Effect of Treatment on Imaging, Clinical, and Serologic Assessments of Disease Activity in Large-Vessel Vasculitis

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ABSTRACT

Objectives

Disease activity in large-vessel vasculitis (LVV) is traditionally assessed by clinical and serological parameters rather than vascular imaging. This study determined the effect of treatment on 18F-fluorodeoxyglose positron emission tomography (FDG-PET) vascular activity in relationship to clinical and serologic-based assessments.

Methods

Patients with giant cell arteritis (GCA) or Takayasu's arteritis (TAK) were prospectively evaluated at 6-month intervals in an observational cohort. Treatment changes were made at least 3 months before the follow-up visit and categorized as increased, decreased, or unchanged. Imaging (FDG-PET qualitative analysis), clinical, and serologic (erythrocyte sedimentation rate, C-reactive protein) assessments were determined at each visit and compared over interval visits.

Results

Serial assessments were performed in 52 patients with LVV (GCA=31; TAK=21) over 156 visits. Increased, decreased, or unchanged therapy was recorded for 36, 23, and 32 visit intervals, respectively. When treatment was increased, there was significant reduction in disease activity by imaging, clinical, and inflammatory markers ($p \leq 0.01$ for each). When treatment was unchanged, all 3 assessments of disease activity remained similarly unchanged over 6-month intervals. When treatment was decreased, PET activity significantly worsened (p=0.02) but clinical and serologic activity did not significantly change. Treatment of GCA with tocilizumab and of TAK with TNF inhibitors resulted in significant improvement in imaging and clinical assessments of disease activity but only rarely did the assessments both become normal.

Conclusions

In addition to clinical and serologic assessments, vascular imaging has potential to monitor disease activity in LVV and should be tested as an outcome measure in randomized clinical trials.

INTRODUCTION

Giant cell arteritis (GCA) and Takayasu's arteritis (TAK), the two major forms of large-vessel vasculitis (LVV), are complex diseases that pose significant management challenges(1-4). Clinical assessment and measurements of acute phase reactants (erythrocyte sedimentation rate, C-reactive protein) are conventionally used to diagnose and monitor disease activity(5); however, accurate determination of disease activity status can be difficult(6). Clinical features of disease can be non-specific (e.g. fatigue, headaches) or potentially related to prior vascular damage rather than active vascular inflammation (e.g. limb claudication, vascular examination abnormalities). Acute phase reactants are often used to guide treatment decisions, yet these markers are not specific for vasculitis(7). Clinically active disease can occur with normal laboratory tests, and persistently abnormal serologic tests without associated clinical symptoms pose clinical conundrums(8),(9). Accurate assessment of vascular disease activity status is critical as untreated inflammation can result in irreversible damage to the large arteries and treatments for LVV carry potential life-threatening risks(10).

Vascular imaging, in particular (18F)-fluorodeoxyglucose (FDG) positron emission tomography (PET), may be useful to detect and monitor vascular inflammation(2, 11). Multiple studies have demonstrated the utility of FDG-PET to diagnose LVV(2, 12-14). Recent EULAR recommendations for imaging modalities in LVV include FDG-PET to diagnose LVV(15). Few studies have described the role of FDG-PET to monitor vasculitis in established cases of LVV(2, 11, 16-18). When patients with LVV undergo prospective imaging-based assessment, a significant burden of ongoing vascular disease activity has been observed on both magnetic resonance angiography (MRA) and FDG-PET during clinical remission, highlighting potential discordance between clinical and imaging assessments at later stages of disease(19). Whether serial imaging should guide treatment decisions is controversial(20), but patients with LVV can develop new arterial lesions on vascular imaging during periods of apparent clinical remission,

and PET activity during remission may predict clinical relapse and angiographic progression of disease(2, 5, 21). There is minimal prospective data about the effects of specific treatment on imaging-based assessment of vascular disease activity in comparison to clinical and serologic assessments. This type of data would provide a more nuanced understanding of drug efficacy in LVV. Glucocorticoids, the mainstay of therapy for patients with LVV, typically improves vascular PET abnormalities(18, 22), but the effect of specific steroid-sparing therapies on vascular disease activity is unknown.

There are no validated outcome measures of disease activity in LVV which has hampered the conduct of successful clinical trials in these diseases. Development of a core-set of outcome measures that incorporate clinical, serologic, and imaging-based assessment of disease activity has been identified as a major unmet need in LVV(4). The primary objective of this study was to determine how changes in treatment impact disease activity as measured by FDG-PET in a prospective, observational cohort of patients with GCA and TAK seen at scheduled 6-month intervals. The secondary objective was to compare imaging, clinical, and serologic based assessments of disease activity in LVV.

MATERIALS AND METHODS

Study Population and Clinical Assessment

Patients with giant cell arteritis (GCA) or Takayasu's arteritis (TAK) were recruited from an ongoing prospective, observational cohort at the National Institutes of Health (NIH). All patients fulfilled the 1990 American College of Rheumatology (ACR) Classification Criteria for TAK or GCA(23, 24) or modified criteria for GCA(25). All patients provided written informed consent (NCT02257866), and the study was approved by ethics and radiation safety committees at the NIH (14-AR-0200).

