Quantitative ultrasound to monitor the vascular response to tocilizumab in giant cell arteritis

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Abstract

Objectives. To characterize the effect of ultra-short glucocorticoids followed by Tocilizumab monotherapy on the intima-media thickness (IMT) in GCA.

Methods. 18 GCA patients received 500mg methylprednisolone intravenously on days 0-2, followed by Tocilizumab (8mg/kg) intravenously on day 3 and thereafter weekly subcutaneous Tocilizumab injections (162 mg) over 52 weeks. Ultrasound of temporal (TA), axillary (AA) and subclavian (SA) arteries was performed at baseline, on days 2-3, at week 4, 8, 12, 24 and 52. The largest IMT of all segments and IMT at landmarks of AA/SA were recorded. IMT was scaled by mean normal values and averaged. Each segment was classified according to diagnostic cut-offs.

Results. 16 patients had TA and 6 had extracranial large artery involvement. The IMT showed a sharp decline on day 2/3 in the TA and AA/SA. In TA, this was followed by an increase to baseline levels at week 4 and a subsequent slow decrease, which was paralleled by decreasing symptoms and achievement of clinical remission. The AA/SA showed a new signal of vasculitis at week 4 in three patients with an IMT increase up to week 8.

Conclusions. Glucocorticoid pulse therapy induced a transient decrease of the IMT in TA and AA/SA. Tocilizumab monotherapy resulted in a slow and steady decrease in IMT of the TA and a smaller and delayed effect on the AA/SA. The data strongly support a remission-inducing effect of Tocilizumab and argue for an important role of ultrasound in monitoring disease activity in GCA.

Keywords:

Giant cell arteritis, tocilizumab, glucocorticoids, ultrasound, vascular response, vasculitis

Key Messages

- Three days of high-dose intravenous glucocorticoids lead to a profound but transient IMT reduction.
- Tocilizumab induces a slow but steady IMT reduction in temporal arteries over 52 weeks.
- Ultrasound remains a valid technique to diagnose GCA even after three days of high-dose glucocorticoids.

Trial registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT03745586

Introduction

Giant cell arteritis (GCA) is the most frequent form of vasculitis in people above 50 years of age. Standard treatment still consists of glucocorticoids (GC).[1] Due to a high relapse rate, the duration of GC therapy is often very long. Two randomized controlled trials (RCT) showed that Tocilizumab (TCZ) may replace GC in maintaining remission, resulting in a reduction of approximately 50% of cumulative GC dose.[2,3] In an attempt to further reduce GC side effects, the "GCA treatment with Ultra-Short glucocorticoids and Tocilizumab" (GUSTO) trial was conducted (NCT03745586). In brief, patients with newly diagnosed GCA were treated with a GC pulse over 3 days, followed by TCZ monotherapy over 52 weeks.[4]

Ultrasound (US) is proposed as the first-line imaging modality to diagnose GCA according to the EULAR recommendations.[5,6,7] However, whether US qualifies to monitor disease activity at the level of the vessel wall and thereby helps to define treatment intensity is unknown. Recent data show, that none of the currently used imaging modalities can reliably differentiate between active vessel wall inflammation and residual local hyperaemia or wall remodelling.[5,8] In PET/CT- and MR-imaging, persistent tracer activity or arterial wall enhancement is present in the majority of patients even if otherwise considered in clinical remission.[5,9,10] In a first approach to define the value of US in monitoring disease activity, longitudinal US studies in GCA have evaluated the halo sign and could demonstrate its disappearance in temporal arteries (TA) in the majority of patients. They also found reduced, but persistently elevated intima-media thickness (IMT) in the supraaortic large arteries during therapy.[11,12] More recently, diagnostic IMT cut-offs and mean normal values for the TA, axillary (AA) and subclavian arteries (SA) were published, a scoring method for the quantitative IMT assessment has been proposed and first studies have evaluated quantitative IMT monitoring in GCA.[13,14,15,16,17,18,19,20]

A tool to assess disease activity in GCA at the level of the vessel wall is of particular importance if therapeutic agents are used which inhibit the IL-6 pathway. As the hepatic acute phase response is under

the control of IL-6, drugs such as TCZ render the two inflammatory markers ESR and CRP unreliable. Therefore, in case of IL-6 blocking therapies, the assessment of the treatment response relies entirely on reported signs and symptoms.

