Sonographic study of vessel wall remodelling of the cranial and axillary arteries in giant cell arteritis under treatment: implications for diagnosis of relapses and impact of tocilizumab treatment

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Abstract

Objective

Giant cell arteritis (GCA) is the most common primary systemic vasculitis and is nowadays commonly diagnosed using vascular ultrasound. Whether repeated ultrasound is helpful in disease management is unclear.

Methods

We conducted a retrospective analysis of 100 patients diagnosed with GCA between 01/2016 and 12/2022. High-resolution ultrasound was performed to assess vasculitic wall thickening in superficial temporal, facial, and axillary arteries at diagnosis and during follow-up. Patients were treated according to current standards, with tocilizumab treatment initiated within 6 months after diagnosis in 38 patients. The course of wall thickening in the different vascular segments was recorded. Patients with and without complete normalisation of wall thickening were compared. The impact of tocilizumab treatment on vessel wall remodelling and the potential benefit of repeated ultrasound examinations for the diagnosis of relapsing disease were assessed.

Results

In the overall cohort (63% females, mean age 72.8±8.9 years), one, two or three arterial territories were affected in 31, 50 and 17 patients. Follow-up ultrasound examinations showed a significant reduction in wall thickening over time: superficial temporal arteries -0.42 mm, facial arteries -0.35 mm, axillary arteries -0.36 mm. Normalisation of wall thickening occurred in 32.6% (superficial temporal arteries), 53.1% (facial arteries), and 35.5% (axillary arteries), with some differences in clinical characteristics between patients with and without complete sonographic remission. Patients treated with tocilizumab showed a slightly faster early reduction in mean intima-media thickness which was lost over time. Repeated ultrasound showed a significant increase in maximum IMT (at least +0.3 mm) in 3.6% of the superficial temporal arteries, 18.4% of the facial arteries, and 21.4% of the axillary arteries in patients with relapsing disease.

Conclusion

Our results help to interpret repeated IMT measurements of the affected cranial and extracranial arteries in patients with GCA undergoing treatment. Repeated ultrasound examinations appear to be of limited diagnostic value in the diagnosis of relapsing GCA.

Key words

giant cell arteritis, diagnostic imaging, temporal arteries, axillary artery, recurrence

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Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitis in the elderly population (1). GCA affects large- and medium-sized arteries, in particular the aorta and its primary branches such as the subclavian/axillary arteries, branches of the external carotid arteries (superficial temporal, maxillary, facial and occipital arteries) and branches of the ophthalmic artery (posterior ciliary arteries, central retinal arteries) (2, 3). Hypoechogenic concentric wall thickening (halo) secondary to inflammation-related myointimal hyperplasia is the typical diagnostic feature of GCA, with pooled estimates for sensitivity and specificity of 80% and 97% for diagnosis of the cranial manifestation of the disease (4). To facilitate the visualisation of vessel wall thickening of the cranial arteries, high resolution compression sonography (HRCS) has been proposed (5-7). The additional sonographic examination of the axillary artery increases the sensitivity for detection of GCA by approximately 15%, while specificity remains high (8).

Over the last two decades, ultrasound has gained an outstanding role in the diagnosis of GCA (9), and fast-track clinics based on sonographic protocols have shown promise in reducing the early ocular ischaemic complications of the disease (10, 11). Some previous work has outlined the course of vasculitic wall thickening over time using sonography (12-20). However, it remains unclear whether surveillance with repeated ultrasound examinations may be useful for disease management.

Here, we characterise the course of vessel wall thickening in three arterial segments typically affected in GCA in patients who underwent follow-up ultrasound studies after initial diagnosis, with a focus on the effects of treatment with tocilizumab (TCZ) and the potential diagnostic value of sonographic follow-up examinations for the diagnosis of recurrent GCA.

Patients and methods

Diagnosis of giant cell arteritis and study inclusion

We analysed patients aged ≥50 years who were diagnosed with GCA at our institution between 01/2016 and 12/2022. The retrospective data analysis was approved by the local ethics committee.

According to the current standard, a diagnosis of GCA was made when at least three of the five following criteria were fulfilled: (i) age ≥50 years; (ii) typical cranial symptoms (new onset persistent headache, jaw claudication, temporal artery tenderness); (iii) extracranial symptoms (polymyalgia rheumatica, new onset upper extremity claudication, fever of unknown origin); (iv) C-reactive protein (CRP) ≥1 mg/dl (normal range <0.5 mg/dl) or erythrocyte sedimentation rate (ESR) >30 mm per one hour (reference range ≤20 mm per one hour); (v) typical imaging findings in vascular sonography (21-23). In ambiguous cases, additional diagnostic studies (temporal artery biopsy, ^{18}FDG-PET-CT) were performed.

To be included in this study, patients were required to fulfil the 2022 ACR/EULAR classification criteria for GCA (24), to have a complete clinical and sonographic work-up at diagnosis (including standardised examination of the superficial temporal, facial, and axillary arteries, as outlined below), and to have undergone at least one sonographic follow-up examination of one or more of the above-mentioned arterial segments with a corresponding clinical assessment.

