Development of a score for assessment of radiologic damage in large-vessel vasculitis (Combined Arteritis Damage Score, CARDS)

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ABSTRACT

Objective. *Outcome assessment in large-vessel vasculitis (LVV) remains challenging and this impairs patient management and the conduct of clinical studies. Previous proposals for outcome tools have not included imaging. This study aimed to develop an imaging score to quantify damage in LVV and to assess the difference between Takayasu (TAK) and giant cell arteritis (GCA).*

Methods. *Ninety-six patients (41 TAK, 55 GCA) were identified from local registries at two University Hospitals in the UK. Radiologic lesions including stenosis, occlusion and aneurysm were evaluated in 25 arterial regions by enhanced computed tomography or magnetic resonance angiography. Lesion correlation with combined damage assessment scores was employed in a multiple regression analysis to define the weight of individual lesions and develop a damage index.*

Results. *A numerical damage index was developed: the "Combined Arteritis Damage Score (CARDS)". The index was derived from a formula: number of regions with mild stenosis × 0.6 + number of regions with moderate to severe stenosis × 1.2 + number with occlusions × 1.6 + number with aneurysms × 0.8 in 25 arterial regions. The median CARDS was higher in TAK than GCA (4.1 and 0.6, interquartile range 1.3–5.7 and 0–3, p<0.001).*

Conclusion. *We have developed a damage assessment tool, CARDS, based on imaging in LVV of potential value to clinical studies and patient management. TAK and GCA differ in the radiologic severity of disease.*

Introduction

Takayasu arteritis (TAK) and giant cell arteritis (GCA) are subtypes of large-vessel vasculitis (LVV). In the Chapel Hill Consensus Conference 2012, TAK and GCA were the only categories within the LVV classification and this was unchanged from the first, 1993 Consensus statement (1, 2). The diagnosis of TAK is often delayed since TAK patients may be asymptomatic or have non-specific symptoms, such as, fever, fatigue, and myalgia. When specific symptoms, such as, pulse loss, claudication, bruits, and blood pressure discrepancy appear, the patient will already be in an advanced stage (3). GCA typically has a more acute symptomatic presentation with temporal arteritis (4, 5), thus the time from symptom to diagnosis is longer in TAK than GCA (median 21.4 month and 2.7 months, respectively, p=0.05) (6). It is important to make the diagnosis early to allow the opportunity for treatment in order to minimise the development of irreversible damage. This is of particular importance in TAK patients of young age and has been standardised in consensus guidelines (7, 8). More recently, biologics, such as, rituximab, anti-TNF antibody therapies and tocilizumab have been used for patients with refractory disease (9, 10), but the evidence supporting these modalities in TAK is weak, in part due to an absence of reliable outcome measures (11-13). In GCA clinical trials, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) levels and characteristic symptoms have been used as outcome measures although their validation has been limited (14-16).

The development of outcome measures have facilitated clinical trials in ANCA-associated vasculitis with direct impacts on patient benefit. The Birmingham Vasculitis Activity Score (BVAS) (17) and Vasculitis Damage Index (VDI) (18) were originally developed to assess vasculitic activity and

the accrual of all cause damage in any vasculitic syndrome including LVV. Although validated in small-vessel vasculitis they have proved less useful in LVV studies (13). In part, this has been due to the narrow range of items attributable to LVV in BVAS and VDI and in addition there has been difficulty in discriminating whether a clinical or radiologic feature results from active disease or irreversible damage. The combined damage assessment (CDA) was developed as a more extended system for damage assessment than the VDI (19).