Due to the sequential administration of GC (3-day pulse) and TCZ (subsequent monotherapy), the GUSTO trial offered a unique opportunity for the assessment and differentiation of the effects of the two drugs on the IMT of the TA, AA and SA. In addition, the feasibility of IMT monitoring with US as a surrogate for disease activity could be assessed and a flexible scoring method evaluated.

Methods

GUSTO Trial (NCT03745586)

GUSTO is a single-arm, single-centre, open-label proof of concept study. 18 patients with newly diagnosed GCA were enrolled and received 500mg methylprednisolone intravenously on day 0-2. TCZ (8mg/kg body weight) intravenously was administered on day 3, followed by weekly subcutaneous TCZ injections (162mg) until week 52. The primary endpoint was the proportion of patients who achieved remission within 31 days and did not relapse until week 24. Secondary outcomes included remission rate until week 52. Remission was defined as complete absence of GCA symptoms; partial remission included the presence of mild symptoms (for details, see study protocol in Supplementary Data S1, available at *Rheumatology* online). The therapeutic response of the IMT was an exploratory secondary outcome.[4] The study complies with the Declaration of Helsinki and the local ethics committee has approved the research protocol; informed consent was obtained from all patients.

Ultrasound

US scans were done at baseline, days 2 or 3 (after the third dose of methylprednisolone), at weeks 4, 8, 12, 24 and 52. The examiner (L.S.), physician with 6 years of US experience, performed all but two scans; he was not blinded to clinical data. To evaluate inter-reader agreement, IMTs from 121 images (15 scans from 5 patients on GE-Logiq-E9), were remeasured on raw images with a GE-Logiq-E10 by an expert (W.A.S.), who was blinded to clinical data. Seven patients were examined using GE-Logiq-E9, 11 with Canon-Aplio-i800. The B-Mode frequency was 18-22 MHz for the TA and 9-16.5 MHz for the AA/SA. Equipment details are listed in Supplementary Table S1, available at *Rheumatology* online. In the TA, the IMT was measured after complete compression. For the AA/SA, measurements were single sided on the deep wall. Measurements were strictly made in B-Mode in longitudinal images for the AA/SA and transverse images after compression for the TA. Colour Doppler was only used for faster identification of the arteries.

The maximum (not landmark based) IMT of bilateral TA segments (common superficial TA (CSTA), frontal branch, parietal branch) were registered. CSTA, in which measurements were not possible due to incompressibility or due to a very proximal TA bifurcation, and biopsied segments were not followed up. Initially, follow-up scans were planned only for abnormal baseline scans. For IMT measurements of the AA/SA, landmarks were specified individually at baseline, usually the mid humeral head for the AA and an arterial branch taking of the superficial wall for the SA were used. In case the IMT at the landmark of the AA/SA was below the diagnostic cut-off, the whole AA/SA were screened for the largest IMT available, and the maximum IMT of the segment was registered. The IMT at the AA/SA landmark was initially only registered in vasculitic segments, i.e. segments with an IMT above the diagnostic cut-off at baseline. While having normal IMT values in the AA/SA at baseline, patient number 7 showed an unexpected IMT increase in subsequent scans, which promoted adjustments of the protocol (see Supplementary Table S2, available at *Rheumatology* online): For subsequent patients, follow-up scans were always performed and for every AA/SA, even if normal at baseline, the landmark based IMT was registered. Again, the rest of the AA/SA segment was only screened for the additional maximum IMT

if the landmark based IMT was below the diagnostic cut-off. Based on the largest registered IMT of the TA and AA/SA, every segment was classified as being above or below the diagnostic cut-off values (i.e. as vasculitic or not-vasculitic) as defined by Schäfer et al. (TA and AA) or Ješe et al. (SA).[13,18] For the IMT as a quantitative measure, the maximum IMT of the TA, and landmark based IMT of the AA/SA were used. To account for the different number of segments in individual patients, the IMT was scaled and averaged as follows. For each TA segment, the IMT was divided by 2 and again by the mean normal value.[13] (See Supplementary Table S3, available at *Rheumatology* online, for diagnostic cut-off and mean normal values) The sum of these values was averaged by dividing it by the number of segments. For the AA/SA, the same calculation was used, omitting the factor 2, due to single sided IMT measurements. (For formula, see Supplementary Figure S1, available at *Rheumatology* online).

