PET-Derived Increased Inflammation in Large Vessels is linked to Relapse-Free Survival in Patients with Giant Cell Arteritis

Der Uptake im FDG-PET in großen Gefäßabschnitten ist mit dem rezidivfreien Überleben bei Riesenzellarteriitis assoziiert

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Key words

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ABSTRACT

Background Despite anti-inflammatory treatment, patients with giant cell arteritis (GCA) experience relapse. We aimed to determine respective relapse predictors focusing on [18F]fluorodeoxyglucose ([18F]FDG)-PET-based parameters.

Material and Methods 21 therapy-naïve GCA patients received [18F]FDG-PET/CT. Patients were divided in two groups: those who relapsed during course of disease and those who did not. Median follow up was 15 months. [18F]FDG-PET/CT was analyzed for visual (PET vascular activity score [VAS]) and quantitative parameters, including Target-to-background-Ratio with liver (TBR_{liver}) and jugular vein (TBR_{jv}) serving as reference tissues. In addition, clinical parameters were tested.

Results 8/21 (38.1 %) had relapse. Clinical parameters could not significantly discriminate between relapse vs no-relapse, including age (p = 0.9) or blood-based inflammatory markers (white blood cell counts [WBC] and c-reactive protein [CRP], p = 0.72, each). PETVAS score could also not differentiate between respective subgroups (p = 0.59). In a quantitative assessment, TBR_{jv} demonstrated a trend towards significance (p = 0.28). TBR_{liver}, however, separated between patients with and without relapse (p = 0.03).

Conclusion [18F]FDG PET quantification of vessels may be useful to identify GCA patients prone to relapse during follow-up.

ZUSAMMENFASSUNG

Hintergrund Patienten mit Riesenzellarteriitis (RZA) erleiden trotz immunsuppressiver Therapie häufig ein Rezidiv (Relapse). Wir haben deshalb untersucht, ob [18F]Fluordeoxyglucose ([18F]FDG) -PET-basierte Parameter geeignet sein könnten, um einen Relapse vorhersagen zu können.

Material und Methoden 21 therapienaive RZA-Patient*innen erhielten ein [18F]FDG-PET/CT. Die Patient*innen wurden dann in 2 Gruppen eingeteilt: Relapse und Non-Relapse. Die mediane Nachbeobachtungszeit betrug 15 Monate. Die [18F]FDG-PET/CTs wurden visuell (PET vascular activity score, VAS) und quantitativ analysiert, einschließlich der Target-to-Background-Ratio (TBR), wobei die Uptakes im Lebergewebe (TBR_{Leber}) und der Jugularvene (TBR_{jv}) als Referenz herangezo-

gen wurden. Zusätzlich wurden klinische Parameter zum Baseline-Zeitpunkt untersucht.

Ergebnisse 8/21 (38,1 %) erlitten einen Relapse. Klinische Parameter konnten nicht zwischen Relapse und Non-Relapse unterscheiden (Alter (p = 0,9) bzw. Entzündungsmarker (Leukozyten und C-reaktives Protein, jeweils p = 0,72)). Auch der PETVAS-Score konnte nicht zwischen den beiden Gruppen differenzieren (p = 0,59). In einer quantitativen Analyse der PET zeigte die TBR_{jv} einen Trend zur Signifikanz (p = 0,28), wohingegen die TBR_{Leber} zwischen Relapse und Non-Relapse differenzieren konnte (p = 0,03).

Schlussfolgerung Eine quantitative Auswertung des [^{18}F]FDG-PET/CT könnte helfen, um RZA-Patient*innen zu detektieren, die einen Relapse unter Therapie erleiden.

Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitis in the elderly and circulatory disturbances may occur in an acute setting, thereby requiring a rapid diagnosis and initiation of anti-inflammatory treatment [1, 2]. Despite adequate, guideline-compatible therapy, up to 50 % of patients still experience relapse during follow-up, triggering further treatment intensification [3]. Moreover, long-term immunosuppression, e. g., by using glucocorticoids is associated with relevant side effects, including on-set of osteoporosis or diabetes mellitus [4, 5]. As such, there is an unmet need to identify high risk individuals prone to treatment failure early in the treatment course or preferably prior to on-set of therapy. For instance, blood-based inflammatory biomarkers were rather less suited to provide predictive information in patients affected with GCA under treatment [6]. As a possible explanation, such a simple analysis of a blood collection may neglect the varying extent of inflammatory disease activity in different vessel wall segments [7]. Morphological, focus-centered imaging such as ultrasound, however, also failed to reliably segregate between individuals prone to early relapse and patients that respond well to treatment [8, 9]. As a functional read-out of the entire inflammatory disease activity, [^{18}F]fluorodeoxyglucose (FDG) PET/CT may overcome those limitations and not surprisingly, visual assessment of vessel wall activity has already demonstrated predictive performance in patients under treatment at time of scan [10]. In this regard, the PET vascular activity score (PETVAS), which allows for a visual grading of metabolic activity, achieved acceptable accuracy to segregate active large vessel vasculitis (LVV) from remission [11]. To date, results on a quantitative [^{18}F]FDG PET/CT evaluation for relapse prediction, however, are limited, in particular for patients that are treatment-naïve at time of scan. In the present proof-of-concept study, we aimed to determine whether [^{18}F]FDG PET-based quantitative parameters proposed by current guidelines may allow to identify those high-risk patients [12] and may outperform a visual assessment like PETVAS or blood-based inflammatory biomarkers prior to treatment initiation.

Material and Methods

Patients

As anti-inflammatory treatment including glucocorticoids affects uptake in the vessel walls even in subjects that have started treatment within a limited time frame of 3 days prior to imaging [13], we included only patients which were therapy-naïve at the time of [^{18}F]FDG-PET/CT. As such, from a cohort of 60 patients with GCA who underwent [^{18}F]FDG-PET/CT at initial diagnosis, 21 patients were retrospectively selected who were therapy-naïve at the time of imaging and were followed up for at least six months after imaging. Parts of this cohort have already been investigated in [14] and [15], but without assessing predictive performance of PET signal in treatment-naïve subjects. Clinical parameters and blood-based inflammatory biomarkers (C-reactive protein [CRP] and white blood cell count [WBC]) were collected at time of scan (i. e., prior to any treatment). Treatment was initiated by board-certified rheumatologists following respective guidelines [2] and included glucocorticoids, methotrexate, azathioprine, leflunomide and tocilizumab. In addition, every third month, follow-up visits of all subjects were conducted and relapse was diagnosed according to current guidelines [2]. Patients were then subdivided into relapse and no relapse for further analysis. All subjects signed written informed consent for diagnostic procedures. The need for approval was waived by the local ethics committee, given the retrospective nature of this investigation (No. of approval: 20 210 319 01).

Relapse during Follow-up

According to the updated EULAR recommendations [2], diagnosis of relapse was established by a board-certified rheumatologist and was defined as the recurrence of active disease with clinical features suggestive of inflammatory activity. Additional symptoms included drop in daily performance, fever, night sweats, and weight loss, as our cohort also included patients with LV-GCA without specific cranial symptoms [16].

[^{18}F]FDG-PET/CT Acquisition and Image Analysis

Patients were scanned using a Siemens Biograph mCT 64 or mCT 128 PET/CT (Siemens, Knoxville, TN, USA). Prior to administration of 283.3 ± 47.3 MBq [^{18}F]FDG, scans were performed after a 1 h waiting period. We used non-contrast-enhanced CT for anatomical co-registration and attenuation correction. Parameters of CT were as follows: 120 KV, 160 mAs, matrix 512 × 512, with a 5 mm slice thickness. Median glucose levels were 104 mg/dl.