All patients had at least two study visits at scheduled 6-month intervals (minimum of 4 months and maximum of 12 months). At each visit, patients underwent a detailed clinical evaluation, imaging assessment, and laboratory investigations. Clinically active disease was defined by the presence of at least one clinical symptom directly attributed to ongoing vasculitis by the investigative team. Abnormal acute phase reactants alone were not considered sufficient evidence of clinical disease activity. Based on clinical assessment, patients were given a physician global assessment (PGA) score ranging from 0-10, where a score of 0 indicates clinical remission and increasing scores indicate increased disease activity. PGA was used as there are no clinical disease activity instruments validated for both GCA and TAK, and disease activity assessments developed for TAK have significant limitations(26, 27). Clinical assessments were performed blinded to imaging data. A detailed history was obtained each visit focused on prior and current therapies taken, including glucocorticoids and other forms of immunosuppression (both traditional disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents). All treatment decisions were made by local, referring physicians rather than the investigative study team. Erythrocyte sedimentation rate by Westergren method (ESR) and C-reactive protein (CRP) were measured at each study visit and considered elevated per institutional-defined laboratory thresholds (ESR > 42mm/hr or CRP ≥ 5mg/L) (28).

Treatment status between visits was categorized as increased, decreased, or unchanged. Treatment change was defined as change in daily prednisone dose by ≥5 mg at the time of the follow-up visit relative to the baseline visit or an addition/50% dose change of a DMARD or biologic therapy at least 3 months prior to the follow-up visit. Visits were excluded from analysis when there was a simultaneous decrease in glucocorticoids and increase in the dose of a DMARD and/or biologic agent occurred between visits. Additionally, response to tocilizumab and TNF inhibitors was specifically studied. For these analyses, interval visits where there was a simultaneous decrease in glucocorticoids with addition of tocilizumab or TNF inhibitors were included.

Imaging Assessment

Patients underwent FDG-PET evaluation at each study visit. Details of the imaging protocol have been previously reported(2, 19). Briefly, all patients ≥18 years of age underwent a whole body FDG-PET/CT scan, acquired 120 minutes after administration of 10mCi FDG, with a Siemens Biograph mCT (Siemens Medical Solutions, Erlangen, Germany). To minimize radiation, pediatric subjects underwent whole body FDG-PET/MRI with a Siemens Biograph mMR (Siemens Medical Solutions, Erlangen, Germany) after administration of 0.1mCi/kg of FDG at 60-minutes uptake time.

Arterial FDG uptake was measured by qualitative assessment, in accordance with recent recommendations(29) and as previously described(2). Briefly, degree of arterial FDG uptake was assessed relative to the liver in 9 arterial territories. Each area was scored from 0 to 3 (0 = no FDG uptake; 1 = FDG uptake less than liver; 2 = FDG uptake equal to liver; 3 = FDG uptake more than liver). A global summary score (Positron Emission Tomography Vascular Activity Score, PETVAS) was calculated by summing the amount of arterial FDG uptake in the 9

territories, with scores ranging from 0-27(2). Changes in PETVAS were assessed over visit intervals. Studies were excluded at the discretion of the readers based on technical quality (e.g. motion artifact or suboptimal image resolution). Since PETVAS is a summary score across multiple vascular territories, a specified PETVAS threshold value was not used to define active vasculitis as scans with focal vasculitis can have low PETVAS and still be considered active(2). Instead, PET activity was defined by two nuclear medicine physicians who independently evaluated each PET scan study blinded to clinical details and determined by consensus whether the scan was consistent with active vasculitis or not based upon global assessment of all available images. Excellent inter-rater reliability (kappa=0.84) has been previously reported by our group using this approach(2).

Statistical Analysis

All values are given as median and range. *P* values <0.05 were considered significant. Wilcoxon signed rank test was used to compare changes in PETVAS, PGA, ESR, and CRP in association with treatment status and with addition/increase of specific medications. Fisher's exact test was used to compare the proportion of subjects with clinically active vasculitis and PET activity in association with treatment status.

RESULTS

A total of 52 patients with LVV (GCA = 31; TAK = 21) provided data from 156 visits between October 2014 and August 2018. The median interval between visits was 6 months (range 5-12 months). The median number of visits per patient was 3 (range 2-6). Six PET studies were excluded due to technical quality issues. **Table 1** shows the baseline demographic data of the patients. Median disease duration at the initial visit was shorter in patients with GCA (1.4 years) versus TAK (4.8 years). The median age of the patients with GCA was 72 years (interquartile range 62-76). At the initial visit, 15 patients with GCA (48%) were on therapy with DMARD and/or biologic agent with 13 of these patients (42%) on methotrexate, and 21 patients (68%) were taking glucocorticoids. The median daily dose of prednisone was 15 mg (range 1-60 mg). In the TAK subgroup, the median age was 30 years (interquartile range 20-37). Five patients <18 years of age were included in the study. Most patients (n=17, 81%) were taking a DMARD and/or biologic agent at the initial visit. Five of the patients (25%) were on combination therapy with conventional DMARD and biologic, and 15 patients (71%) were on glucocorticoid treatment. The median daily dose of prednisone was 10 mg (range 2-50 mg).