Statistics

Statistical analysis was performed using Stata version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.), plots using R version 4.0.3 (R Core Team (2020)).[21] The scaled IMT were analysed separately for TA and AA/SA using linear mixed effects model with the time point as categorical covariate and random intercepts and slopes for patient and branch. Models were fitted with restricted maximum likelihood. The fitted values at each time point and the change from baseline were calculated with 95% confidence intervals (CIs) using Satterthwaite's approximation for the degrees of freedom and the t-distribution. Inter-reader agreement was assessed using the intra class correlations (ICC) and Krippendorff's alpha. The ICC represents the fraction of the total variance that is within reader; values close to 1 indicate a high correlation between the two readers. It was calculated from linear mixed models of the scaled IMT determined by the two readers including random intercepts for patient, branch (if applicable) and time point. Separate models were fitted for each branch and overall. For Krippendorff's alpha 0 represents no agreement and 1 perfect agreement. It was calculated using the difference function for ratio data and accompanied by bootstrap 95% CI based on 1000 repetitions.

Results

The main characteristics of the 18 patients are shown in Table 1. Sixteen patients had involvement of TA (cranial GCA (cGCA)), 6 patients had cGCA and involvement of large extracranial arteries and 2 patients had no vasculitis on US examination. Five patients dropped out before week 24, 3 due to non-response and 2 due to adverse events. Of the 18 patients, 3 achieved remission within 31 days and 14 within 24 weeks after a mean of 11.1 weeks (95% CI 8.3-13.9). Partial remission was achieved by 14 patients within 24 weeks after a mean of 6.3 weeks (95% CI 3.7-8.7).[4]

In total, 96 US scans were performed. For the TA, of the potential 108 segments (18x6), 92 segments could be classified into vasculitic/not-vasculitic segments at baseline: 14 CSTA unavailable due to proximal bifurcation and/or incompressibility and one anatomic variant (singular frontal branch) with loss of one parietal branch and CSTA. Moreover, due to 16 unilateral and 2 bilateral TA biopsies, only 72/92 segments could be scaled for IMT follow-up. For the AA/SA, 70/72 segments were available for classification into vasculitic/not-vasculitic segments at baseline, and 66/72 for scaled IMT follow-up. Omitting biopsied segments and dropouts, 45 TA and 50 AA/SA segments were available for scaled IMT follow-up at week 52.

The development of the IMT over 52 weeks is displayed in Figures 1 and 2. Figure 1 shows the fitted mean IMT values, the model coefficients are shown in Supplementary Table S4, available at *Rheumatology* online. The individual mean scaled IMT for the TA and AA/SA are displayed in Figure 2. Supplementary Figure S2, available at *Rheumatology* online, shows the Box-plots of scaled IMT, split up by segment and week. Figure 3 displays the proportion of vasculitic segments for individual patients. Supplementary Table S5, available at *Rheumatology* online, shows more detailed information about the proportion of vasculitic segments on a patient and segment level.

Overall mean scaled IMT development (Figure 1)

In the TA, a sharp decline in IMT on day 2/3 was observed, followed by an increase to approximately baseline levels at week 4. This was followed by a steady decrease until week 52. For the AA/SA, a comparable decline in IMT was observed at day 2/3 with a subsequent slow increase up to week 8, a plateau until week 24 and a subtle decline thereafter until week 52. Because only 6 patients had involvement of extracranial large arteries, the individual IMT courses need to be considered.

Individual mean scaled IMT development (Figure 2) and proportion of vasculitic segments (Figure 3)

At week 4, 8 patients showed a rebound to larger IMT values compared to day 2/3 in the TA and 4 of them had larger IMT values compared to baseline. In the AA/SA at week 4, 3 patients had segments above the diagnostic cut-off for the first time, and 2 patients with baseline AA/SA involvement showed a rebound of the IMT. Of the 6 patients with AA/SA vasculitis, 5 had landmark based IMT at baseline. The largest IMT of the AA/SA was reached after 4, 8, 12, 24 and 52 weeks respectively for one patient each. An example with normal baseline IMT and new onset vasculitis at week 12 in the AA is shown in Supplementary Figure S4, available at *Rheumatology* online.

