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## **Interferon signature in giant cell arteritis aortitis**

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## Abstract

**Objectives:** Molecular mechanisms underlying large-vessel involvement in giant cell arteritis (LV-GCA) are largely unknown. Herein, we explore the critical involvement of pro-inflammatory signaling pathways in both aorta and T cells from patients with LV-GCA.

**Methods:** We analyzed transcriptome and interferon gene signature in inflamed aortas from LV-GCA patients and compared them to non-inflammatory control aorta. Differential transcriptomic analyses of circulating CD4<sup>+</sup> and CD8<sup>+</sup> T cells were also performed between patients with active GCA (not under any immunosuppressants or corticosteroid doses higher than 10 mg/day by the time of blood collection) and healthy donors. Interferon-alpha serum levels were measured using ultra-sensitive technique (HD-X Simoa Planar Technology) in GCA patients according to disease activity status.

**Results:** Transcriptomic analyses revealed 1042, 1479 and 2075 significantly dysregulated genes for aortas, CD4<sup>+</sup> and CD8<sup>+</sup> cells from LV-GCA patients, respectively, as compared to controls. A great enrichment for pathways linked to interferons (type I, II and III), JAK/STAT signaling, cytokines and chemokines was seen across aortas and circulating T cells. A type I interferon signature was identified as significantly upregulated in the aorta of patients with LV-GCA, notably regarding *EPSTI1* and *IFI44L* genes. *STAT3* was significantly upregulated in both aorta and T cells and appeared as central in related gene networks from LV-GCA patients. Interferon-alpha serum levels were higher in patients with active GCA when compared to those in remission (0.024 vs. 0.011 pg/mL;  $p=0.028$ ).

**Conclusion:** LV-GCA presents a clear type I interferon signature in aortas, which paves the way for tailored therapeutical targeting.

**Keywords:** Giant cell arteritis, Large-vessel vasculitis, Aortitis, Interferon signature, JAK/STAT

## 1. Introduction

Giant cell arteritis (GCA) is a granulomatous large-vessel vasculitis that affects patients older than 50 years, representing the most common type of primary vasculitis [1]. Besides the mainly affected external carotid branches causing the polymorphic and typical cephalic manifestations of GCA, the aorta and its main branches may also be inflamed [2]. The proportion of GCA patients described with large-vessel vasculitis (LV-GCA) has increased over the past few decades, mostly due to a wider use of aorta imaging such as computed tomography angiography (CTA), magnetic resonance angiography (MRA) or positron emission tomography with computed tomography (PET/CT), which are able to detect large-vessel inflammation in up to 83% of patients [3,4]. Compared to those with cranial phenotype, LV-GCA patients have a more relapsing disease, requiring longer treatment with higher cumulative dose of corticosteroids [5]. Furthermore, at twice the risk of having aortic aneurysms (*vs.* general population), up to 30% of GCA patients develop aneurysm or dissection [6], whose inherent risk of rupture represents a major cause of mortality in GCA [7]. Vascular pathophysiology in GCA derives from studies of inflammatory temporal arteries, but as its positivity is limited in LV-GCA [7], the pathophysiological process driving the aortitis subset might not be exactly the same as compared to cranial disease. Moreover, the difficulty in obtaining aortic samples makes the comprehension and management of LV-GCA phenotype even more challenging.

New insights into GCA pathogenesis have emerged as increasing attention is being given to type I interferons (e.g., alpha) in LVV [8]. This cytokine signals through the Janus kinase-signal transducer of activators of transcription (JAK/STAT) pathway, inducing the expression of interferon-stimulated genes, the so-called “interferon

signature” [9]. Type I interferon signatures have been reported in several autoimmune diseases, but barely in vasculitis [9–11]. Recently, type I interferon transcripts were demonstrated to be increased in the vessel wall of an immunodeficient mice trans-  
engrafted with inflamed temporal arteries from GCA patients, and inhibiting JAK1 and JAK3 in this chimeric model was effective to disrupt core vasculogenic effector pathways [12]. Indeed, as the JAK/STAT pathway also transduces the signals from several other pro-inflammatory cytokines, its blockade became a paradigm in the treatment of many immune-mediated diseases [13], especially those with an associated interferon signature [9]. While clinical trials evaluating JAK inhibitors in GCA are currently ongoing, whether signaling through JAK/STAT pathway plays a major role in large-vessel inflammation remains unclear.