Interval Change in Treatment

There was an increase in treatment preceding 36 study visits in 27 patients. No change in treatment preceded 23 visit intervals in 21 patients. Decreased treatment preceded 32 visit intervals in 24 patients. Nine visit intervals were excluded from the analysis as simultaneous decrease in glucocorticoids and increase in the dose of a DMARD and/or biologic agent occurred between visits. Interval treatment changes involved glucocorticoids (n=46), tocilizumab (n=17), TNF inhibitors (n=7), or another DMARD and/or biologic (n=33).

Increased Treatment

In the increased treatment group, simultaneous increase in glucocorticoids and other immunosuppressive drugs occurred during 14 of 36 (39%) visit intervals. Over four visit intervals, there was increase in glucocorticoids only, whereas over 18 visit intervals, there was increase in dosage/addition of DMARD and/or biologic agent without any significant difference in glucocorticoid dose. At the baseline visit, the PET scan was interpreted as active vasculitis in 30 patients (83%), 25 patients (69%) had clinically active disease, and 25 patients (69%) had an elevated CRP or ESR. Median PETVAS significantly improved from baseline to 6-month follow-up visit (23.5 vs 18; p<0.01). Concomitantly, significant improvement in median PGA scores (2 vs 0, p<0.01), CRP (6.2 vs 2.0, p<0.01) and ESR (24 vs 9, p<0.01) was also observed (**Figure 1**). There was a significant decrease in the number of patients with clinically active vasculitis from baseline to 6-month follow-up visit (25 patients (69%) vs 14 patients (39%), p=0.02). However, many patients continued to have vascular FDG-PET uptake that, while improved from the baseline visit, was still interpreted as active vasculitis at the follow-up visit (30 patients (83%) vs 24 patients (67%), p=0.17) (**Figure 2**).

Unchanged Treatment

Treatment status was unchanged over 32 visit intervals. FDG-PET data, available following 30 of these 32 visit intervals, did not show any change in the PETVAS score (21 vs 21, p=0.95). Similarly, PGA (0 vs 0, p=0.48), CRP (3.9 vs 3.4, p=0.57), and ESR (13.5 vs 13, p=0.55) remained stable over follow-up (**Figure 1**).

Decreased Treatment

Decreased treatment was noted over 23 visit intervals. Simultaneous reduction in glucocorticoids plus other immunosuppressive drugs occurred during three visit intervals. Decrease in daily glucocorticoid dose without any change in other immunosuppressive drugs occurred during 16 visit intervals. Decrease in DMARD/biologic with no change in

glucocorticoid dose occurred during four visit intervals. PETVAS score was available following 21 visit intervals. Compared to the baseline visit, there was significant increase of PETVAS at 6-month follow-up (16 vs 20, p=0.02). In contrast to imaging assessment, there were no significant differences in PGA (0 vs 0, p=0.52), CRP (1.9 vs 4.4, p=0.10), or ESR (12 vs 16, p=0.07) (**Figure 1**).

Response to Specific Biologic Therapies

Tocilizumab

Tocilizumab was initiated after the initial visit in 17 patients with GCA. Most of these patients were taking prednisone (76%) and methotrexate (59%) at the initial visit. Every patient had active vasculitis by PET at the initial visit. PETVAS significantly improved after treatment with tocilizumab (25 vs 21.5, p<0.01). There was also significant improvement in PGA (2 vs 0, p<0.01), CRP (6.7 vs 0.3, p<0.01), and ESR (22 vs 3, p<0.01) (**Figure 3A**). There was a significant decrease in the median daily dose of prednisone (7mg to 3mg; p<0.01) and weekly dose of methotrexate (20mg to 0mg; p=0.03) with addition of tocilizumab. PET scan activity improved in 8 out of 9 patients with GCA who were started on tocilizumab later into the disease process without a change in glucocorticoid dosing between interval assessments (PETVAS 24 vs 20, p=0.01), including 5 patients who were treated for persistent mild clinical disease activity with tocilizumab alone without addition of any glucocorticoid therapy (PETVAS 24 vs 19.5, p=0.03). Despite significant improvement in PETVAS, only three patients (18%) had normalization of PET activity after treatment with tocilizumab. In contrast, clinical remission after tocilizumab occurred in 14 of these patients (82%). Representative images of FDG-PET response to tocilizumab are shown in **Figure 4**.

Tocilizumab was initiated after the baseline visit in three patients with TAK. All patients had improvement in PETVAS and acute phase reactants, but only one patient achieved clinical

remission. One patient with TAK taking tocilizumab at the baseline visit had active vasculitis by clinical and imaging assessment despite normalization of acute phase reactants, prompting discontinuation of tocilizumab.

