal study AAV-PRO, Beck's depression inventory (BDI), Short Form 36 (SF36), BVAS and Vasculitis Damage Index (VDI) were completed at baseline (t1) and after 3-6 months (t2). In addition, patient data such as diagnosis, therapies, relapses, and organ manifestations were recorded. Data were analyzed by t-tests and correlation-based regression analyses.

Results: 156 patients with AAV participated. The mean BVAS was 1.4 ± 3.74. Median AAV-PRO domain scores were higher in patients reporting "active disease" compared to patients reporting "in remission" ($p<0.001$). In the correlation analyses all AAV-PRO domain scores correlated strongly with the BDI (all $r\geq0.319$, all $p\leq0.001$) as well as all eight SF36 subdomains (all $|r|\geq0.267$, all $p\leq0.001$). The regression analyses showed that AAV-PRO domains were strongly predicted by BDI and SF36 domains ($|\beta|\geq0.240$ for the strongest predictor of each domain). In the longitudinal comparison (t1/t2) there were no decisive changes of the overall results.

Conclusion: Our data show convergent validity of all AAV-PRO subdomains with the established questionnaires BDI and SF-36. The AAV-PRO domains scores were not correlated

with clinician derived instruments including the BVAS and VDI. Thus, we regard the AAV-PRO as a valuable addition that might complement traditional endpoints like activity and damage in clinical trials.

Importance and Significance

- AAV-PRO domain scores are associated with the patient's perception of disease activity, measures of depression and generic measures of HRQoL including the SF-36
- The correlation between AAV-PRO scores and clinician derived measures of activity and damage, including the BVAS and VDI was low in this study.
- AAV-PRO may complement traditional outcomes in future clinical trials and studies in AAV.

1. Introduction

In patients with anti-neutrophile cytoplasmatic antibody (ANCA-)associated vasculitis (AAV) disease activity and damage are assessed by using standardized tools such as the Birmingham vasculitis activity score (BVAS) and the vasculitis damage index (VDI) (1,2). However, it has been shown, that patients and physicians often diverge in their disease assessment (3). Until recently, patient-reported outcomes had not been made measurable by an ANCA-associated vasculitis (AAV) specific patient-reported outcome (PRO) instrument. The OMERACT vasculitis group first identified this gap; a 29-item AAV-PRO questionnaire was then developed and validated by Robson and colleagues in 2018 in a large AAV cohort in the United Kingdom and the United States which was subsequently endorsed by OMERACT in 2017 (4,5). A recent systematic review of outcome measurements reported the BVAS (disease activity), VDI (disease damage) and AAV-PRO (health related quality of life) measures are the three outcomes with the strongest psychometric properties of all instruments used in AAV, when assessed using COSMIN and OMERACT frameworks. Specifically for HRQoL, AAV-PRO demonstrated face validity, correlations of the six AAV-PRO domains with EQ-5D-5L: −0.78 to −0.55; and discrimination between active disease and remission $p<0.0001$ for all comparisons in the validation study.

PRO measurements provide information regarding the quality of health care from the patient's perspective (6). It is to be expected that in the foreseeable future new medical treatments will be required to demonstrate improvements not only in clinical scores, mortality rates, laboratory findings and imaging, but also in the field of PROs. This would constitute an important step towards a more patient-centered care. Therefore, PRO tools will be of increasing importance, especially in diseases with a severe impact on patient's lives.

Generic PRO questionnaires such as the short-form 36 (SF-36) have been in use for quite some time in a great variety of illnesses (7). However, rare and complex, multi-systemic diseases like AAV with potentially grave sequalae such as destructive sinusitis, tracheal stenosis, end-stage renal disease, debilitating polyneuropathy and chronic fatigue call for a disease specific outcome measurement due to their unique appearance and gestalt.

The aim of this study was to explore if and how the AAV-PRO correlates with traditional outcome instruments used such as BVAS and VDI as well as other outcome instruments to assess patient's perspective in clinical trials in AAV and to validate the AAV-PRO in a German AAV cohort. It was our objective to investigate the influence of disease activity, damage, the extent of depression, health-related quality of life, organ manifestations, number of relapses, applied treatments and sociodemographic factors on the AAV-PRO domains in a prospective, two center trial. To the best of our knowledge, this is the first study to compare the AAV-PRO with the SF36 and the BDI.