Data on molecular pathways that could drive large-vessel lesions in GCA are lacking. By using transcriptomic analysis of aorta and circulating T cells from LV-GCA patients, we aimed to assess the pathways involved in this phenotype.

## 2. Methods

### 2.1. Study population

The study population consisted of 43 patients with active GCA (33 newly diagnosed and 10 relapsing patients), with median age of 72 [interquartile range 65.75-78] years, all fulfilling the American College of Rheumatology criteria [14]. LV-GCA was defined as the presence of inflammation of the aorta (aortitis) or its primary branches in large-vessel imaging (i.e., CTA, MRA and/or PET/CT). Disease activity was defined as unequivocal evidence of symptoms attributable to GCA (i.e., new ischemic vascular and/or cranial sign of GCA, systemic clinical features) along with increased concentrations of serum acute-phase reactants (i.e., C-reactive protein and erythrocyte sedimentation rate). Regarding LV-GCA, new vascular lesions or worsening of pre-existing lesions such as stenosis or aneurysms on angiography imaging (e.g., CTA or MRA) or 18-fluorodeoxyglucose uptake on PET/CT were also considered for activity assessment. Demographic, clinical and treatments characteristics of patients are indicated in **Table 1**. Blood samples from these patients were obtained before the introduction or escalation of immunosuppressive therapy and were submitted to the transcriptomic and cytokine analyses described below. Sera from 15 GCA patients in remission were used for cytokine measurement. Thirty-nine sex- and age-matched healthy donors (HD) were used as controls. Blood samples from HD were obtained from the Établissement Français du Sang (Hôpital de la Pitié-Salpêtrière, Paris). Aortic tissue samples were obtained from GCA patients undergoing surgical repair for vascular complications of aortitis (i.e., aneurysm, dissection or stenosis) in our facilities prior to the study conception. Non-inflammatory aorta samples (CTRL) were provided by the Human Tissue Bank from Saint Louis Hospital. The study was approved by our institutional ethics review board (CPP-Île-De-France VI; RIB: 1867484) and was

performed according to the Helsinki declaration. All patients gave written informed consent.

## **2.2. Transcriptomic data of aorta**

Aorta tissue samples ( $n_{\text{CTRL}} = 9$  and  $n_{\text{GCA}} = 10$ ) for this study were obtained in 10 $\mu\text{m}$  cuts. For paraffin extraction, aorta slides were immersed in two consecutive reservoirs containing limonene and ethanol, respectively, being rehydrated with glycerol 3%, and then extracted from the slides and transferred into Eppendorf tubes. Samples were then incubated with DNAase-I for 15 minutes at 20°C, being successively washed thereafter. After centrifugation, supernatant containing RNA was collected and stored at -80°C. Deparaffinized tissue was warmed until 55°C and lysed using High Pure FFPE RNA Isolation Kit (Prosigna, Life Science Roche®). Then, it was incubated overnight at the same temperature. After RNA isolation, samples were submitted to full transcriptomic analysis. All samples passed QC tests for RNA quality, hybridization and noise. Samples were collected in Affymetrix CEL format and were normalized and analyzed using *limma* R package. Enrichment analysis of different gene sets within samples and groups was assessed using *GSVA* and *limma* R packages as previously described [15].