Regarding the effects of intravenous GC on the IMT, the following was observed: Of 16 patients with TA involvement at baseline, 15 still showed at least one segment above the diagnostic cut-off at day 2/3. The single patient without any segment above the cut-off value at day 2/3 had the only pathological segment biopsied at baseline. Of the 3 patients with AA/SA vasculitis at baseline, all had multiple segments above the diagnostic cut-off at day 2/3. For the TA, the IMT of only 4/50 vasculitic segments and for the AA/SA, the IMT of only 1/10 vasculitic segments dropped below the diagnostic cut-offs in response to GC pulse therapy.

Inter-reader agreement

The inter-reader agreement of the IMT measurements was excellent, with the overall ICC of 0.98 (95% CI 0.97 – 0.99) and overall Krippendorff's alpha 0.97 (95% CI 0.95 – 0.98) being close to 1. (see Supplementary Table S6, available at *Rheumatology* online, for details)

Discussion

The GUSTO trial is the first study allowing separate and comparative assessment of the effect of GC and of TCZ on signs of vessel wall inflammation in GCA using IMT measurements with US. Furthermore, the 52-week duration of the study made long-term monitoring possible. GC-pulse therapy led to a profound, yet transient decrease in IMT. Thereafter TCZ monotherapy resulted in a slow but steady decrease of the IMT in the TA, with less pronounced effect on the IMT of the AA/SA. The presented US findings of cranial arteries support the clinical results of a remission-inducing effect of TCZ and they show the potential of US to monitor disease activity.

While older studies examined the qualitative halo sign in GCA treated with GC standard therapy,[11,12] prior data on quantitative IMT measurements with TCZ treatment without long-term GC therapy is not available. Also, no prior study examined the IMT quantitatively before and after intravenous GC. Although the IMT was reduced in our study, pathological segments in all assessable patients were still present on day 2-3. Thus, based on the proposed diagnostic IMT cut-offs,[13,15,18] the diagnosis of GCA could still be made after three consecutive days of 500mg methylprednisolone intravenously in all 15 patients. This indicates that the IMT may serve as a diagnostic tool for GCA even after high dose intravenous GC. This contrasts with MRI data reporting a loss of diagnostic accuracy after as little as two days of prednisone with standard oral dosing.[22]

The short-lasting decrease in IMT in response to GC may be best explained by a strong anti-oedematous effect. It contrasts to the slow decrease in IMT induced by TCZ. TCZ not only suppresses the acute phase response but also acts on maturation of B-lymphocytes and recruitment of Th17 cells.[23] The

kinetics of the IMT decline in response to TCZ may suggest that indirect cellular effects came into play and gradually reduced inflammation. Of note, the slow and sometimes delayed control of vessel wall inflammation in the TA by TCZ parallels the observed slow clinical response. Patients showed gradual improvement of signs and symptoms and achieved complete remission after a mean of three months only.[4] Collectively, the US data suggest synergic effects of GC and TCZ in inducing clinical remission, and they may explain the success of a rapid GC reduction.

There appears to be a different effect of TCZ on TA and AA/SA in some patients. Based on earlier studies[12] and our own experience, we did not expect the IMT of AA/SA to normalize within one year. However, the development of new vasculitic segments of AA/SA in three patients was surprising, even more so, that two patients simultaneously showed an excellent response in the TA. The rebound of the IMT in the TA at week 4, the development of new onset vasculitis of the AA/SA in three patients and the increasing IMT of AA/SA in two patients until week 24 or later, might be due to a slower than expected onset of action of TCZ, in spite of the rapid achievement of therapeutic blood levels with the chosen TCZ treatment regimen.[4] In some patients, TCZ cannot stabilize the IMT reduction after the effect of the intravenous GC wears off. Also, TCZ shows less efficacy in IMT reduction in the larger arteries compared to the TA. This finding is consistent with previous studies with conventional therapy.[12] The observed unequal response of large vs. medium sized arteries may suggest the need to check the IMT of large arteries during the first weeks of treatment with IL-6 inhibitors.