2. Patients and Methods

Study design

We conducted a prospective, non-interventional clinical cohort study that included patients from the Rheumatology departments of the medius Klinik Kirchheim and the University of Tübingen. The trial was conducted according to the principles of the Helsinki Declaration and was approved by the ethics committee of the University of Tübingen (project number 777/2020BO2).

Men and women aged ≥18 years who were able to give informed consent and have been diagnosed with AAV according to the 2012 Chapel Hill definition (8) were included while

patients with secondary vasculitides associated with infectious diseases, other inflammatory diseases, and malignancies were excluded.

Data collection and questionnaires

All patients gave their written consent to participation. To capture the patient's perspective, all included patients completed three questionnaires at baseline (t1) and after 3-6 months (t2):

(i) The AAV-PRO. Being a profile measure it contains 29 items in six different domains: 'organ-specific symptoms' (OSS), 'systemic symptoms severity' (SSS), 'treatment side effects' (TSE), 'social and emotional impact' (SEI), 'concerns about the future' (CAF) and 'physical function' (PF). The five possible responses are scored 0 – 4 according to increasing severity (5).

(ii) The Beck Depression Inventory (BDI) is a depression inventory suitable for assessing the severity of depression or screening for depressive symptoms. The original version was revised in 1966 to BDI II, which was applied in this study. For each of the 21 items, 0 to 3 points are assigned and added to a total score that indicates mild (≥ 13 points), moderate (≥ 20 points), and severe depression (≥ 29 points) (9).

(iii) The Short Form-36 (SF-36) is a widespread and frequently used health-related quality of life questionnaire that can be used in various diseases as well as in the healthy population. It consists of 36 items assigned to 8 health dimensions: 'physical functioning' (PF), 'role functioning physical' (RFP), 'role functioning emotional' (RFE), 'energy and fatigue' (EF), 'emotional well-being' (EWB), 'social functioning' (SF), 'physical pain' (Pain) and 'general health perception' (GH) (7).

Further, the patients were asked to report whether they currently considered their disease to be active or in remission. The Birmingham Vasculitis Activity Score version 3 (BVAS) was

used to measure disease activity. The 56 findings listed in the BVAS are weighted differently according to their severity and 1 - 9 points are assigned for each symptom (2). Long-term damage was assessed with the Vasculitis Damage Index (VDI), which contains a total of 64 items from 10 organ-related categories and one category for treatment side effects (1). The VDI, the number of major and minor recurrences as well as information on patients' age, sex, diagnosis, disease duration, ANCA status, organ manifestations and all previous therapies were obtained from our digital patient records. Current blood values such as inflammatory parameters and ANCA state were obtained at each clinical visit.

For the second timepoint (t2) data acquisition was identical to t1. For patients with a follow-up interval of >6 months, the follow-up questionnaires were collected by mail. In these cases, BVAS and blood samples could not be examined at t2, and the previous values were used for VDI, recurrences, and organ manifestations according to the principle "last-observation-carried-forward".

Statistical analysis

Data were analyzed using the SPSS, version 28.0. In addition to descriptive statistics such as frequency distribution, minimum, maximum, mean and cross-tabulations, various methods of analytical statistics such as correlation analyses, t-tests, and regression analyses were performed. We used a significance criterion of $\alpha = 0.05$ per test.

3. Results

Study population

156 patients with AAV participated: 81 GPA, 26 MPA, and 41 EGPA. Demographic and clinical characteristics are shown in table 1. The mean age was 57.4 $\pm$ 16.4 years, 50.6% of the

participants were female. 80.8% of patients were in stable remission based on the BVAS assessment (BVAS = 0) and 71.8% considered themselves to be in remission. 68 (43.5%) of the patients had no reports of relapses so far, while another 68 patients (43.5%) had a history of one or two relapses. Twenty (12.8%) patients had three or more relapses.