## **2.3. Transcriptomic data of circulating CD4+ and CD8+ T cells**

CD3+ T cells were isolated from PBMCs of active GCA patients and HD by negative isolation using Dynabeads® untouched™ Human T Cells Kit (Thermofisher Scientific) according to the manufacturer's instructions. Patients included in transcriptomic analysis did not receive steroid doses higher than 10mg/day nor immunosuppressants by the time of their blood collection. CD4+ cells were isolated by positive selection using Dynabeads® CD4 isolation kit according to the manufacturer's instructions. CD8+ cells



were isolated from the previous CD4<sup>-</sup> fraction by positive selection using Dynabeads® CD8 isolation kit. Then, total RNA from CD4<sup>+</sup> or CD8<sup>+</sup> cells was extracted using the NucleoSpin® RNA kit (Macherey-Nagel®), according to the manufacturer's instructions. Total RNA was quantified by a NanoDrop ND-1000 spectrophotometer. Samples with RNA concentration <20ng/μL were excluded. For quality control, RNA dilution was performed using Agilent RNA 6000 Nano Kit and 1μL of the sample was run on the Nano chip using an Agilent 2100 electrophoresis bioanalyzer. The quality of total RNA was assessed by the profile of the electropherogram and by the RNA integrity number (RIN). All included samples showed a RIN >7.3. For Illumina Beadarrays, cRNA samples were prepared using Illumina TotalPre-96 RNA Amp kit (LifeTechnologies) and hybridized to Illumina Human HT-12 v4 Beadarrays. Raw data were then normalized and analyzed using *limma* R package. Enrichment analysis of different gene sets within samples and groups was assessed using *GSVA* and *limma* R packages [15].

#### **2.4. Gene network analysis**

Statistically upregulated pathways seen in GCA patients with respect to interferons, JAK/STAT pathways, cytokines and chemokines were selected. Genes with LogFC > 0 as compared to HD were extracted and a network linking genes together was created using *igraph* R package and STRING protein interaction database. This network analysis relies on whether the respective proteins are already known to interact together [16]. Pathways' enrichment analyses of transcriptomic data were performed, and gene network graphs were subsequently built for aorta and circulating CD4<sup>+</sup> and CD8<sup>+</sup> T cells.

#### **2.5. Type I interferon gene signature**

In order to specifically evaluate type I interferon activity in our transcriptomes, we searched for upregulated gene signatures from several publications regarding distinct autoimmune diseases [10,17–20]. In order to quantify the interferon signature in both aorta and circulating lymphocytes, we used a two-step procedure: first with the aforementioned *GSEA* R package [15], where enrichment scores for each patient and pathway involved in the dataset were computed; and then with the *limma* R package, where direct differential analysis of the presented genes was performed to assess for significance.

## **2.6. Interferon-alpha serum levels**

Interferon-alpha was measured in the serum of patients with active or in remission GCA, as well as HD. Inactivated (1% Triton X100; Sigma-Aldrich®, Saint-Quentin-Fallavier, France) plasma samples were tested for interferon-alpha using ultra-sensitive kits (Simoa® IFN- $\alpha$  Advantage Kit, Quanterix®, Netherlands) with HD-X Simoa Planar Technology, according to manufacturer's instructions.

## **2.7. Statistics**

Continuous variables are presented as means  $\pm$  standard error of mean (SEM) or as medians and interquartile range [IQR]. Categorical variables are presented as counts and proportions (%). Statistical comparisons were performed by using unpaired moderated Student's t-tests for quantitative data. All statistical tests were two-tailed with a significance threshold of 0.05. Statistical significance was evaluated using R statistical software version 4.1 and GraphPad Prism version 8.4.2 for Windows (GraphPad Software, San Diego, CA, USA).

### 3. Results

#### 3.1. Interferon gene signature in GCA aortitis

First, we performed aortic tissue transcriptome analysis of GCA patients with LV (n = 10) and compared them to non-inflammatory aorta controls (n = 9). We identified 1042 genes that were significantly dysregulated, being 447 and 595 up- and down-regulated in GCA as compared to controls, respectively. Overall, upregulated pathways were related to interferons, JAK/STAT pathway, pro-inflammatory cytokines and chemokines (**Figure 1A**). Notably, types I, II and III interferons' pathways appeared upregulated in aortic tissue from GCA patients.