TNF Inhibitors

Infliximab was initiated after the initial visit in seven patients with TAK. All seven patients had an improvement in PETVAS following initiation of infliximab (21 vs 16, p=0.02) (**Figure 3B**). All patients had active vasculitis at baseline by PET, and five patients continued to have active vasculitis by PET at follow-up visit despite treatment. Representative images are shown in **Figure 5**. There was significant improvement in clinical assessment of disease activity in these patients (4 vs 2, p=0.02); however, five out of seven patients (71%) continued to have clinically active disease at follow up. There was no significant change in CRP (6.4 vs 3.8, p=0.21) or ESR (26 vs 16, p=0.06) in these patients. All patients treated with infliximab were also treated with methotrexate, but the weekly dose of methotrexate was not statistically different before and after initiation of infliximab. There were no significant differences in daily prednisone dose before and after infliximab treatment (10 vs 12.5mg, p=0.78).

TNF inhibitors were initiated after the baseline visit in three patients with treatment-refractory GCA (infliximab=2; adalimumab=1). All three patients had evidence of large-vessel involvement with PET activity at the baseline visit. Improvement in PET activity and clinical assessment was observed in only one of these patients at the 6-month follow-up visit.

DISCUSSION

This study details changes in disease activity, as measured by vascular FDG-PET uptake, in relation to changes in treatment over 6-month intervals in patients with LVV. The findings represent an important step to demonstrate that FDG-PET has the necessary performance characteristics of a potential treatment response biomarker in LVV. In association with increases in treatment, there were significant improvements in clinical, serologic, and imaging-based measures of disease activity. When there was no significant interval change in treatment status, disease activity as measured by clinical, serologic, and imaging-based markers remained similarly unchanged. Intriguingly, when treatment was reduced, vascular activity by FDG-PET significantly worsened while clinical and serologic markers of activity did not significantly change, suggesting FDG-PET may be more sensitive to detect early-stage worsening of disease activity. Subgroup analysis in GCA and TAK also showed similar changes in PETVAS (data not shown).

While vascular activity by FDG-PET consistently improved in response to increases in therapy, vascular PET abnormalities rarely normalized. Many studies have reported decrease in arterial FDG uptake with corresponding improvement in clinical and serological parameters with addition of treatment (**Supplementary Table**)(11, 16-18, 30-37). However, most of these studies were case-reports with retrospective study designs, relatively short follow-up intervals between imaging assessments, and exclusive focus on the effect of glucocorticoid monotherapy. Using a prospective study design and a novel metric of global vascular disease activity (PETVAS), significant reduction of PET activity in the aorta and primary branches was demonstrated in response to different treatments in GCA and TAK. On average, PETVAS decreased by 5.5 in response to increased treatment. A recent study demonstrated that a decrease in PETVAS by 1 point on average corresponded with significant clinical improvement in response to treatment with an infliximab biosimilar therapy(38). While PET scan findings

improved in most patients who had clinical responses to increased treatment, the follow-up PET scan normalized in response to treatment in the minority of patients. Longer duration of follow-up with repeat imaging may be useful to see if the FDG-PET uptake continues to improve with treatment; however, histology and autopsy data also demonstrate persistent vascular disease activity in LVV during established clinical remission(2, 39-41).

This study offers an opportunity to assess prospectively the effect of specific medications on imaging-based assessment of disease activity. Recently, two randomized clinical trials demonstrated efficacy of tocilizumab in GCA in relationship to clinical and serologic outcome measures(42, 43). Since imaging data was not systematically studied as an outcome measure in either trial, the effect of tocilizumab on vascular disease activity is currently unknown. In this study, there was significant improvement in clinical, serologic, and imaging assessments over a 6-month interval in 17 patients with GCA treated with tocilizumab. Although 14 out of 17 patients achieved clinical remission on tocilizumab, PET scan findings normalized in only three of these patients. These results are consistent with a small study of nine patients with GCA treated with tocilizumab that showed persistent vessel wall enhancement in 33% patients on magnetic resonance angiography up to one year after initiation of treatment(44). The current study also demonstrates a beneficial effect of tocilizumab on PET activity that is independent of potential concomitant glucocorticoid use, as PET activity significantly improved in a subset of patients with GCA who were treated for mild active disease with tocilizumab alone without any glucocorticoids. Among the few patients with TAK treated with tocilizumab, subsequent change in PET activity was variable. Results from a recent randomized trial of tocilizumab in TAK have not demonstrated convincing efficacy (45).

Observational cohort data suggests that TNF inhibitors are effective to improve clinical disease activity and reduce angiographic progression of disease in TAK but sustained remission is rare

and accrual of vascular damage is still common(46, 47). All seven patients with TAK in this study treated with TNF inhibitors experienced significant improvement in clinical and vascular disease activity; however, acute phase reactants did not significantly improve, only two patients achieved clinical remission, and PET normalized in only two patients. Clinical trial data has demonstrated that TNF inhibitors are not effective to treat GCA (48). In this study, three patients with treatment-refractory GCA were treated with TNF inhibitors with clinical and imaging improvement seen in only one patient.