Treatment and follow-up

Patients were treated according to a standardised protocol. Initial treatment consisted of high-dose oral prednisolone (1 mg per kg per day, maximum 60 mg/day). In case of visual ischaemic complications oral treatment was preceded by an intravenous methylprednisolone pulse (250 to 1,000 mg per day for three days). Subsequent tapering aimed at a daily prednisolone dose of 15 mg and 5 mg at three months and 12 months after treatment initiation, respectively. When relapses occurred during glucocorticoid tapering (see below), the prednisolone dose was increased and steroid-sparing agents (TCZ, methotrexate) were introduced at the discretion of the treating physicians.

Regular follow-ups were scheduled at

quarterly intervals, with repeated ultrasound imaging ordered by the treating physicians, as clinically indicated (usually at 6 and 12 months and annually thereafter). Unscheduled ultrasound imaging was performed if recurrence was suspected. For the purposes of this study, time intervals during the follow-up period were categorised as follows: t0 (diagnosis); t1 (6±2 months), t2 (12±3 months), t3 (24±4 months), t4 (36±6 months).

Relapses were defined by typical clinical symptoms of GCA and a subsequent treatment intensification resulting in improvement or resolution of these symptoms (25). As a subset of patients was treated with TCZ, elevated acute phase reactants were taken into account as an indication of relapse but were not considered to be necessary to classify a clinical event as a relapse.

Ultrasound protocol

Ultrasound examinations were carried out by sonographers experienced in the sonographic workup of giant cell arteritis, using a LOGIQ E9 device (General Electric, Milwaukee, USA).

We used 18 MHz hockey stick transducers to examine the cranial arteries. HRCS was performed along the entire visible course of the superficial temporal artery and its branches as well as the facial artery. Determination of intima-media thickness (IMT) by this sonographic method relies on summarised measurement of the near and far arterial wall (5-7). An arterial segment was considered to be affected by GCA if it displayed a hypoechogenic, circumferential wall thickening (halo), consistent with reduced compressibility (26). Vascular wall thickening was defined as moderate when IMT values were between 0.7-1.0 mm as determined by HRCS and as marked if IMT exceeded >1.0 mm. Measurements were taken at the site of most pronounced wall thickening of the respective arterial segments. In the absence of significant wall thickening, the frontal and parietal branches of the superficial temporal arteries were measured at the level of the upper edge of the auricle, and the facial arteries were measured at the intersections with the mandible.

Table I. Baseline characteristics of the overall cohort of one hundred patients.

Parameters	Overall cohort, n=100
Female sex, n (%)	63 (63.0)
Age (years), mean ± SD	72.8 ± 8.9
Headache, n (%)	73 (73.0)
Jaw claudication, n (%)	60 (60.0)
Permanent visual loss, n (%)	36 (36.0)
Polymyalgia rheumatica, n (%)	29 (29.0)
Fever, n (%)	21 (21.0)
Constitutional symptoms, n (%)	59 (59.0)
One vascular territory affected by vasculitis, n (%)	31 (31.0)
Two vascular territories affected by vasculitis, n (%)	50 (50.0)
Three vascular territories affected by vasculitis, n (%)	17 (17.0)
More than two cardiovascular risk factors, n (%)	62 (62.0)
Manifest cardiovascular disease*, n (%)	22 (22.0)
Daily prednisolone dose (mg) at the time of the first ultrasound scan (t0)#, mean ± SD	233 ± 415
Daily prednisolone dose (mg) after 6 ± 2 months of treatment (t1), mean ± SD	9.0 ± 10.0
Daily prednisolone dose (mg) after 12 ± 3 months of treatment (t2), mean ± SD	5.3 ± 2.5
Daily prednisolone dose (mg) after 24 ± 4 months of treatment (t3), mean ± SD	4.3 ± 8.9
Daily prednisolone dose (mg) after 36 ± 6 months of treatment (t4), mean ± SD	1.8 ± 2.6
Tocilizumab treatment started within 6 months after diagnosis, n (%)	38 (38.0)
Methotrexate treatment started within 6 months after diagnosis, n (%)	17 (17.0)
C-reactive protein (mg/dl), mean ± SD	5.5 ± 6.9
Thrombocytosis, n (%)	25 (25.0)
Anaemia, n (%)	45 (45.0)

#Twenty-three patients received intravenous methylprednisolone pulses at baseline.
*Cardiovascular disease: coronary artery disease including prior myocardial infarction, cerebrovascular disease including prior stroke, peripheral arterial disease.

For examination of the axillary arteries we applied standard linear transducers (frequency range 5–8 MHz). IMT measurements were made in the longitudinal section of the axillary arteries, just distal to the origin of the subscapular arteries. Hypoechogenic, circumferential wall thickening was considered typical for extracranial GCA if the IMT exceeded the cut-off value of 1.2 mm (8). Vasculitic wall thickening was defined as moderate when IMT was between 1.3 and 2.0 mm and as marked when IMT exceeded 2.0 mm.

A significant change in vessel wall thickening from a previous measurement was defined as a change of at least one category between two time points.

Statistical analysis

Statistical analysis was performed using the software SPSS Statistics v. 29 (SPSS Inc., Chicago, IL, USA). Mann-Whitney U-test was applied for comparison of continuous variables and χ^2 test was used for comparison of categorical variables. ANOVA analysis for variance was performed with demographic, clinical, laboratory and treatment parameters as independent variables. *p*-values less than 0.05 were considered statistically significant. Results for categorical variables are presented as absolute numbers with percentages, and continuous variables are displayed as mean ± standard deviation (SD).