Next, by using both *igraph* R package and STRING protein interaction database, we constructed a network of the most up-regulated genes in aortic tissue of GCA patients as compared to CTRL (**Figure 1B**). The most significant genes involved in this network were *STAT3*, interferon regulatory factor 7 (*IRF7*) and the protooncogene *SRC*. Additional genes involved in type I interferon signaling (i.e., *STAT1*, *IRF1*) and in other inflammatory pathways such as NFκB (i.e., *RELA*) and tumor necrosis factor alpha (i.e., *TRAF6*) were also densely connected in the network and relevant in the interferon context.

We then aimed to precisely assess the relevance of type I interferon signaling and plotted all the genes' normalized enrichment fold changes between aorta samples of CTRL and GCA patients. Using both literature [10,17–20] and knowledge, we established and manually curated an interferon-specific gene signature and computed a signature score that allows a statistical estimation of enrichment using *limma* R package. The following type I-specific interferons response genes were selected: *IFI44L*, *ISG15*, *MX1*, *MX2* and *EPSTI1*. The customized type I interferon signature was

significantly enriched in GCA aortas as compared to controls, with *EPSTI1* and *IFI44L* genes being the most involved genes in this result (**Figure 2**).

### **3.2. Dysregulated molecular pathways in circulating CD4+ and CD8+ T cells in GCA**

The microarray gene analysis of purified CD4+ T cells of active GCA patients (n = 27) and HD (n = 39) revealed 1479 significantly dysregulated genes between these groups. Among them, 509 and 970 were up- and down-regulated in GCA versus HD, respectively. The network of the most up-regulated genes in CD4+ T cells highlighted *STAT3* and ubiquitin C in GCA (**Figure 3A**). In addition to inflammatory pathways-related genes seen in aortas (ie, *RELA*, *TRAF6*), *IL6* was found to be a relevant contributor of the network.

As for CD8+ T cells, microarray gene analysis between active GCA patients (n = 19) and HD (n = 34) demonstrated 2075 significantly dysregulated genes, being 921 up-regulated and 1154 down-regulated in GCA versus HD. Consistent with that observed for CD4+ T cells, top up-regulated genes network in CD8+ T cells revealed *STAT3* and *ubiquitin C* as central in GCA, and *STAT5A* was also relevant besides other activated inflammatory pathways-related genes (ie, *RELA*, *TRAF6*) (**Figure 3B**).

As seen in the aorta, among upregulated pathways in CD4+ and CD8+ T cells, those linked to interferons (type I, II and III), JAK/STAT, cytokines and chemokines were outlined (**Supplementary Figure 1 and 2**), regardless of the presence of aortitis (data not shown). Genes composing the unique interferon signature, however, were not significantly dysregulated in circulating lymphocytes.

### **3.3. JAK/STAT pathway dysregulation in aorta and circulating T cells of GCA**

As type I interferons signal through JAK/STAT pathway, we were interested in investigating the specific expression of this pathway throughout aortic tissue and circulating T cells. The comparative heatmap of these genes' expressions between active GCA patients and CTRL (aorta) or HD (T cells) are represented in **Figure 4**. In the aorta (top panel), *STAT1* and *STAT2* transcripts were significantly upregulated as compared to controls. Overall, there was a tendency towards upregulation among all STATs in aortic tissue, except for *STAT5A* (no difference) and *STAT5B* (downregulated). This tendency was inversely reproduced in circulating lymphocytes, as most of differentially expressed STAT transcripts tended to be downregulated in CD4+ (middle panel) and CD8+ (bottom panel) T cells of GCA patients. *STAT3* was the sole exception for that, being significantly upregulated in both CD4+ and CD8+ T cells of GCA patients. Also, *STAT5A* appeared upregulated in CD8+ T cells from active patients as compared to HD.

### **3.4. Higher serum interferon levels in active GCA patients**

Finally, we aimed to determine whether interferon signature could be accompanied by elevations in the serum level of type I interferon. Interferon-alpha concentration was shown to be significantly higher in patients with active GCA (aGCA, n = 41) as compared to that of patients in remission (rGCA, n = 15) (0.024 vs. 0.011pg/mL;  $p = 0.028$ ). There was no statistical difference regarding HD (n = 27) (0.017pg/mL) (**Figure 5**). The increase seen among active patients occurred regardless of the presence of aortitis (data not shown).