In contrast to small-vessel vasculitis, the visualisation of vascular pathology by imaging in LVV has the potential to provide information on both activity and damage. Disease activity may be reflected by wall thickness or oedema detected by magnetic resonance imaging or angiography (MRI/MRA), enhanced CT, ultrasound (US) and with 18F-fluorodeoxyglucose (FDG) uptake detected by positron emission tomography (PET). In the advanced stage, damage is assessed by stenosis, occlusion, aneurysm or dilatation which are irreversible lesions detected by MRI, enhanced CT, US and angiography (13, 20, 21). Current assessment tools in TAK employ clinical and laboratory variables but not imaging and have had limited usefulness (22, 23). This study aimed to develop an imaging damage score in LVV by determining the optimised weight of imaging findings and to assess the difference between TAK and GCA and the correlation between the new imaging measure and other indices.

Methods

Patients

96 sequential patients with LVV and disease below the head and neck attending the vasculitis clinic at Addenbrooke's Hospital, Cambridge and Botnar Research Centre, Oxford were identified by retrospective chart review. These patients all had imaging abnormalities defined as arterial wall thickness, stenosis, occlusion or aneurysm/dilation by enhanced CT or MRI/MRA, and defined as FDG uptake by PET/CT once. All patients met Chapel Hill 2012 Consensus definitions of LVV (1). TAK was defined as having arterial lesions of the aorta and/or primary branch vessels attributed to vasculitis and younger than 40 years at disease onset (6, 24). GCA was defined as having arterial lesions of the aorta and/or primary branch vessels attributed to vasculitis and older than 50 years at disease onset. In accordance with current UK ethical guidelines, ethical approval was not required because this work includes only retrospective data collected during routine clinical care or audit.

Data elements

Age at disease onset, age at diagnosis, sex, clinical symptoms at diagnosis, CRP, and ESR levels at diagnosis, use of oral glucocorticoids (converted to the equivalent prednisolone dose), immunosuppressant and, biologic exposure and cumulative glucocorticoid dose were assessed retrospectively. There is no established gold standard for damage assessment in TAK. Therefore CDA scores were used to determine the 'weight' of lesions defined by imaging (25). CDA was chosen because it includes more items than VDI, 135 items in 17 categories and is potentially more sensitive. Recent large-scale clinical trials in small-vessel vasculitis are employing the CDA (26). CDA was measured on the date when imaging was performed. At the same time, physician global assessment (PGA) of damage using a 10-point Likert scale was also measured (26).

Imaging

For the imaging definitions of lesions and their distribution subjects were selected with reference to cohorts from the USA, Italy, China and Japan (the total number of patients was 762) (27-30). Namely, wall thickness, stenosis, occlusion and aneurysm (including dilation). We employed enhanced CT or MRA with images from the neck to the abdomen (20, 31). Furthermore, stenosis was sub-classified as mild, <50% or moderate to severe, 50-99% narrowing. The following arterial regions were evaluated in 25 subjects; carotid artery, vertebral artery, brachiocephalic artery, subclavian artery, axillary artery, ascending aorta, aortic arch, descending aorta, abdominal aorta, celiac artery, superior mesenteric artery, renal artery, iliac artery, pulmonary artery bilaterally and coronary artery including right coronary artery, left anterior descending coronary artery, left circumflex coronary artery and left main trunk. All images were reviewed by a vascular radiologist and a rheumatologist trained in vascular radiology. Imaging review was blinded with regard to the clinical features. Coronary artery lesions were included if detected on coronary angiography performed for symptomatic reasons.

Surgical interventions including angioplasty, stent, bypass surgery, heart valve replacement, heart transplant and pneumonectomy were evaluated. The procedure was counted twice when the patient had a second intervention within the same arterial region. In a subset of patients, quality of life (QOL) data was available: EuroQol five dimension (EQ-5D) (32), short-form 36 health status questionnaire (SF-36) (33) and patient visual analogue scale (PTVAS) (26, 34).