Results

Patients' characteristics

We included a total of 100 patients with an established diagnosis of GCA (63 females, 37 males), with a mean age of 72.8±8.9 years.

At baseline, vasculitic wall thickening in one, two or all three of the vascular territories examined was detected in 31, 50, and 17 patients, respectively. Two patients with typical clinical symptoms (visual loss, headache, jaw claudication) had negative findings on the above-mentioned standard sonographic protocol but exhibited a typical halo sign of the occipital and vertebral arteries.

In 61 patients, glucocorticoid treatment had already been started at the time of the initial ultrasound scan. In 38 patients, treatment with TCZ was initiated within the first 6 months after diagnosis. A further 17 patients received methotrexate treatment during follow-

up. Details of patients' characteristics including mean prednisolone doses at baseline and follow-up examinations are outlined in Table I.

Superficial temporal arteries

At initial diagnosis, the mean value of individual maximum wall thickness of the superficial temporal arteries in the overall cohort was 1.02±0.44 mm. Categories of superficial temporal artery wall thickening of the overall cohort during follow-up are shown in Figure 1A. A total of 86 patients presented with a vessel wall thickening ≥0.7 mm in at least one segment of the superficial temporal arteries (mean value of the maximum wall thickness 1.12±0.40 mm at the time of diagnosis). Compared to patients without superficial temporal artery wall thickening, these patients were significantly older (74.2±8.1 *vs.* 64.5±9.1 years, $p<0.001$) and tended to have higher mean CRP levels (5.9±7.2 mg/dl *vs.* 3.1±3.2 mg/dl, $p=0.084$) and lower rates of both thrombocytosis (24.1% *vs.* 38.5%, $p=0.272$) and anaemia (44.6% *vs.* 61.5%, $p=0.255$). There were no significant differences regarding clinical symptoms, cardiovascular risk profile and pre-existing cardiovascular disease.

Ultrasound follow-up of the superficial temporal arteries was performed in 74 out of the 86 patients with wall thickening at the time of diagnosis. Within a mean follow-up time of 24.3±12.0 months, we observed a mean reduction in maximum wall thickness of -0.42±0.46 mm. A reduction to normal values (<0.7 mm) was achieved in 28 patients and a reduction from marked to moderate vessel wall thickening was seen in 20 patients. In a considerable number of patients (n=26) the vessel wall remained thickened in at least one superficial temporal artery segment, and in one patient we observed an increase in individual maximum vessel wall thickening from moderate to marked. Mean values of superficial temporal artery vessel wall thickness over time in patients with wall thickening at the time of diagnosis are outlined in Table II.

Compared to patients with persistent superficial temporal artery wall thickening, patients with complete resolution of wall thickening were younger (complete regression: 72.0±8.8 years *vs.* no or incomplete regression: 74.8±8.5 years) and had higher mean initial CRP levels (complete regression 6.5±7.2 mg/dl *vs.* incomplete or no regression 4.2±6.4 mg/dl). However, these differences were not statistically significant ($p=0.057$ and 0.051, respectively). We found significant differences between both groups with regard to the proportion of female patients (complete regression: 73.7% *vs.* no or incomplete regression: 45.0%, $p<0.01$), the frequency of constitutional symptoms (complete regression: 70.0% *vs.* no or incomplete regression: 51.7%, $p=0.03$)