Although some variations in timing and amplitude of the IMT changes in individual patients are notable, nearly all vasculitic arterial segments of the TA followed a similar pattern and a substantial number of segments ultimately normalized over 52 weeks (see Figure 3A). Taken together, IMT appears to serve as a tool to monitor remission in cGCA more so than in extracranial large arteries. However, the very slow changes argue against a plausible value of IMT in the early recognition of relapse and/or non-responders. To fully answer these important questions, multicentre efforts will have to be deployed.

IMT monitoring was feasible, but we frequently observed thrombosis of adjacent segments after biopsy, had one anatomical variant of the TA and either due to a proximal bifurcation or incompressibility, many CSTA could not be rated with our equipment and method. Thus, we believe an IMT scoring system should be flexible to account for such limitations. The presented scaled IMT would meet these demands. Due to the potentially divergent responses of large vs. medium sized arteries, both territories should be scored individually, or their individual developments should remain comprehensible. Also, only using a dichotomous rating like in Figure 3 results in loss of relevant information (i.e. multiple segments dropping below the diagnostic cut-off only after week 24) and should be accompanied by non-binary, quantitative IMT follow-up like in Figure 1 and 2. Incorporating IMT surveillance into GCA trials would be especially helpful with anti-IL-6 therapy and could facilitate inclusion of patients with rare clinical presentations, e.g. inflammation or fever of unknown origin, who are consistently excluded from trials. If US monitoring of IMT is used in trials, we expect patients in clinical remission but with increasing IMT to be reclassified as active disease.

This study has the following limitations: The sample size, particularly the low number of patients with extracranial large artery involvement, precludes generalization of our findings. Furthermore, the very low number of relapsing patients did not allow for identification of US findings predicting relapse. The examiner (L.S.) was not blinded to signs and symptoms and the examinations were not repeated in a blinded fashion by a second expert. Finally, the IMT measurement protocol of the AA/SA had to be changed while the trial was ongoing, however, this did not affect the results for the TA.

In summary, this study shows a clinically important role of IMT measurements in diagnosing GCA despite commenced GC treatment and in monitoring gradual achievement of remission. This latter finding is of particular importance if IL-6 blocking strategies are used, as they render the acute phase proteins unreliable in the quantification of disease activity. The data furthermore support the notion of different reaction profiles of cranial arteries and large arterial vessels to TCZ.

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PV initiated the study and was responsible for funding. LS, LC, LB, SR and PV were involved in the study conception, design and implementation and data interpretation. LS and FL performed ultrasound scans and marked biopsy sites. LC, GS, FK and AS performed study visits. SR and LB were involved in study statistics. WAS performed the independent reading on a subset of IMT measurements. LS, FL and PV wrote the manuscript. All authors read and approved the manuscript.

Disclosure statement

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Data sharing

Research data will be available upon reasonable request. All requests should be submitted to the corresponding author for consideration.

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Table 1 . Patients characteristics (n = 18).

Age [years]	72 (67,75)
Female	12 (67%)
Ethnicity: Caucasian	18 (100%)
BMI [kg/m^2]	24 (23,26)
Prior GC treatment[a]	11 (61%)
Days since GCA symptom onset	28 (21,59)
CRP at screening [mg/l]	61 (50,78)
CRP at baseline [mg/l]	44 (18,62)
ESR at screening [mm/h]	83 (61,89)
ESR at baseline [mm/h]	71 (44,79)
Cranial symptoms	15 (83%)
Headache	12 (67%)
Jaw claudication	10 (56%)
Visual symptoms	6 (33%)
PMR symptoms	10 (56%)
Weight loss >2kg/4 weeks	6 (33%)
Positive TA ultrasound	16 (89%)
Aortitis on MRI	14 (78%)
Vasculitis on cranial MRI	14 (78%)
Positive histology (inflammatory infiltrate)	13 (72%)

[a]for a median of 1 (min 1, max 7) days. Values are n (%, referring to 18) or median (lower quartile, upper quartile). BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GC = glucocorticoids; GCA = giant cell arteritis; MRI = magnetic resonance imaging; PMR = polymyalgia rheumatica; TA = temporal artery.

Figure 1. Development of the overall mean scaled IMT from baseline to week 52. For all 18 patients the raw data is shown in grey and the development overall (Model fit) with the 95% CI is shown in red. CI = confidence interval, IMT = intima-media thickness.