Statistical analysis

Statistical analysis was performed using SPSS software, v. 22.0J (IBM Japan). Normally distributed continuous data were summarised with means and either SDs or 95% confidence intervals (95% CIs) and were analysed using parametric tests (Student's *t*-test) and Pearson correlation coefficient. Non-normally distributed data were summarised with medians and interquartile range (IQR) and were analysed using non-parametric tests (Mann-Whitney U-test) and Spearman's correlation coefficient. Categorical data were summarised with percentages and were analysed using a chi-square test or, Fisher's exact test. A multiple regression analysis was constructed using a forced entry method and a step-wise method. Intra- and inter-observer reliability of imaging scores were evaluated by calculating intraclass correlation coefficients. Unless otherwise specified, *p*-values less than 0.05 were considered significant.

Results

Total patient damage and imaging findings

96 patients (74 female, 77%) with LVV were evaluated. The median CDA score was 6 (IQR 2–9). In the distribution of organ systems involved in the CDA, vascular disease was the most frequent, present in 67 patients (69.8%), followed by cardiac (60.4%), then 'other' (41.7%). The category of 'others' included surgical intervention and side effects of medication. There were no patients with damage of the nose, sinuses or subglottis. 58 patients (60.4%) were evaluated by enhanced CT and 38 (39.6%) by MRA.

Stenosis was the most frequent lesion, present in 65.6% of patients: 'mild' in 36.5% and 'moderate to severe' in 52.1%. Other lesions were wall thickness (42.7%), occlusion (26%), and aneurysm (14.6%). Stenosis was distributed the most widely in 23 of 25 arterial regions (92%), followed by wall thickness in 17 of 25 (68%), occlusion in 16 of 25 (64%) and aneurysm in 12 of 25 (48%). The most frequently involved arterial region was the left subclavian artery in 35% patients, followed by the descending aorta (33%), aortic arch (29%) and left carotid artery (28%).

Weight of imaging findings

Multiple regression analysis was performed with a forced entry method to determine the optimised weight of imaging findings. CDA was set as an independent variable, and the total number of lesions with stenosis, occlusion or aneurysm in 25 arterial regions as the dependent variables. The lesions before surgical intervention were carried over to reflect cumulative damage. If the patient had had a surgical intervention, the corresponding lesion prior to surgical intervention was scored.

As a result, a regression model was achieved, the Equation representing CDA and weights of imaging findings were as follows; CDA = 3.271 + mild stenosis - 0.646, moderate and severe stenosis - 1.202, occlusion - 1.555, and aneurysm - 0.830 (Table I). These regression coefficients were simplified and employed as the lesion weighting. The number and weight of lesions in each region derived a damage index: the "Combined Arteritis Damage Score (CARDS)" with CARDS = number of mild stenosis × 0.6 + number of moderate to severe stenosis × 1.2 + number of occlusions × 1.6 + number of aneurysms × 0.8. The maximum value is 40 if all 25 arterial regions have occlusions. The median CARDS in the combined TAK/GCA population was 1.7 (IQR 0 to 4.75). The inter-observer reliability using the intra-class correlation coefficients in 30 patients selected randomly was 0.92 (95% CI 0.835 to 0.961) between a vascular radiologist and a rheumatologist. The intra-observer reliability assessed by a radiologist was 0.94 (95% CI 0.829 to 0.978) in 15 patients and by a rheumatologist was 0.91 (95% CI 0.765 to 0.969) (Supplemental Table I).

Table I. Weight of imaging by multiple regression analysis.

	Regression coefficient	*p*	95% confidence interval	
Intercept	3.271	<0.001	2.330	4.213
Stenosis mild(<50%)	0.646	0.041	0.028	1.284
Stenosis moderate to severe(>50%)	1.202	<0.001	0.755	1.849
Occlusion	1.555	0.001	0.678	2.432
Aneurysm	0.830	0.029	0.085	1.574

A multiple regression analysis was constructed using a forced entry method. *P* values less than 0.05 were considered significant.