#### 4. Discussion

We performed for the first time a transcriptomic analysis of the aortic tissue of LV-GCA patients, and then compared the implicated pathways in both aorta and peripheral T cells in GCA. Notably, an enriched unique interferon signature was identified in patients with LV-GCA. Signaling through *STAT3* appeared key not only in inflamed aortas but also in circulating CD4<sup>+</sup> and CD8<sup>+</sup> T cells of GCA patients. Interferon-alpha appeared systemically relevant as well, with higher serum levels in active patients, possibly representing a link between vascular and systemic inflammation.

The interferon signature is increasingly shaping the knowledge of immune-mediated diseases [9]. Despite the growing recognition of GCA clinical phenotypes, precise pathophysiological mechanisms driving LV-GCA remain widely unexplored due to the limited availability of tissue samples for study [21]. In inflamed temporal arteries, type II interferon (i.e., gamma) have been consistently identified as central in GCA vascular inflammation [22–25], but very little has been reported on type I interferons. Both can induce interferon-stimulated genes by using the common JAK/STAT signaling pathway. Upon activation, interferon-alpha receptor signals via JAK1 and TYK2, and STAT1/2/3, while interferon-gamma receptor does it through JAK1/2, and mostly STAT1 [9,13]. Herein, we demonstrate an upregulated type I interferon signature in inflamed aortas of GCA patients, ultimately leading to increased expression of interferon-related genes. Although the specific interferon signature seen in the aorta was not observed in circulating lymphocytes, interferon-related pathways were also upregulated in circulating lymphocytes, albeit to a lesser degree. This fact underscores an existing dissociation between vascular and systemic inflammation in GCA, and it is possible that the source of tissue-level type I interferon is other than these lymphocytes.

We had previously shown a similar signature in the aortitis of Takayasu's arteritis (TAK), the other prototype of large-vessel vasculitis [26]. The implication of type I interferon in GCA vascular inflammation seems relevant as blocking interferon-gamma solely was insufficient to abrogate inflammation in cultured *ex vivo* temporal arteries from GCA patients [23]. The potential role of type I interferon in this setting had first been demonstrated in an animal model, where Zhang and colleagues engrafted inflamed temporal arteries into immunodeficient mice and reconstituted them with immune cells from GCA patients, showing increased transcripts of both type I and II interferon in vasculitic arteries [12]. Our study supports the idea that a combined action of interferons might also extend to human aortic tissue in GCA, shedding new light on the mechanisms and potential therapeutic targets in LV-GCA.

Understanding vessel wall inflammatory pathways is critical in avoiding permanent vascular damage. Corticosteroids have been for long the cornerstone of GCA therapy, but by not affecting the interferon-gamma-producing Th1 cells implicated in vascular inflammation [22], temporal artery T cell infiltration persists over time [27]. Interferon-gamma isolated blockade in *ex vivo* temporal arteries decreased STAT1 activation and expression, but not that of STAT3, allowing to hypothesize that IL-6 could also be involved in this process [23]. Indeed, IL-6 overexpression and signaling via STAT3 has been implicated in the progression of abdominal aortic aneurysms, and blocking STAT3 is able to slow this process [28–30]. However, the significance of IL-6-STAT3 axis is less clear in large-vessel vasculitis. Zhang *et al.* had already put this into question by demonstrating distinctly low levels of STAT3-dependent genes in temporal arteries from their chimeric mice models [12]. From a clinical perspective, a phase III trial in TAK evaluating the IL-6 blockade with tocilizumab failed to meet its primary endpoints [31], and a non-negligible portion of GCA patients have persistent aortic inflammation