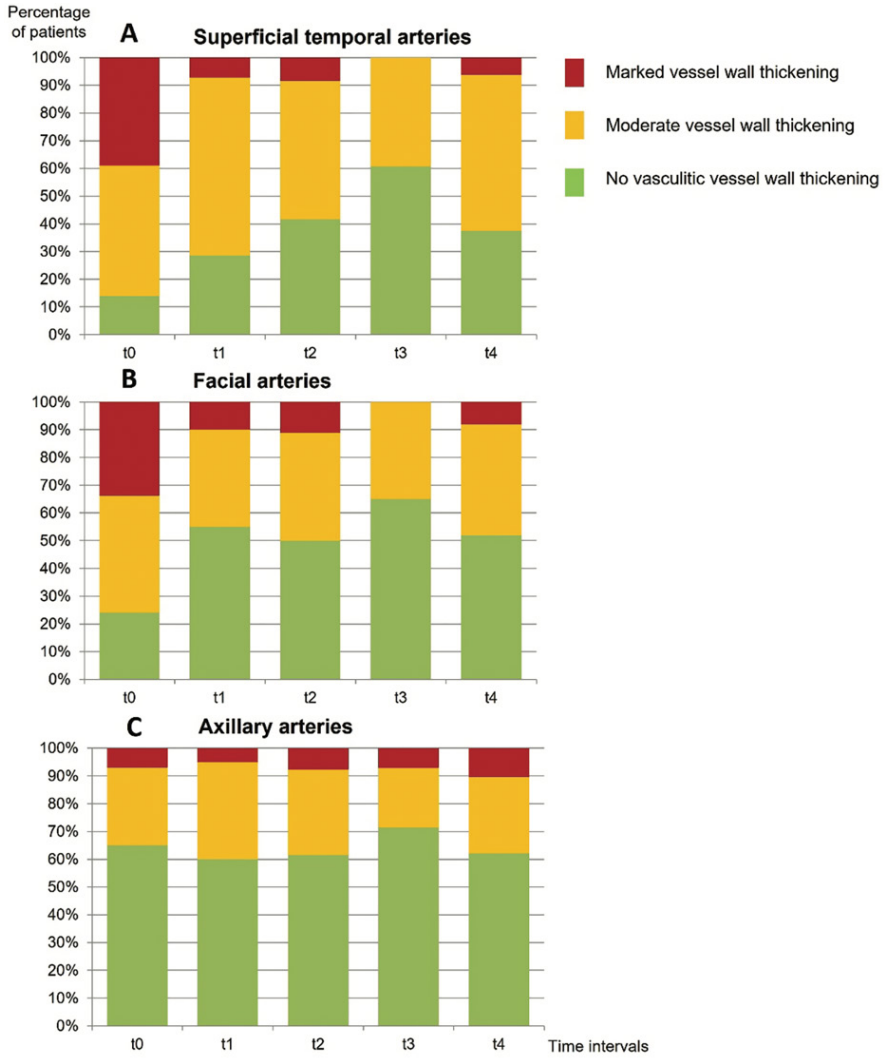

Fig. 1. Categorisation of maximum arterial wall thickness at different time points (overall cohort, including patients with and without wall thickening in the respective arterial segments at diagnosis). Superficial temporal arteries (**A**) and facial arteries (**B**): 0=no wall thickening (<0.7 mm); 1=moderate wall thickening (0.7-1.0 mm); 2=marked wall thickening (>1.0 mm). Axillary arteries (**C**): 0=no wall thickening (<1.2 mm); 1=moderate wall thickening (1.2-2.0 mm); 3=marked wall thickening (>2.0 mm).

Table II. Mean values of maximum wall thickness over time in patients with initial wall thickening in the respective arterial segments at the time of diagnosis.

Visit	Superficial temporal arteries	Facial arteries	Axillary arteries
t0 (diagnosis)	1.12 ± 0.40	1.14 ± 0.45	1.73 ± 0.59
t1 (6 ± 2 months)	0.83 ± 0.24	0.67 ± 0.24	1.56 ± 0.43
t2 (12 ± 3 months	0.75 ± 0.25	0.74 ± 0.24	1.30 ± 0.47
t3 (24 ± 4 months)	0.63 ± 0.14	0.67 ± 0.14	1.28 ± 0.68
t4 (36 ± 6 months)	0.77 ± 0.36	0.72 ± 0.19	1.46 ± 0.50

and polymyalgia rheumatica (complete regression: 40.0% *vs*. no or incomplete regression: 21.7%, p=0.048), as well as the rate of thrombocytosis (complete regression: 33.3% *vs*. incomplete or no regression: 12.8%, p=0.01).

Facial arteries

The facial arteries were assessed in 83 patients at baseline, with a mean overall wall thickness of 1.00±0.47 mm. Categories of facial artery wall thickening of the overall cohort during follow-up are shown in Figure 1B.

Sixty-three patients displayed a vessel wall thickening in at least one facial artery at the time of diagnosis (mean wall thickness of 1.14±0.45 mm). Again, these patients were significantly older (75.0±8.0 years *vs*. 66.7±8.9 years, p<0.001), and their mean CRP levels were slightly lower (4.7±5.4 *vs*. 7.0±8.9 mg/dl, p=0.095). Patients with an initial facial artery wall thickening reported constitutional symptoms less frequently than the group without thickening (46.0% *vs*. 76.5%, p=0.026). In particular, fever was less common in this subgroup (12.7% *vs*. 35.3%, p=0.03). There were no other meaningful differences between groups.

Ultrasound follow-up of the facial arteries was performed in 49 of the 63 patients with facial artery wall thickening at diagnosis. Within a mean follow-up of 25±11.4 months, a mean reduction in wall thickness of -0.35±0.52 mm was seen. A reduction to the normal range was achieved in 26 patients; a reduction from marked to moderate vessel wall thickening was seen in 8 patients. No change in vessel wall thickening during follow-up was found in 14 patients, while one patient showed an increase in vessel wall thickening from moderate to marked. Mean values of facial artery vessel wall thickness over time in patients with wall thickening at the time of diagnosis are outlined in Table II.

Compared with patients with persistent facial artery wall thickening, those patients with a complete normalisation of facial artery wall thickness were younger (complete regression: 72.0±9.3 years *vs*. no or incomplete regression: 74.43±7.91 years) and more frequently had fever at the time of diagnosis. Neither difference was statistically significant. A significantly higher proportion of patients with a complete regression of wall thickening had thrombocytosis at initial diagnosis (36.6% *vs*. 9.5%, p=0.003).

Axillary arteries

Categories of axillary artery wall thickening of the overall cohort during follow up are shown in Figure 1C. Thirty-five out of 100 patients presented with extracranial involvement in the form of vascular vessel wall thickening in at least one of the two axillary arteries at the time of initial diagnosis. The initial mean total axillary artery wall thickness in the entire cohort was 1.14±0.57 mm, whereas patients presenting with axillary artery lesions displayed an initial mean axillary artery wall thickness of 1.73±0.59 mm. In addition to a significant difference in mean platelet count (axillary artery wall thickening: 396±113 G/l *vs*. normal axillary arteries: 354±122 G/l, p=0.045), there were no significant differences between the two subgroups at baseline.