The regression coefficients were simplified and employed as weight of lesions. We defined the number and weight of lesions in each artery as a damage index and propose the name: "Combined Arteritis Damage Score (CARDS)';

CARDS= number of mild stenosis × 0.6 + number of moderate and severe stenosis × 1.2 + number of occlusions × 1.6 + number of aneurysms × 0.8.

Table II. Assessment for damage and quality of life in patients with Takayasu arteritis and giant cell arteritis.

	TAK, n=41	GCA, n=55	*p*-value
CDA, mean (SD)	7.4 (3.8)	5 (4.0)	0.005
PGA, median (IQR)	5 (4-7)	2 (1-5)	<0.001
	TAK, n=16	GCA, n=15	
SF-36 (Physical component summary), mean (SD)	31.2 (9.5)	35 (10.9)	0.198
SF-36 (Mental component summary), mean (SD)	42.8 (9.6)	52.4 (7.3)	0.004
PTVAS, mean (SD)	51.7 (30)	64 (18)	0.04
EQ5D, median (IQR)	0.655 (0.542-0.752)	0.796 (0.62-0.796)	0.119

Normally distributed continuous data were summarised with means and SD and were analysed using parametric tests (Student's *t*-test). Non-normally distributed data were summarised with medians and interquartile ranges and were analysed using non-parametric tests (Mann-Whitney U-test). *p*-values less than 0.05 were considered significant.

CDA: combined damage assessment; PGA: physician global assessment of damage; SF-36: short-form 36 health status questionnaire; PTVAS: patient visual analogue scale; EQ5D: Euro quality of life-5 dimensions.

Comparison between TAK and GCA for validation

• *Patient characteristics*

Forty-one TAK patients and 55 GCA patients were studied (Supplemental Table II). Mean age at onset in TAK was 29.5 years and GCA was 64.7 years ($p<0.001$). The delay from symptom onset to diagnosis was longer in TAK than GCA (median 31.5 months and 3 months, respectively $p<0.001$). Median disease duration was longer in TAK than GCA (median 100.4 months and 36.5 months, $p<0.001$). Median CRP and ESR level at diagnosis was higher in GCA than TAK (median CRP 81 mg/l and 30 mg/l, $p<0.001$, median ESR 96 mm/h and 34.5 mm/h, $p<0.001$). At the time of recent assessment these levels were typically low or normal and not different between

TAK and GCA (Supplementary Table II). Some patients did not satisfy ACR classification criteria since we defined TAK as younger than 40 years and GCA as older than 50 years at disease onset having arterial lesions of the aorta and/or primary branch vessels attributed to vasculitis. The patient treatment histories are described in Supplemental Table III.

• *Damage*

Median CDA was higher in TAK than GCA (median 7 and 4, p=0.003) (Table II) reflected by higher frequencies of 'vascular' and 'other' CDA items in TAK than in GCA. The frequency of ocular damage was higher in GCA than in TAK (Fig. 1). Median PGA for damage was also higher in TAK than GCA (median 5 and 2, p<0.001).

• *Quality of life*

QOL was assessed in a subgroup of clinic patients: TAK 16, GCA 15. TAK patients had worse scores than GCA for the Mental component summary of SF36 (mean 42.8 and 52.4, p=0.004), and for PTVAS (mean 51.7 and 64, p=0.04). There was a trend for the Physical component summary of SF36 to be lower in TAK than in GCA (mean 31.2 and 35, p=0.198) (Table II).

• *Imaging findings*

Moderate to severe stenoses, occlusions and aneurysms were more commonly seen in TAK than in GCA (Fig. 2a, 2b). The most frequently involved arterial region in 25 vessels in TAK was the aortic arch in 39% of patients with increased wall thickness, the celiac artery in 31% of patients with stenoses, the left subclavian and superior mesenteric artery in 10% of patients with occlusions, the ascending aorta in 22% of patients with aneurysms, the left renal artery in 15% of patients having had surgical interventions. (Supplemental Fig. 1). The most frequently involved arterial region in 25 vessels in GCA was the descending aorta in 29% of patients with increased wall thickness, the left subclavian artery in 26% of patients with stenosis, the right subclavian and axillary artery in 5% of patients with occlusion, the ascending aorta in 5% of patients with aneurysm. (Supplemental Fig. 2).