AAV-PRO Domain Scores and relation to other outcomes

Median AAV-PRO domain scores were higher in patients reporting 'active disease' compared to patients reporting 'in remission' ($p<0.001$) (table 2). Patients who rated their disease as active also had significantly higher mean scores in the BDI and all 8 domains of the SF-36 (all $p<0.001$). When the patient cohort was divided based on objective disease activity (BVAS ≥ 1) the results were heterogenous (table 3).

Over time there was a high correlation of the scores for all AAV-PRO domains between baseline and follow-up (all $r\geq0.704$, all $p<0.001$). The same was seen for BDI ($r=0.750$, $p<0.001$) and all SF-36 subdomains (all $r\geq0.539$, all $p<0.001$).

Correlation analyses

In the correlation analyses of the AAV-PRO domains age was correlated with domain PF (t1: $r=0.190$, $p=0.018$, t2: $r=0.169$, $p=0.043$) as well as TSE (t1: $r=-0.209$, $p=0.009$, t2: $r=-0.166$, $p=0.046$). Patients with longer disease duration showed lower values in SEI (t1: $r=-0.232$, $p=0.004$), TSE (t1: $r=-0.173$, $p=0.031$) and CAF (t1: $r=-0.180$, $p=0.025$, t2: $r=-0,182$, $p=0.028$). No evidence for relationship was seen between the AAV-PRO domains and therapies, sex, the number of relapses as well as the number of organ manifestations. However, correlations with AAV-PRO domains were observed for some specific organ manifestations. Pulmonary manifestations ($r=0.169$, $p=0.035$) and ENT (t1: $r=0.199$, $p=0.013$) correlated with higher

values in the domain OSS, while renal manifestations were negatively correlated with OSS scores (t1: r=-0.255, p=0.001, t2: r=-0.236, p=0.004). Neuropathies were correlated with higher scores in the domains PF (r=0.217, p=0.007) and SSS (r=0.246, p=0.002) at t1 and with all AAV-PRO domains at t2 (r=0.181, p≤0.029).

As demonstrated in table 4, correlation analyses revealed strong correlations with the BDI (all r≥0.319, all p≤0.001) and with all eight SF-36 subdomains (all |r|≥0.267, all p≤0.001). BVAS and VDI, correlated weakly with AAV-PRO domains.

To further investigate the possible relationship between the changes between the AAV-PRO domains, the BDI, and the SF-36 domains over time, correlation analyses were performed between the differences of each variable (t2 - t1). With few exceptions in the domains OSS and TSE, significant correlations of the differences were found between t1 and t2 (all |r|≥0.155, p≤0.029).

Regression analyses

The two strongest predictors of each AAV-PRO domain at t1 are shown in figure 1. OSS was mainly predicted by the BDI, the number of relapses and the SF-36 domains ‘physical functioning’, ‘pain’ and ‘general health’. For SSS it was ‘pain’ and ‘energy and fatigue’ in the SF-36. The strongest predictor of TSE was the BDI. It was also associated with SF-36 ‘energy and fatigue’, ‘emotional well-being’, ‘social functioning’ and ‘pain’. Especially SEI, but also CAF were predominantly predicted by the BDI and SF-36 ‘emotional well-being’. Overall, the strongest association was seen between PF and SF-36 ‘physical functioning’ (t1: |β|=0.9, t2: |β|=0.718, all p<0.001).

The AAV-PRO domain SEI was found to have high predictive power for the BDI (|β|≥0.503, all p<0.001). High β-values were also found in all analyses regressing the SF-36 subdomains on the AAV-PRO domains (all |β|≥ 0.159, p≤0.196).

A detailed depiction of all regression analyses for each of the six AAV-PRO domains can be found in the supplement table 1.

4. Discussion

In this trial we applied the AAV-PRO questionnaire in German AAV patients from two large German vasculitis centers.

In our cohort patients and physicians agreed in 80.0% of cases regarding the assessment of their state of disease. All six AAV-PRO domains scored higher in patients that considered their disease to be active. Also, in patients with physician-confirmed active disease, i.e. BVAS ≥ 1, four out of six AVV-PRO domains reached significantly higher values. Counterintuitively, the domain “organ-specific symptoms” did not discriminate between active and inactive diseases at t1.