Ultrasound follow-up of the axillary arteries was performed in 82 of 100 patients. At a mean follow-up of 24.5±12 months, a mean reduction in axillary artery wall thickness of -0.03±0.49 mm was found in the overall cohort. In the 31 patients with initial axillary artery wall thickening who presented for follow-up examinations, we observed a mean reduction in wall thickness of -0.36±0.47 mm. A complete reduction to normal range was achieved in only 11 patients; a reduction from marked to moderate vessel wall thickening was detected in 2 patients. Axillary artery vessel wall thickening remained without significant change during follow-up in almost half of the patients (n=17), and one patient showed an increase in vessel wall thickening from moderate to marked. Mean values of axillary artery vessel wall thickness over time in patients with wall thickening at the time of diagnosis are outlined in Table II.

Compared to patients with persistent wall thickening, those with a complete normalisation of axillary artery thickness were significantly more likely to suffer from visual loss at the time of diagnosis (45% *vs*. 19%, p=0.010). No other clinically meaningful differences were observed.

Impact of treatment with tocilizumab

In 38 patients, TCZ treatment was initiated during the first 6 months after diagnosis. When analysing those patients with initial superficial temporal artery wall thickening, we found no difference in mean wall thickness reduction in patients treated with TCZ compared to those without TCZ treatment (-0.47±0.79 mm *vs*. -0.40±0.24 mm, p=0.296). There were no significant differences between both groups regarding the proportion of patients with complete normalisation of temporal artery wall thickness (TCZ 10.7% *vs*. no TCZ 26.7%, p=0.392).

Patients with initial facial artery wall thickening treated with TCZ had a significantly greater reduction in wall thickening compared to patients without TCZ (-0.81±0.75 mm *vs*. -0.33±0.34 mm, p=0.035). However, the rate of patients with complete normalisation of facial artery wall thickness was not significantly different between the two groups (TCZ 12.9% *vs*. no TCZ 27.4%, p=0.637).

Of the 35 patients who initially presented with vasculitic wall thickening of the axillary arteries, 12 were treated with TCZ. Thirty-one patients presented for at least one follow-up visit, 8 of whom were treated with TCZ. The mean reduction in axillary artery wall thickness in the individuals treated with TCZ was -0.54±0.64 mm, compared to a mean reduction of -0.31±0.52 mm in the 23 patients without TCZ treatment (p=0.162). However, a complete normalisation of wall thickness was less frequent with TCZ treatment (1 out of 8 patients) compared to the group of patients who did not receive TCZ treatment (11 out of 23 patients; p=0.034).

The comparison of the wall thickness over time (mean value of individual maximum values) of the different vascular segments in patients with and without TCZ treatment is shown in Figure 2.