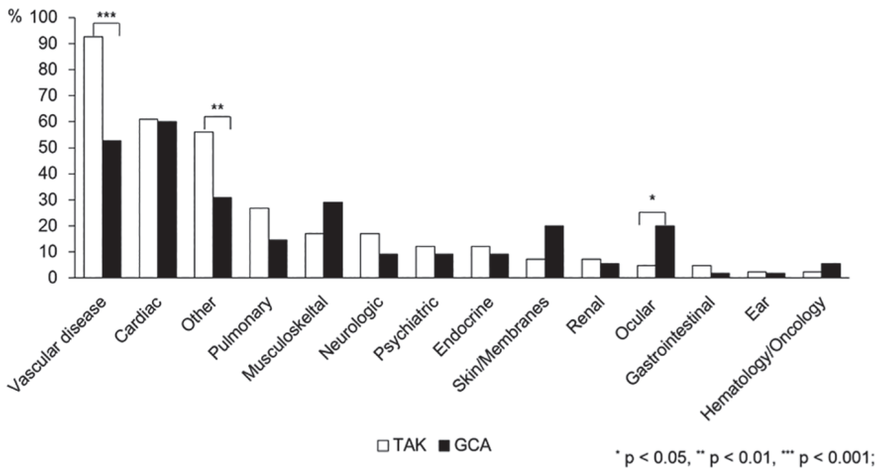

Fig. 1. Spread of organ systems involved in the CDA between Takayasu arteritis and giant cell arteritis.

Items of CDA were compared between Takayasu arteritis and Giant cell arteritis. Combined damage assessment (CDA) includes more items than VDI, 135 items in 17 categories. The category of 'others' included surgical intervention and side effects of medication.

Categorical data were summarised with percentages and were analysed using a chi-square test, Fisher's exact test. p-values less than 0.05 were considered significant.

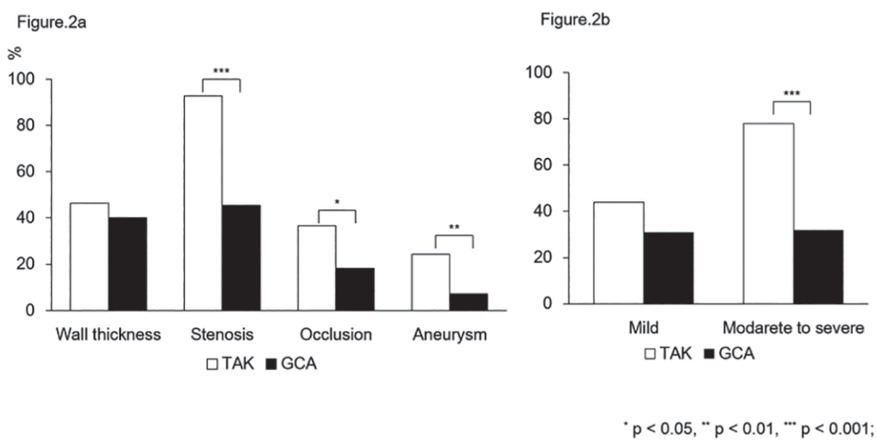

Fig. 2. Frequency of each lesion between Takayasu arteritis and Giant cell arteriti.

2a. Frequency of wall thickness, stenosis, occlusion and aneurysm were compared between Takayasu arteritis and Giant cell arteritis.