Figure 2. Development of the individual mean scaled IMT from baseline to week 52. For all 18 individual patients, the mean scaled IMT is shown for the TA and for the AA/SA combined. Only patients number 4 and 5 did not show any pathological IMT throughout the study. The colour coding (not in remission, partial remission and remission) shows the relation of the IMT to the clinical status. The circles and triangles represent the timepoints of the ultrasound examinations or drop-outs (circles for TA, triangles for SA/AA). TA = temporal artery, AA = axillary artery, SA = subclavian artery, IMT = intima-media thickness.

Figure 3. Proportion of vasculitic segments for individual patients (TA (A) and AA/SA (B)). In A, the biopsied TA segments were already omitted at baseline and day 2-3. (A heat map of the TA including the biopsied segments is shown in Supplementary Figure S3, available at *Rheumatology* online) At week 52, the denominator drops by one in five patients due to an additional biopsy after week 24. (n) = segments above diagnostic cut-offs; (N) = available segments; colour coding = proportion of vasculitic segments (0 – 100%); white square = missing value; light-blue square = drop out; n/N = column total.

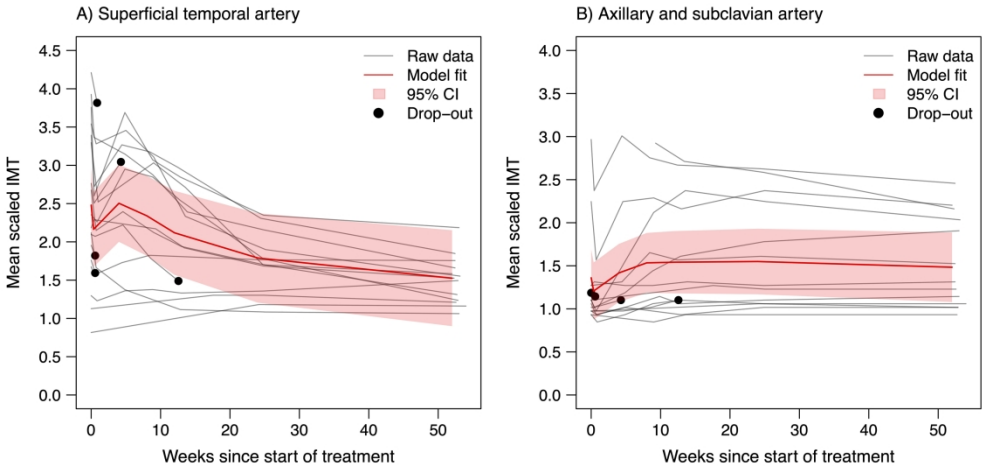

Figure 1 Development of the overall mean scaled IMT from baseline to week 52. For all 18 patients the raw data is shown in grey and the development overall (Model fit) with the 95% CI is shown in red. CI = confidence interval, IMT = intima-media thickness.

266x127mm (300 x 300 DPI)