Vascular PET activity significantly increased in association with reduction in immunosuppressive treatment for LVV, without corresponding significant worsening in clinical or serologic disease activity. There are several potential explanations for this observation. FDG-PET may be especially sensitive to detect subclinical recurrence of vascular inflammation. Alternatively, increase in PET activity with reduction in treatment could be related to increased metabolic activity from vascular repair or a secondary cause such as worsening atherosclerosis(49). Novel PET ligands that target specific immune cell populations may improve accuracy to detect of vascular inflammation; however, FDG is rapidly cleared from the blood pool and distributed into the arterial wall, making it the best radiotracer currently available to study metabolic activity in the large arteries. Previous work has demonstrated the amount of vascular PET activity during clinical remission predicts clinical relapse(2). One limitation of the current study is the lack of longitudinal follow-up data to determine whether change in PET activity over time in relationship to treatment status predicts clinical relapse or angiographic progression of disease.

There are several other study limitations to consider. This study was not an inception cohort, and most of the patients had established disease and were on treatment at the baseline visit. A recent study demonstrated rapid reduction in vascular PET uptake after initiation of high-doses of prednisone in patients with newly-diagnosed GCA(50). By including many patients at later

stages of disease, the average prednisone dose at the baseline visit in this study was modest and unlikely to have impacted serial measurements. Given the observational study design, selection bias could influence patient recruitment and treatment decisions. However, all treatment decisions for patients in this study were made by local, referring physicians rather than the study investigators. The referring physicians had access to all test results including the FDG-PET scans which could have influenced treatment decisions; however, treatment based on PET findings alone in absence of corresponding clinical symptoms or angiographic progression of disease is not considered standard of care. Qualitative rather than semi-quantitative metrics were used to monitor PET activity because semi-quantitative assessment of FDG-PET has not been standardized in LVV.

In conclusion, this study identified, in relationship to changes in treatment, concordant and discordant changes in disease activity measured by FDG-PET compared to conventional approaches (clinical and serological assessments). These findings support a need to study FDG-PET as a potential outcome measure of vascular activity in clinical trials in LVV and to evaluate imaging findings in relationship to long-term clinical outcomes in observational cohorts of patients with LVV.

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FIGURE LEGENDS:

Figure 1 Changes in imaging, clinical, and serologic measurements of disease activity following treatment among patients with large-vessel vasculitis (giant cell arteritis or Takayasu's arteritis). PET scan activity as measured by the Positron Emission Tomography Vascular Activity Score (PETVAS) significantly improved over 6-month intervals following increased treatment, remained unchanged when there was no change in treatment, and significantly worsened following decreased treatment (**Panel A**). Clinical disease activity, as measured by the physician global assessment (PGA), and serologic activity, as measured by C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), significantly improved in response to increased treatment but did not significantly change over 6-month intervals when treatment was not changed or was decreased (**Panels B-D**). Note: overlapping data points from different patients may occur in this figure.

Figure 2. Change in FDG-PET scan activity and clinical activity following increased treatment in large-vessel vasculitis. Of 36 instances where treatment was increased in the interval between study visits, PET activity was observed in 30 (80%) baseline assessments and clinical activity in 25 (69%) baseline assessments. Following an increase in treatment, PET activity remained present in 24 (67%) of the 6-month follow-up assessments and clinical activity persisted in 14 (39%) of the 6-month follow-up assessments.

Figure 3. Changes in measures of disease activity in large-vessel vasculitis in response to specific treatments. PET activity (PETVAS), clinical activity (PGA), and serologic activity (CRP, ESR) all significantly improved in 17 patients with giant cell arteritis who were treated with tocilizumab over a 6-month interval (**Panel A**). PET activity and clinical activity, but not serologic activity, significantly improved in seven patients with Takayasu's arteritis treated with

infliximab (**Panel B**). Note: overlapping data points from different patients may occur in this figure.

Figure 4. An example of a patient with giant cell arteritis with improvement in vascular inflammation as measured by FDG-positron emission tomography following initiation of treatment with tocilizumab. A 72 year-old woman with large-vessel giant cell arteritis presented for initial evaluation 2 years into disease course on prednisone 5mg/day. She reported fatigue, malaise, and chronic limb claudication. Physician global assessment = 2. Levels of acute phase reactants were normal (ESR=8mm/hr; CRP=0.5mg/L). FDG-PET computed tomography imaging showed moderate/severe FDG uptake (green/red) throughout the aorta and arch vessels (PETVAS=27). **Panel A** (baseline visit) shows whole body imaging with axial view inset demonstrating PET activity in the ascending and descending aorta. The patient was treated with tocilizumab 162mg every other week and prednisone 5mg/day was continued without a change in dose. At the follow-up visit 6 months later, there was substantial improvement, but not complete normalization, of arterial FDG uptake (PETVAS=24). **Panel B** (follow-up visit) shows whole body imaging with axial view inset showing improved but persistent PET activity in the ascending and descending aorta.