2b. Stenosis was classified into two stages. Mild stenosis was defined as <50%, moderate to severe stenosis as 75-99%.The following arterial regions were evaluated in 25 subjects; carotid artery, vertebral artery, brachiocephalic artery, subclavian artery, axillary artery, ascending aorta, aortic arch, descending aorta, abdominal aorta, celiac artery, superior mesenteric artery, renal artery, iliac artery, pulmonary artery bilaterally and coronary artery including right coronary artery, left anterior descending coronary artery, left circumflex coronary artery and left main trunk.

Categorical data were summarised with percentages and were analysed using a chi-square test, Fisher's exact test. p-values less than 0.05 were considered significant.

• *Combined Arteritis Damage Score (CARDS)*

The number of lesions in 25 vessels was counted and multiplied by the weighting as follows; number of mild stenoses × 0.6 + number of moderate to severe stenoses × 1.2 + number of occlusions × 1.6 + number of aneurysms × 0.8. As a result, the median CARDS was higher in TAK than GCA (4.1 and 0.6, p<0.001) (Table IIIA). Moreover, it was possible to identify three variables as predictors of a higher CARDS in TAK with multiple regression analysis with a step-wise method (Table IIIB). The use of biologic agents and constitutional symptoms at diagnosis were predictors for a lower CARDS. The disease duration was a predictor

Table III. Comparison and assessment for damage with CARDS between Takayasu arteritis and giant cell arteritis.

III**A**

	TAK, n=41	GCA, n=55	*p*-value
CARDS, median (IQR)	4.1 (1.3-5.7)	0.6 (0-3)	<0.001

Non-normally distributed data were summarised with medians and interquartile ranges and were analysed using non-parametric tests (Mann-Whitney U-test). *p*-values less than 0.05 were considered significant.
CARDS, Combined Arteritis Damage Score;

III**B**

Log_{10} CARDS	Regression coefficient	*p*	95% confidence interval	
Intercept	0.684	*p*<0.001	0.472	0.895
Disease duration	0.002	0.001	0.001	0.004
Constitutional symptom at diagnosis	-0.402	0.001	-0.630	-0.173
Use of biologics	-0.227	0.033	-0.434	-0.020

A multiple regression analysis was constructed using a step-wise method. *p*-values less than 0.05 were considered significant.
CARDS: Combined Arteritis Damage Score.
Log_{10} CARDS: The variable CARDS was logarithmically transformed.

for a higher CARDS. In a single correlation study for TAK, CARDS did not correlate with CRP or ESR at assessment, disease duration or onset age. In the subset studied, QOL tools did not correlate with CARDS or CDA. In GCA, there were no associations with multiple regression analysis. In a single correlation study, CARDS was higher in younger patients. CARDS correlated with the number of surgical interventions positively. CARDS did not correlate with CRP, ESR at assessment. CDA was positively correlated with the physical component score of SF36 and PTVAS.

Discussion

Outcome assessment in LVV remains challenging and this impairs patient management and the conduct of clinical studies. Previous proposals for outcome tools have not included imaging, so an attempt has been made to standardise and quantify image assessment in LVV by the development of an imaging damage score, CARDS, and to compare the results between TAK and GCA patients.

Wall thickness was excluded from CARDS because it was not possible to compose multiple regression equations with wall thickness and it is controversial whether wall thickness represents activity or damage. Tso *et al*. compared vessel wall oedema with disease activity in 24 TAK patients: MRA revealed vessel wall oedema in 94% of active disease patients, and in 56% of those in clinical remission (35). Arnaud *et al*. compared MRI findings to PET scan with semi-quantitative assessment of FDG uptake graded 0-3 in 28 TAK patients (36). There were no associations between the semi-quantitative assessment of FDG uptake and the presence of vascular wall thickening and gadolinium uptake. Occasionally, it is difficult to distinguish wall thickness from artefact but this manifestation requires further study.

We carried over the lesions before surgical intervention, giving one point in CARDS, because we wanted to reflect the cumulative vascular damage and to distinguish between patients who improved by intervention and patients with fewer lesions from disease onset.