under tocilizumab [32,33]. While IL-6 appeared relevant in our CD4+ T cells gene network, but not in the aorta, STAT3 was consistently reproduced in the interaction networks of both aorta and circulating T cells, suggesting that other mediators (e.g., interferon-alpha) could be the ones that signal through STAT3. Furthermore, us and others [12] have demonstrated STAT1 and STAT2 as significantly upregulated in GCA vasculitic arteries, pointing to a need for multiple pathway blockade to control large-vessel inflammation. The recognition of the JAK/STAT pathway involvement in LVV has highlighted this therapeutical target as of interest [34], with *in vitro* JAK inhibition in both GCA and TAK showing promising results [12,26]. The ongoing trials with JAK1/2 inhibitor baricitinib (NCT03026504) and preferential JAK1 inhibitor upadacitinib (NCT03725202) are expected to shed new light on the impact of JAK inhibitors in GCA.

Another major challenge in GCA management is the reliability on currently available biomarkers. Although erythrocyte sedimentation rate and C-reactive protein are widely used, their sensitivity and specificity in detecting disease relapse are quite limited [35]. By using an ultra-sensitive technique of cytokine detection, we have shown interferon-alpha serum levels to be significantly higher in patients with active GCA as compared to those in remission. Although there was no statistical difference between GCA patients and healthy donors, the mean levels of serum interferon alpha observed in patients with active GCA tended to be higher than HD. The correlation of interferon-alpha with disease activity could be useful for LV-GCA patients, for which imaging modalities are not yet fully validated as disease activity assessment tools [36]. Also, considering the tissue-level interferon overexpression reported by us and others [12], we could hypothesize that interferon-alpha represents a common inflammatory link between vascular and systemic inflammation in GCA.



We acknowledge some limitations. The number of available aortic samples may have not given us enough statistical power to clarify some tendencies. However, it was sufficient to show that *STAT1* and *STAT2* were significantly upregulated in GCA aortitis, and to highlight *STAT3* as central in our gene interaction networks. Our study was also not powered enough to uncover differences between GCA clinical phenotypes for T cells. Finally, as we used whole aortic tissue for transcriptomic analyses, we could not identify the cellular source of type I interferon, and this matter remains to be elucidated.

In conclusion, the unique type I interferon signature in GCA patients with aortitis provides new pathophysiological insights into disease mechanisms. The upregulated signaling pathways pave the way for new therapeutical targets.

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## Figures Legends

### Figure 1. Upregulated pathways and gene network in GCA aortitis.

**A:** Comparative heatmap showing selected and significantly upregulated pathways in aortas (with Benjamini-Hochberg-adjusted  $p$  values  $< 0.05$ ) from non-inflammatory aorta controls (CTRL) and LV-GCA patients, with a focus on JAK/STAT, type I and II interferons, cytokines and chemokines-related pathways. **B:** Gene network constructed from upregulated gene pathways seen in transcriptomic analysis of GCA inflamed aortas (Figure 1A) and the STRING database. Genes are represented by nodes colored according to the number of connections each one of them has, and eventually annotated with the associated gene name. The more densely connected a node is, the more central it is in the gene network, and the more likely it is to have an important function.

### Figure 2. Type I interferon specific gene signature in GCA aortitis.

A type I interferon signaling-related gene signature was analyzed gene-by-gene in GCA and control (CTRL) transcriptomic microarray samples of aortic tissues. The customized signature was enriched in GCA aortas as compared to CTRL (enrichment = 1.22; adjusted  $p$  value =  $1.18e-9$ ). Normalized fold changes (FC) are relative to the absolute maximal FC available within the full differential transcriptome analysis between HD and GCA samples, with its enrichment score being shown in logarithmic scale (LogFC). Differences between CTRL and GCA were assessed using unpaired standard t-tests, and  $p$  values were corrected using the Benjamini-Hochberg procedure.

\*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

### Figure 3. Gene interaction networks of circulating CD4+ and CD8+ T cells in GCA.

Gene networks constructed from upregulated gene pathways seen in transcriptomic analysis of MACS-sorted circulating T cells (**Supplementary Figure 1 and 2**) and the STRING database. Circulating CD4<sup>+</sup> and CD8<sup>+</sup> T cells in GCA are presented in panel A and B, respectively. Genes are represented by nodes colored according to the number of connections each one of them has, and eventually annotated with the associated gene name. The more densely connected a node is, the more central it is in the gene network, and the more likely it is to have an important function.