Patients with a greater number of relapses and those with ear-nose-throat involvement and polyneuropathy scored higher in the “organ-specific symptoms” domain compared to those with pulmonary and/or renal manifestations. While the latter is attributed to substantial medical implications and increased long-term risks by physicians, patients on the other hand do not report a moderate chronic impairment of renal function or a lung nodule to be compromising for their lives; most likely because they often are asymptomatic in these regards. These findings are in line with previous investigations (10,11). It is noteworthy, that this observation was not paralleled by a correlation between the AAV-PRO and the VDI. The VDI adds up all items concerning disease and treatment related damage. However, it does

not weigh them regarding their clinical impact on patients since all VDI items are equally weighted and provide for 1 point each. E.g., a patient with chronic kidney disease, persisting proteinuria and steroid induced hypertension will receive a score of 3 on the VDI, while a patient with debilitating polyneuropathy which might have led to occupational disability and a loss of job only will score 1. Thus, limiting one's perspective on the VDI in assessing the long-lasting impact of AVV bears the danger of underrating and distortion on behalf of physicians.

Other AAV trials confirmed the discrepant perception and weighting of symptoms between patients and physicians. Herlyn et al. reported that patients did not primarily rate organic symptoms, but rather fatigue and reduced energy levels as what burdened them the most 12. Other studies confirmed that bio-psychological factors have a greater overall impact on the quality of life than clinical factors, with fatigue playing a major role in this regard (13,14). In keeping with these findings, it is noticeable that in our study, the SF-36 domain 'energy and fatigue' showed one of the strongest correlations with all AAV-PRO domains at both timepoints. This even applies to domains such as that on organ-specific symptoms, with which no correlation would have been expected in terms of content. Thus, the AAV-PRO is capable of capturing symptoms like fatigue that severely affect our patients but are not recorded by traditional AAV instruments.

There were no relevant differences in AAV-PRO scoring when evaluating gender, age, disease duration and applied treatments. One would have expected patients with higher disease burden and a history of more immunosuppressive treatments to be more compromised in various dimensions of everyday life. It can be speculated if this may be regarded as a tribute to a generally good treatment tolerability and if it possibly reflects a more restrictive use of

glucocorticosteroids (GC) which are generally associated with extensive side effects and a reduced quality of life in various autoimmune conditions (15,16). However, our evaluation did not explicitly address the impact of GC.

This is the first trail comparing the AAV-PRO with the BDI and the SF-36. The AAV-PRO demonstrated substantially significant correlations with the BDI and the corresponding dimensions of the SF-36. The strongest effects were seen in the domains “social and emotional impact”, “concerns about the future” and “treatment side effects”. Firstly, this confirms the AAV-PRO’s convergent validity. Secondly, the conclusion must be drawn that patients with depressive moods or disorders will generally score higher on the AAV-PRO. Albeit depression occurs more frequently in AAV patients (17), this remains a caveat since depression is not necessarily linked to AAV which might be a confounder when interpreting its results.

The results of AAV-PRO measurements and their correlations remained stable at t2 confirming good test-retest reliability shown in the validation study (5).

Our study has certain limitations. Firstly, the number of calculations in the correlation and regression analyses limits the power with the given sample size. Therefore, the replicability of our results should be assessed in the future, possibly with a larger multicenter cohort. Secondly, further investigations of the AAV-PRO in a greater number of patients with active vasculitis should be undertaken since the greater part of our patients were in stable remission or had low disease activity. Strengths of our study are its prospective longitudinal design, standardized patient evaluation in two closely linked vasculitis centers and its real-

world patient population, which is due to the consecutive recruitment from inpatient and outpatient care.

In summary, we confirm the AAV-PRO questionnaire's validity in a German AAV cohort. We demonstrate its discriminative power between disease activity states and the strong influence of affective disorders being a potential confounder and – most importantly – we explored its capability of highlighting the individual significance our patients attribute to the repercussions of their disease. In our opinion, the AAV-PRO contributes to overcoming the frequently existing mismatch between the patient's and the physician's assessment of the disease. Thus, we consider the AAV-PRO to be a valuable and meaningful addition in the evaluation of AAV patients.

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