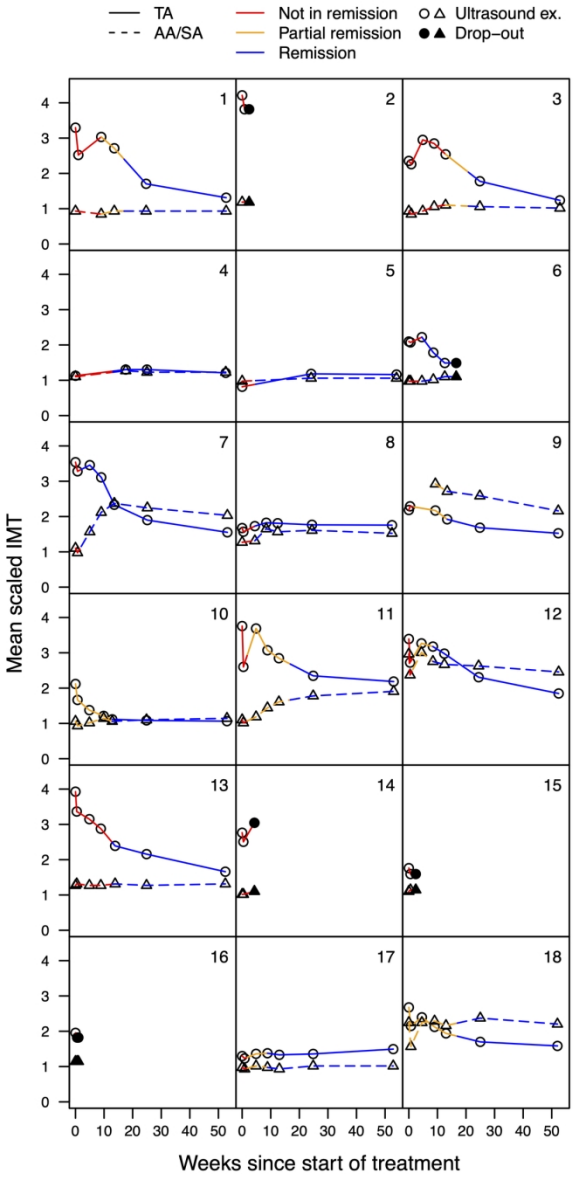

Figure 2 Development of the individual mean scaled IMT from baseline to week 52. For all 18 individual patients, the mean scaled IMT is shown for the TA and for the AA/SA combined. Only patients number 4 and 5 did not show any pathological IMT throughout the study. The colour coding (not in remission, partial remission and remission) shows the relation of the IMT to the clinical status. TA = temporal artery, AA = axillary artery, SA = subclavian artery, IMT = intima-media thickness.

101x203mm (300 x 300 DPI)

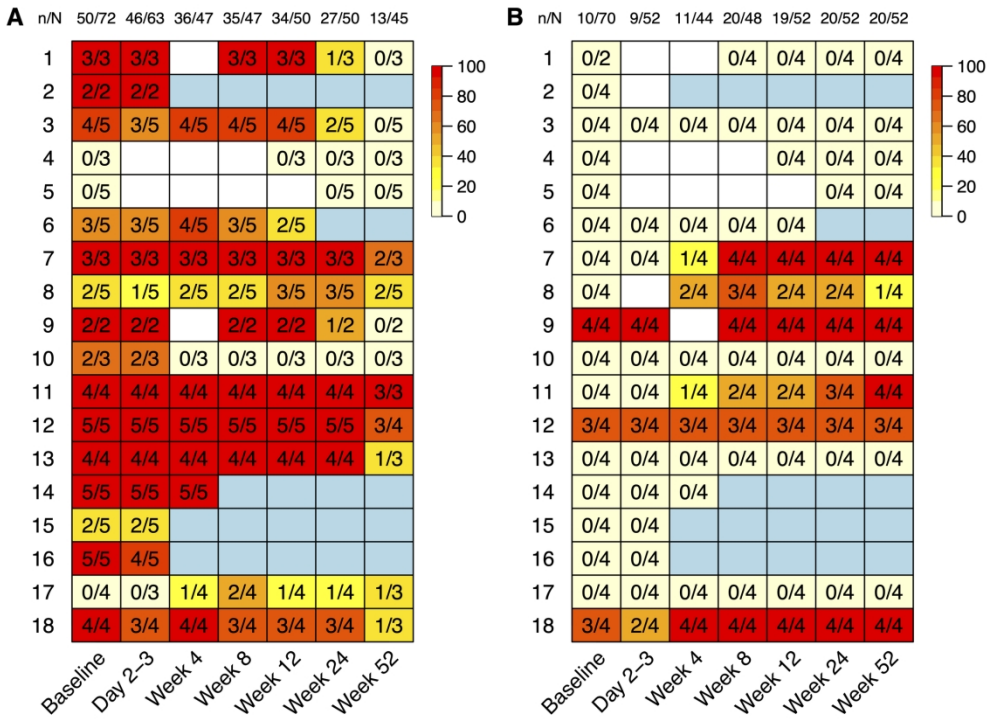

Figure 3 Proportion of vasculitic segments for individual patients (TA (A) and AA/SA (B)). In A, the biopsied TA segments were already omitted at baseline and day 2-3. (A heat map of the TA including the biopsied segments is shown in supplementary Figure S3) At week 52, the denominator drops by one in five patients due to an additional biopsy after week 24. (n) = segments above diagnostic cut-offs; (N) = available segments; colour coding = proportion of vasculitic segments (0 – 100%); white square = missing value; light-blue square = drop out; n/N = column total.

203x152mm (300 x 300 DPI)