Additionally, stenosis was classified into two stages of severity in CARDS. This simplified evaluation, but it may also be useful to subdivide stenosis more strictly when we assess longitudinal change. In this study, the subgroup, 'aneurysm', was not subdivided by angiographic severity because it was difficult to determine severity subgroups although it was possible to measure the size of aneurysms.

In the inter-observer reliability, the correlation coefficient was high between a radiologist and rheumatologist which supports the general use of CARDS not only by radiologists but also by suitably trained rheumatologists.

Because there is considerable evidence of angiographic differences between TAK and GCA, an internal validation was performed by comparing CARDS between syndromes. This required using age of onset to assist in diagnostic categorisation because asymptomatic TAK patients in the early stage did not fulfill ACR criteria although they had characteristic arterial lesions. Previous reports have described phenotypic differences in addition to the noted age disparity with TAK below and GCA above 50 years of age by latent class analysis (6). CARDS was higher in TAK than in GCA. Our results clarified that there are differences in severity, although similarities in the pathology and distribution of vascular lesions have led to claims that TAK and GCA are one disease (37, 38). One reason for this difference may relate to the delay from onset to diagnosis, which is longer in TAK than in GCA. Some TAK patients are often in an advanced stage before diagnosis. This may be reflected by the lower CRP and ESR at diagnosis in TAK since activity of some patients has already subsided.

The use of biologic agents and constitutional symptom at diagnosis were identified as predictors for a lower CARDS and this requires confirmation. If the patients have constitutional symptoms, they will be diagnosed and treated earlier with the potential to reduce irreversible damage. This needs further verification although there is a possibility that use of biologics decreases irreversible damage. CARDS did not correlate with CRP and ESR at assessment in TAK and GCA, unsurprisingly, because CARDS is intended as a measure of damage but not activity.

CARDS was higher in younger patients than older patients at age of onset of GCA. Schmidt *et al*. described patients with large-vessel lesions in GCA were younger than those with classic temporal arteritis (39). It is possible that GCA patients with temporal arteritis reduce irreversible damage since they are di-

agnosed and treated at an early stage.

In contrast to small-vessel vasculitis the visualisation of vascular pathology by imaging provides a major opportunity in LVV. The imaging diagnosis remains the gold standard since lesions visualised by the imaging represent the activity or damage in LVV directly. It is unclear whether PET is sufficiently sensitive to become the gold standard for activity assessment in LVV and carries high radiation exposure (36, 40).

In specific activity measures of TAK, three tools have been described (22, 23, 41). On the other hand, in specific damage measures, only the Takayasu Arteritis Damage Score has been reported (42). This outcome measure also evolved from DEI.TAK and does not include imaging assessment. Therefore, outcome measures are needed to include not only physical findings but also imaging. The benefits of CARDS are that a patient can be evaluated in a short time and longitudinal changes assessed or compared with other patients in a semi-quantitative manner. CARDS has the potential to represent not only the results of radiologic imaging but also indirectly all cause damage because it is derived from an association between imaging and the CDA.

This study had some limitations. It was a two centre retrospective study with a small sample size that reduces statistical power and may be influenced by referral bias. Another limitation is that both CT and MRI were included for imaging assessment. Efficacy of both modalities in LVV has already been established (20,31), and their features such as spatial resolution are different, which might influence the radiological results, but there were no significant differences in the CARDS between CT and MRI (Supplemental Table IV). Further validation with replication in another cohort, change over time, and correlation with longer term outcomes to establish CARDS will be needed.

Conclusions

In conclusion, a key goal of treatment of LVV is the control of disease activity in order to prevent the accrual of disease related damage. Especially, there are no clinical trials with large numbers although it has been reported biologics are useful in TAK in some case reports recently. Without reliable assessment tools it will be difficult to introduce newer agents. A damage assessment tool based on imaging has been developed in LVV and this should be potential of value to clinical studies and patient management.

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