Figure 5. Example of a patient with Takayasu's arteritis with improvement in vascular inflammation as measured by FDG-positron emission tomography following initiation of treatment with tumor necrosis factor inhibitor and methotrexate. A 15 year-old girl with Takayasu's arteritis presented for initial evaluation 1 year into disease course on tocilizumab 162mg every other week and prednisone 10mg/day. She reported ongoing headaches, visual disturbance, postural light-headedness, fatigue, malaise, and abdominal pain. The physician global assessment = 8 and the levels of acute phase reactants were normal (ESR=4mm/hr; CRP=0.2mg/L). FDG-PET magnetic resonance imaging showed moderate (green) to severe

(red) FDG uptake with associated increased wall thickness in the abdominal aorta (**Panel A**, white arrows) and carotid arteries (**Panel B**, white arrows) with PETVAS score of 15. Tocilizumab was discontinued and she was treated with infliximab, methotrexate, and increasing doses of glucocorticoids. At the follow-up visit 6 months later on infliximab 7.5mg/kg every 4 weeks, methotrexate 20mg weekly and prednisone 20mg daily, there was substantial reduction in vascular wall thickness on angiography and normalization of FDG-PET activity (PETVAS = 10) in the abdominal aorta (**Panel C**, white arrows) and carotid arteries (**Panel D**, white arrows).

TABLE 1 Study Population Characteristics at the Initial Visit

	TAK	GCA	P-value
Number of patients	21	31	
Age, year, (median, IQR)	30 (20-37)	72 (62-76)	<0.01
Female, n (%)	16 (76)	23 (74)	1.00
Glucocorticoid, n (%)	15 (71)	21 (68)	1.00
DMARD/biologic, n (%)	17 (81)	15 (48)	0.02
C-reactive protein, mg/L, (median, IQR)	4.5 (1.9-38.8)	5.4 (1.1-11.1)	0.77
ESR, mm/hr, (median, IQR)	19 (12-34)	15 (8-26)	0.54
Active PET, n (%)	13 (62)	28 (90)	0.02
Clinically active disease, n (%)	12 (57)	17(55)	1.00
Disease duration, (median, IQR)	4.8 y (1.4 y – 14.9 y)	1.4 y (0.6 y- 2.7 y)	<0.01

TAK = Takayasu's arteritis; GCA = giant cell arteritis; IQR = interquartile range; n = number; DMARD = disease modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; PET = positron emission tomography; y = year.