Relapses and vessel wall thickness

Thirty-six patients experienced dis-

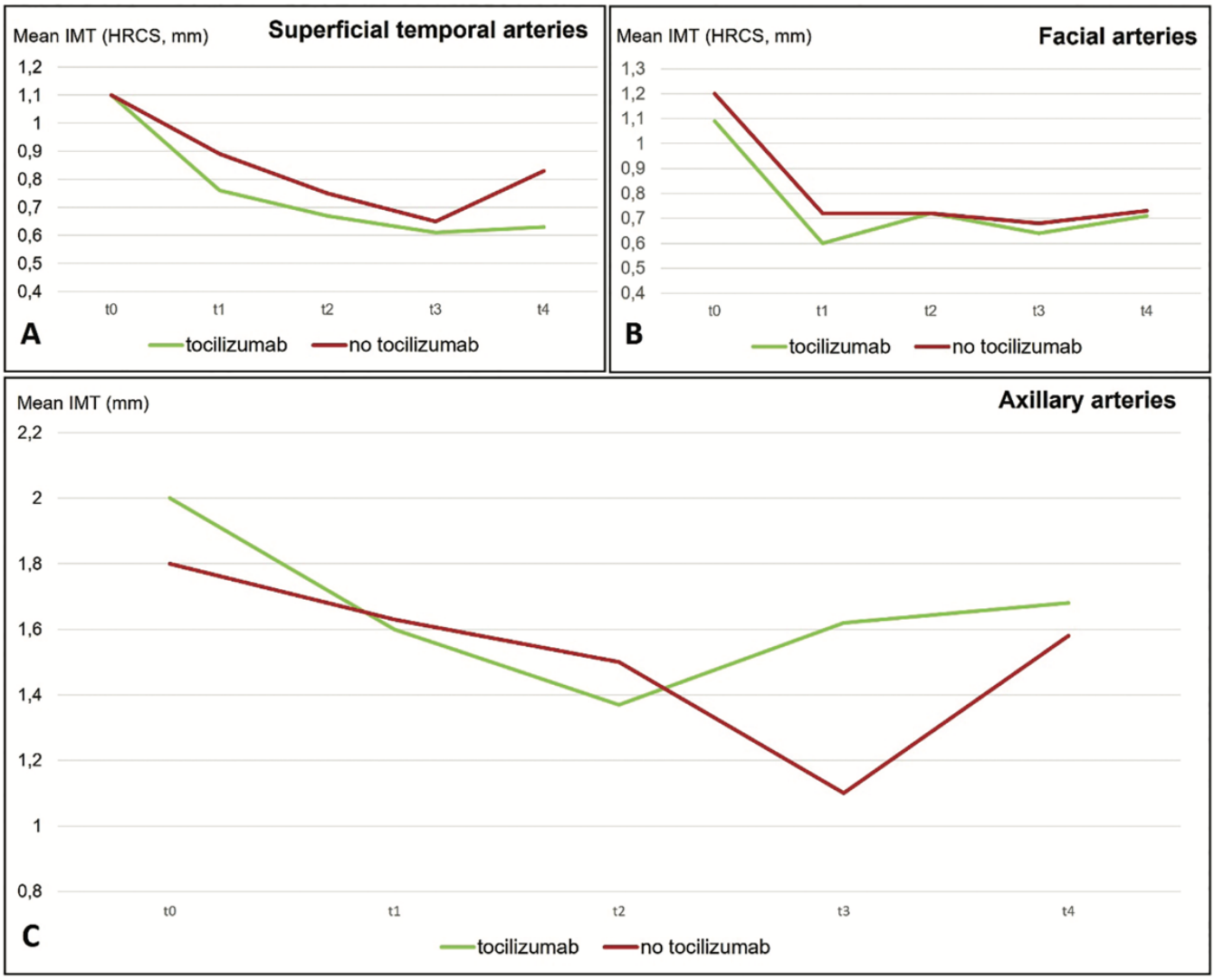

Fig. 2. Mean values of wall thickness of the temporal, facial, and axillary arteries over time in patients with and without early initiation of TCZ treatment. For analysis of each segment only patients with vasculitic involvement at the time of initial diagnosis were included.

ease flares (mean number of relapses 0.6±1.0; eleven patients with two or more relapses). Compared to patients without relapses, patients who relapsed were significantly more likely to have thrombocytosis (38.2% *vs*. 19.4%, p=0.03) and anaemia (67.7% *vs*. 35.5%, p<0.01) at the time of diagnosis. No other significant differences were found between the two groups.

The superficial temporal arteries were measured in 56 cases of relapsing disease. Compared to the last documented previous measurement, mean values of maximum wall thickness declined from 0.72±0.46 mm to 0.66±0.26 mm. In 6 patients with relapses, superficial temporal artery wall thickness declined substantially (at least -0.3 mm), whereas a significant increase (at least +0.3 mm) was seen in only two cases. In the remaining 48 relapse episodes, no significant change (wall thickness changes between -0.2 and +0.2mm) was noted (Fig. 3A).

The facial arteries were measured in 38 cases of recurrent disease. Compared to the last documented previous measurement, mean values of maximum wall thickness decreased from 0.77±0.51 mm to 0.66±0.23 mm. In 3 patients with recurrences, superficial facial artery wall thickness declined substantially (at least -0.3 mm), whereas a significant increase (at least +0.3 mm) was seen in 7 cases. In the remaining 28 relapses, no significant change (wall thickness changes between -0.2 and +0.2 mm) was noted (Fig. 3B).

The axillary arteries were measured in 42 cases of recurrent disease. Compared to the last documented previous measurement, mean values of maximum wall thickness remained stable (premeasurement: 1.15±0.46 mm; recurrence: 1.15±0.5 mm). Axillary artery wall thickness either significantly decreased (at least -0.3 mm) or increased (at least +0.3 mm) in 9 patients, respectively. In the remaining 24 relapses, no significant change (wall thickness changes between -0.2 and +0.2mm) was observed (Fig. 3C).

Discussion

Vessel wall thickening in arterial territories affected by GCA is a result of myointimal hyperplasia as a response-to-injury-mechanism secondary to the transmural vasculitic process itself