**Figure 4. JAK/STAT signaling pathway in aorta and circulating CD4<sup>+</sup> and CD8<sup>+</sup> T cells.**

Comparative heatmap showing selected and significantly upregulated genes in CD4<sup>+</sup>, CD8<sup>+</sup> T cells and aortas (with Benjamini-Hochberg-adjusted  $p$  values  $< 0.05$ ) between controls and GCA patients. Red represents non-inflammatory aorta controls (CTRL) or healthy donors (HD) and light blue patients with active GCA. Within the heatmap, the stronger the yellow the higher is the expression of the respective transcripts, while the darker the blue, the lower is the expression of the related genes. Genes in bold are significantly dysregulated as compared to controls ( $p < 0.05$ ).

**Figure 5. Interferon-alpha serum levels in GCA patients.**

Type I interferon (ie, alpha) serum levels from GCA patients with active disease (aGCA,  $n = 41$ ), remission (rGCA,  $n = 15$ ) and HD ( $n = 27$ ). Data was compared using unpaired t-tests and \* represents  $p$  value  $< 0.05$ .

HD: healthy donors, IFN: interferon.



**Table 1. Main characteristics of GCA patients**

<b>Parameters</b>	<b>GCA patients (n = 43)</b>
<b>Demographic</b>	
Age, median [IQR] years	72 [65.75-78]
Female gender, n (%)	30 (69.7)
Origin, n (%)	
- Europe	37 (86.1)
- North Africa	5 (11.6)
- America	1 (2.3)
Newly diagnosed, n (%)	33 (76.7)
Relapsed, n (%)	10 (23.3)
- Disease duration, median [IQR] months	135.5 [53.25-229.3]
<b>Clinical and laboratory features</b>	
General signs, n (%)	33 (76.7)
Headache, n (%)	28 (65.1)
Polymyalgia rheumatica, n (%)	23 (53.5)
Aortitis, n (%)	21 (48.8)
- Aneurysms	9/21 (42.9)
- Arterial wall thickening alone	7/21 (33.3)
- Stenosis	3/21 (14.3)
- Dissection	3/21 (14.3)
Jaw claudication, n (%)	17 (39.5)
Visual symptoms, n (%)	6 (13.9)
Stroke, n (%)	3 (6.9)

Positive temporal artery biopsy, n (%)*	16/33 (48.5)
CRP, median [IQR] mg/L	53 [21-100]
<b>Treatments</b>	
Corticosteroid at the time of blood collection, n (%)	23 (53.5)
- Prednisone daily dose, median [IQR] mg	50 [10-70]

\*Temporal artery biopsy was performed in 33 patients.

General signs denote fever, fatigue and weight loss; visual symptoms stand for arteritic anterior ischemic optic neuropathy (n = 4), central retinal artery occlusion (n = 1) and diplopia (n = 1).

IQR = interquartile range

**Author's contributions:** MV, PR and DS conceptualized the study. MV, PR, AM-D and ALJ were involved in data collection and analysis. PR, MV and AM-D did the statistical analysis. MV, PR, AM-D and DS verified the underlying data. MV and DS wrote the initial draft of the manuscript. GD-J, MR, DK and PC critically contributed to the article. All authors revised and approved the submitted version. DS had the final responsibility for the decision to submit for publication.

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**Data availability statement** Data are available on reasonable request. Transcriptome data from MACS-sorted CD4+ and CD8+ T cells from healthy donors and Giant cell arteritis-affected patients are available on request to Pr. DS: david.saadoun@aphp.fr. They are presented as deidentified patient tabular data (rows = normalized gene expression and columns = patients) in a plain text format. Reuse is permitted if data are not altered in any way and if original authors are correctly cited in the subsequent publications. Raw CEL files were standardized and normalized using *limma* R package and standard methods (notably RMA normalization).