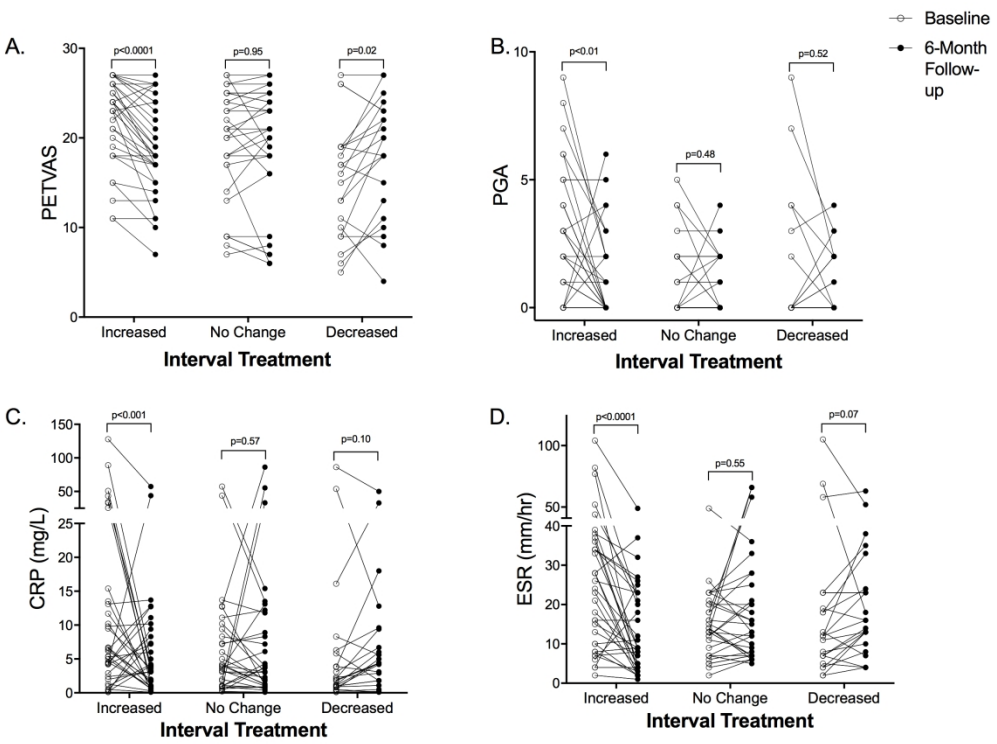

Figure 1

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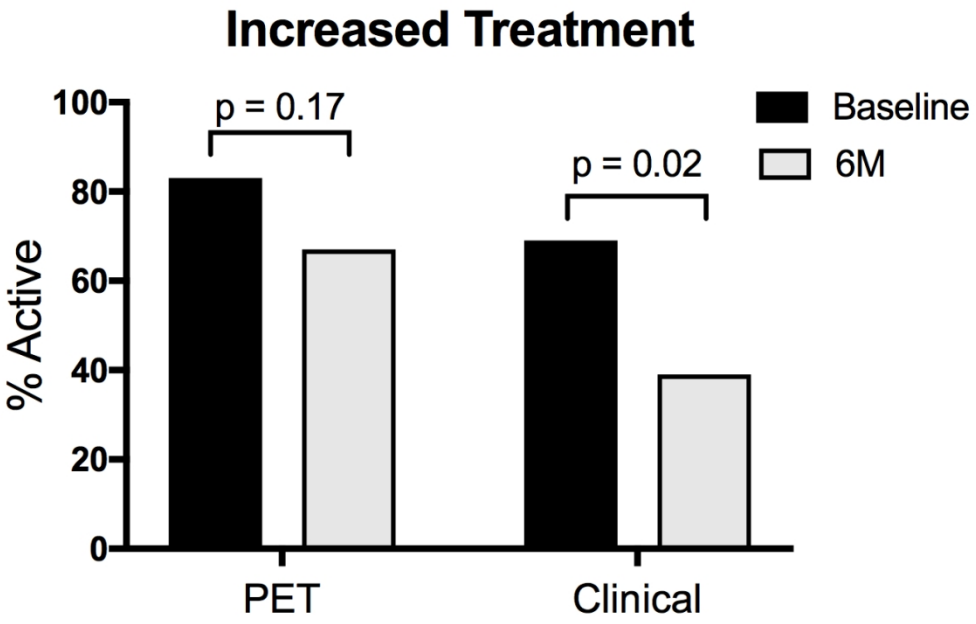

Figure 2

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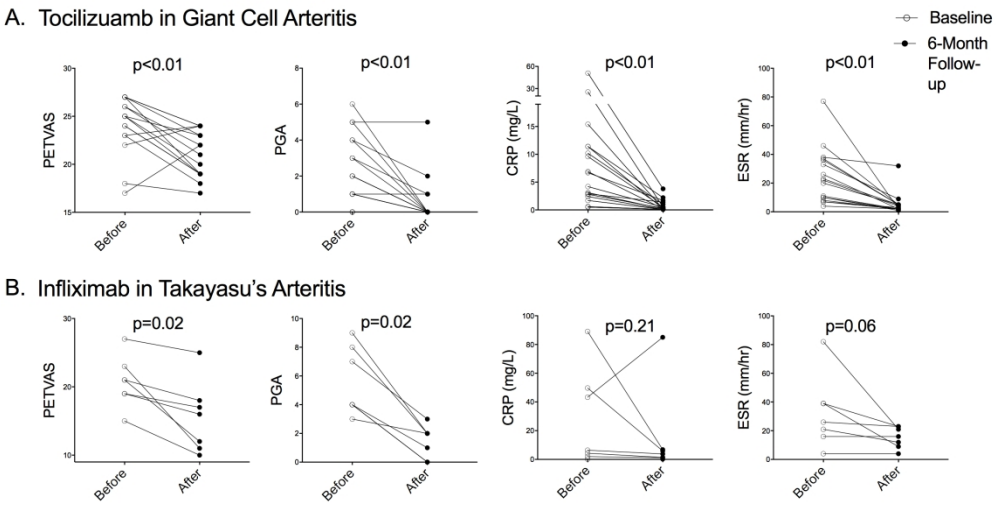