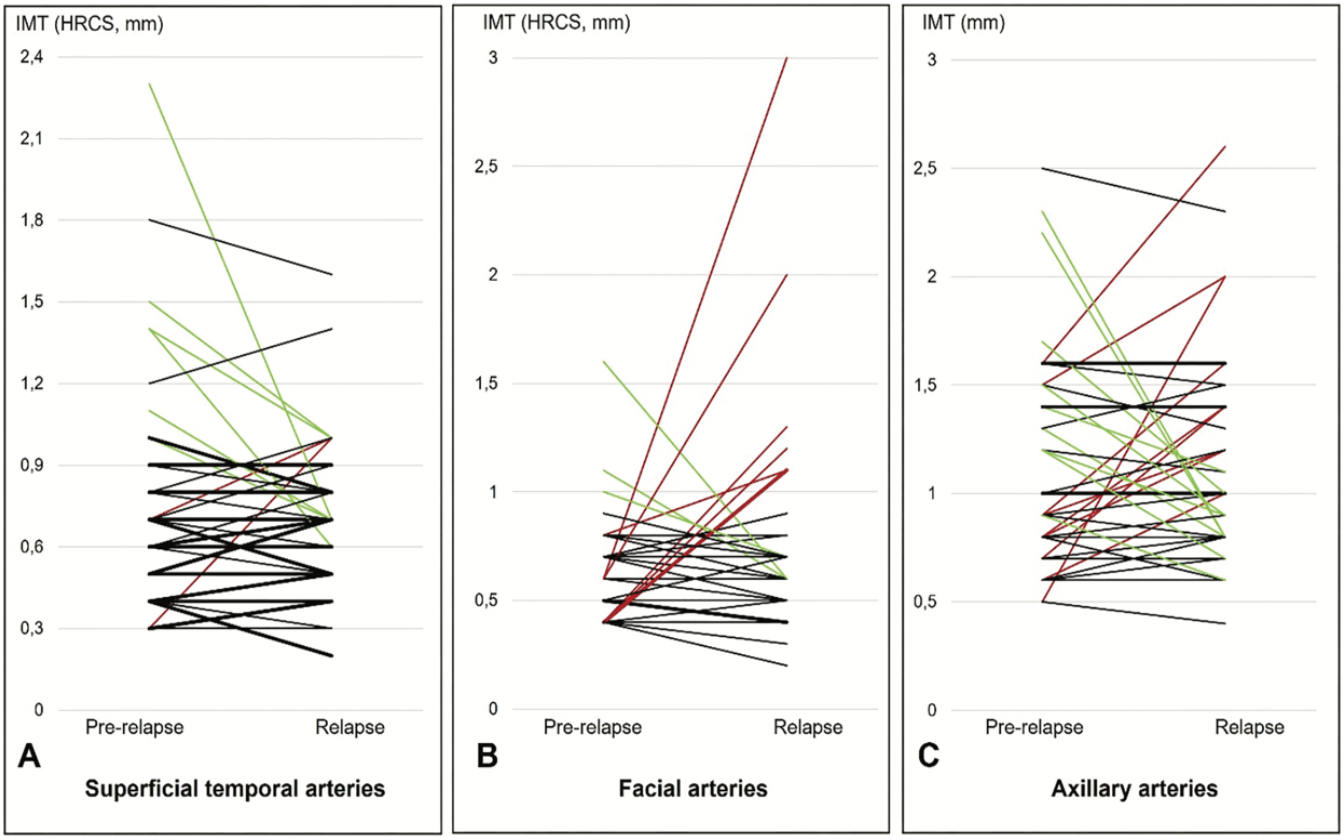

Fig. 3. Comparison of superficial temporal, facial, and axillary artery wall thickness (individual maximum values) between the last visit before recurrence and at the time of relapse in patients who experienced relapsing disease. Green lines, significant wall thickness reduction of >0.3 mm at the time of relapse compared to previous visit; black lines, stable wall thickness (±0.2 mm) compared to previous visit; red lines, significant wall thickness increase >0.3 mm at the time of relapse compared to previous visit. Bold lines indicate wall thickness courses of more than one patient.

(27). Myointimal hyperplasia, on the one hand, is the underlying pathology of cranial and extracranial ischaemic complications in GCA. On the other hand, it represents the diagnostic hallmark of morphological imaging modalities used to diagnose GCA, including ultrasound (halo sign) (28). Ultrasound of the cranial and extracranial arteries has long been established as the initial diagnostic tool for the diagnosis of GCA, with excellent diagnostic accuracy (9).

Much more difficult than the initial diagnosis is the reassessment of patients with established GCA who experience recurrent symptoms on treatment. Clinical judgement regarding treatment has become even more challenging in recent years with the introduction of TCZ into the treatment algorithm, making humoral inflammatory markers unreliable in assessing disease activity. Persistent wall thickening can be indistinguishable sonographically from newly developed vascular lesions. In view of these considerations, it is crucial to gain knowledge of the progression of vasculitic wall thickening over time in the arterial segments typically affected. Our study now sheds light on the dynamics of vasculitic remodelling of the cranial and extracranial arteries in GCA under treatment, as depicted by serial sonography. Main results can be summarised as follows:

1. Despite regression of mean IMT values over time, persistent wall thickening can be found in a considerable number of patients, with differences between the cranial arteries (less common) and the axillary arteries (frequent).
2. Some subgroups seem to have higher rates of resolution of wall thickening of the specific vascular segments (cranial arteries: females, patients with constitutional symptoms or polymyalgia rheumatica; axillary arteries: patients with visual loss as presenting symptom).
3. TCZ in addition to glucocorticoid treatment may enhance early decline in vessel wall thickening, however this effect does not appear to be clinically relevant and disappears over time.
4. In most cases of recurrence, repeated assessment of the cranial arteries does not support the clinical decision, whereas sonography of the axillary arteries supports the diagnosis of relapse in about one in four patients.

In their inaugural publication in 1997, Schmidt *et al*. reported that the superficial temporal artery halo sign disappeared within a mean of 16 days (range 7–56 days) after initiation of glucocorticoid treatment (29). Early variation of the superficial temporal artery halo sign within the first week after commencement of glucocorticoid treatment has also been reported by Hauenstein *et al*. and more recently by the TABUL-study group (16, 30). However, other studies have shown inconsistent results, with complete disappearance of the halo sign in at least 50% of patients between 8 weeks and 6 months (31, 32). Axillary artery lesions are known to react less promptly and to a smaller degree