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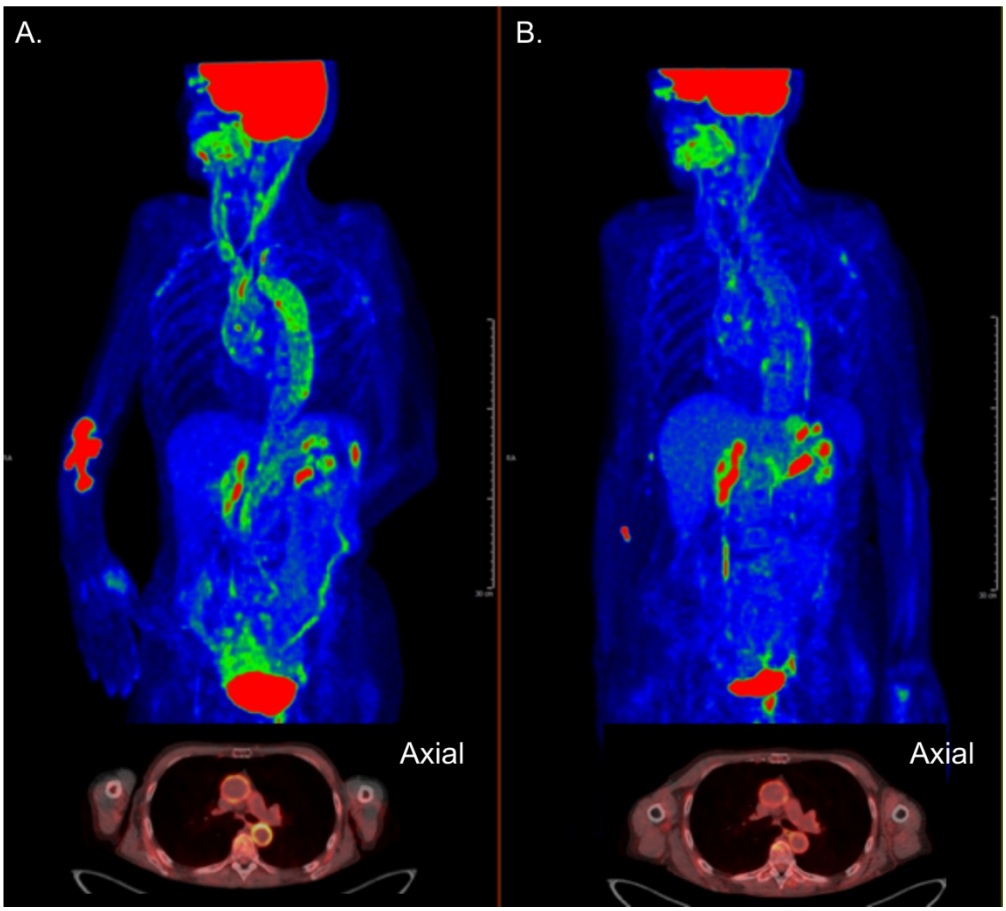

Figure 4

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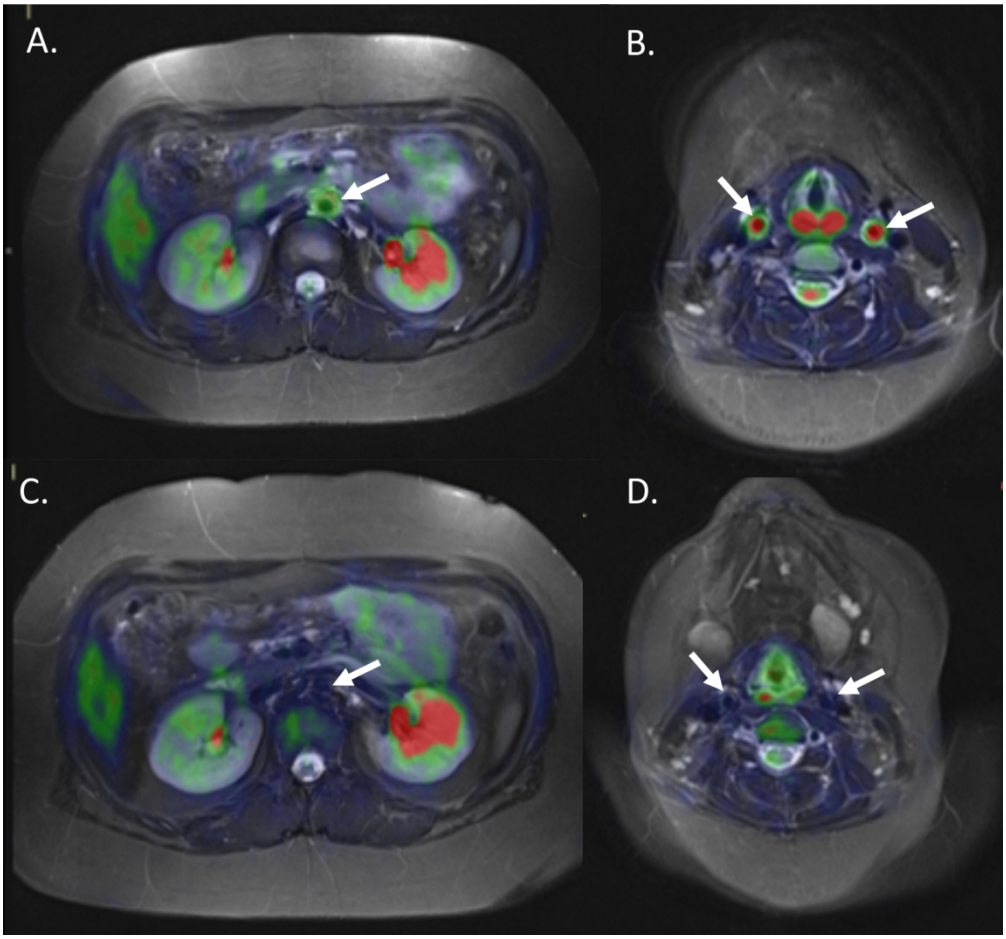

Figure 5

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