to immunosuppressive treatment. Early cross-sectional studies showed regression of stenotic lesions in some, but not all cases, and complete regression of wall thickening in about a third of cases (12, 19). Further evidence on the course of vessel wall thickening in the cranial and extracranial arteries in GCA comes from prospective studies with serial ultrasound assessment. Nielsen *et al*. found a disappearance of the temporal halo sign in almost 60% of patients at 8 weeks, with no further significant changes after 15 weeks and 24 weeks. The large arteries (axillary and carotid arteries in this study) responded less well (15). Ponte *et al*. in the abovementioned study documented a continuous reduction in cumulative arterial wall thickness (summarised IMT of segments with the halo sign) and the number of segments with halo sign up to week 12 of treatment, but no further response between weeks 12 and 24. After 24 weeks of treatment, the rate of patients with a halo sign of the temporal or axillary arteries decreased from 96%/22% to 33%/14%, respectively (16). Based on an analysis of 50 patients, Schäfer *et al*. provided details on the course of vessel wall thickening not only in the superficial temporal and axillary arteries, but also in the facial, vertebral and carotid arteries. A subgroup of patients even underwent weekly follow-up intervals for the first 100 days of treatment. The mean number of affected cranial and extracranial large arteries decreased steadily within one year of treatment. In contrast to the aforementioned studies, the authors observed a more rapid reduction in mean IMT in the axillary and vertebral arteries, whereas the reduction in mean IMT in the superficial temporal arteries appeared to be slower (20). Due to the variable ultrasound methodology and the different time points for follow-up imaging in the respective studies, the available evidence cannot be integrated easily, and results are partly contradictory. The expected IMT values of different arterial segments at different times during treatment vary substantially between studies. A multicentric approach with a larger sample size would be desirable.

Of particular interest is previous research on the impact of interleukin-6 inhibition with TCZ on vascular remodelling in GCA patients. In the Swiss GUSTO trial, a monocentric study investigating TCZ monotherapy after a three-day induction course with high-dose intravenous methylprednisolone, the study design allowed the effects of glucocorticoid treatment and TCZ treatment to be assessed separately. After inducing a rapid decrease in IMT of both superficial temporal and axillary arteries with glucocorticoid treatment (by day 3), IMT increased again back to initial values (up to 4 weeks for the superficial temporal arteries and up to 8 weeks for the axillary arteries). Thereafter, a steady decrease was observed until week 52 for the superficial temporal arteries, whereas the axillary arteries showed a plateau until week 24, followed by a slight decrease until week 52. Schäfer *et al*. found no significant differences in IMT decrease between patients with and without TCZ in addition to glucocorticoid treatment (18). In our study, the reduction in wall thickening of the cranial arteries was slightly more pronounced in the first year of treatment with TCZ, but this difference was not significant and levelled off with further observation, probably due to more rapid glucocorticoid reduction with TCZ. After a steady decline until approximately two years of treatment, we observed a repeated increase in mean IMT in the long term, particularly in the axillary arteries. Taken together, the current limited evidence suggests additional effects of glucocorticoids and TCZ on vessel wall remodelling in GCA, with different dynamics related to the different modes of action of the drugs (acute sharp decline with GC, possibly correlated to an anti-oedematous effect; more protracted decline with TCZ due to the well-known effects on different immune cells) (33).

In some studies of serial ultrasound assessment, investigators have been surprised by the occurrence of new lesions or significant progression of pre-existing wall thickening, in some patients without symptoms of relapse (15, 33). This raises the question of the diagnostic value of repeated ultrasound for the objective diagnosis of suspected relapses. Just recently, Haaversen *et al*. demonstrated the limited value of ultrasound in the diagnosis of relapsing GCA (sensitivity 61.2%, specificity 72.3%) (34). In line with these findings, we also showed that only a few of our patients diagnosed with a relapsing disease had a significant increase in wall thickening. In particular, ultrasound of the superficial temporal arteries had a highly limited diagnostic yield (significant increase in only two of 56 cases of relapsing disease). A significant increase in axillary artery wall thickness was seen in a higher proportion of patients with relapses (9 out of 42), but a significant decrease was seen in the same proportion of patients. Therefore, we conclude from our data that repeated ultrasound of the superficial temporal arteries may not be useful in suspected relapses, whereas ultrasound of the axillary artery can contribute to the diagnosis of relapsing GCA in some but not all patients. Our findings, however, are in contrast to the study by Ponte *et al*. Although these authors documented a significantly lower number of segments with halo and maximum halo thickness, they reported that in 84% of patients with relapse who had a repeat ultrasound within 2 weeks of relapse, ultrasound showed an increase in halo IMT (sum and maximum), with or without an increase in the number of arterial segments with halo. However, the magnitude of the individual IMT changes compared to the pre-relapse ultrasound was not reported in this study (16).

Our study has some limitations, mainly related to the retrospective data collection. The time intervals for repeated clinical/sonographic assessment after diagnosis were not fixed, and not all patients were seen at all defined time intervals. Ultrasound studies did not include complete analysis of the three vascular segments at all single visits. The retrospective nature of our study also prevented us from calculating cumulative prednisolone doses. Due to the different ultrasound methodology compared to other studies (use of HRCS instead of colour duplex sonog-

raphy), we were not able to calculate previously suggested scores for quantification of wall thickness.

In conclusion, our study provides clinically important evidence on the course of vessel wall remodelling in GCA during treatment with glucocorticoids with or without additional TCZ. The mean values of IMT of the cranial and extracranial arteries observed in our study can be used as an aid in interpreting wall thickness measurements obtained at different time points during immunosuppressive treatment. The diagnostic value of repeated ultrasound examination of the superficial temporal arteries and/or axillary arteries in suspected recurrences should be investigated in a prospective longitudinal study.

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