[^{18}F]FDG PET data was reconstructed following recommendations of the manufacturer. Further details can be found in [14]. Image analysis was performed according to the current guidelines [12] and performed by a first reader (MF, KVG) and confirmed by an expert reader (RAW) in inconclusive cases. Visual analysis yielded the modified PETVAS score (based on 11 investigated vessel segments) [10]. To assess inflammatory activity in the vessels, circular volumes of interest (VOIs) were manually drawn for the fol-

lowing 11 segments: ascending aorta, aortic arch, descending and abdominal aorta, innominate artery (brachiocephalic trunk), both carotid arteries, both subclavian arteries, and iliac artery. This yielded a total of 231 VOIs to obtain maximum standardized uptake (SUV_{max}) of the vessels. For each patient, averaged SUV_{max} was calculated for further analysis. To determine the background ratio (vessel wall-to-liver and vessel wall-to-blood pool), additional VOIs were placed on healthy liver tissue and in the jugular vein (jv) [12]. For the latter reference tissue, mean SUV (SUV_{mean}) was used [12]. According to current guidelines [12], we then defined the respective target-to-background ratios (TBR) as follows:

TBR_{liver} = averaged SUV_{max} artery / SUV_{max} liver	Eq. 1;
TBR_{jv} = averaged SUV_{max} artery / SUV_{mean} jv	Eq. 2.

Statistical Analysis

For statistical analysis, Prism (version 9.4.1 (GraphPad, San Diego, CA, USA)) was applied. For continuous variables, mean ± standard deviations are presented. Kaplan–Meier curves and log-rank comparison were used to compare patients with and without relapse based on the median of the clinical or PET parameters. Median time to relapse is presented in months with respective hazard ratio (HR) and 95 % confidence intervals (95 % CI). A p-value of < 0.05 was considered to be statistically significant.

Results

Patients' Characteristics

Follow-up was median 15 months. 8/21 (38.1 %) patients relapsed after a median of 3.5 months, and the remaining 13/21 (61.9 %) patients were relapse-free by the end of follow-up. Patient characteristics are shown in ▶ **Table 1**.

Clinical Parameters and PETVAS could not identify Patients Prone to Relapse

Investigating blood-based inflammatory biomarkers and clinical parameters, respective median for age was 73 years (WBC, 7.5×10^9/L; CRP, 3.13 mg/dl). When investigating the performance of those parameters to segregate between patients with and without relapse, no significance was reached: Age, HR = 0.91 (95 % CI = 0.23–3.66), p = 0.9; WBC, HR = 1.29 (95 % CI = 0.32–5.23), p = 0.72; and CRP, HR = 0.78 (95 % CI = 0.19–3.16), p = 0.72.

We then tested the prognostic performance of [^{18}F]FDG-PET/CT to differentiate between patients with and without relapse. On a visual level, median PETVAS score was 18. Comparable to clinical and laboratory parameters, however, no significant segregation between subjects with and without relapse was found (HR = 0.69, 95 % CI = 0.17–2.83, p = 0.59).

▶ **Table 1** Patients' characteristics. Percentages are given in parentheses. CRP = C reactive protein. WBC = White blood cell count. ESR = erythrocyte sedimentation rate. Immunosuppressive therapy (= methotrexate, tocilizumab, azathioprine, leflunomide).

Clinical parameters	
Female	15/21 (71.4)
Age at diagnosis (years) (median)	73
Relapse (n)	8/21 (38.1)
Time of first relapse after initial diagnosis (median in months)	3.5
Immunosuppressive therapy in addition to glucocorticoids	12/21 (57.1)
Laboratory values prior to treatment	
CRP at the time of initial [^{18}F]FDG-PET/CT (mg/dl)	6.4 ± 6.7
WBC at the time of initial [^{18}F]FDG-PET/CT (x10^9/L)	8.5 ± 3.1
ESR at the time of initial [^{18}F]FDG-PET/CT (mm/1st hour)	63.8 ± 35.0
Blood glucose level at time of PET (mg/dl) (median)	104

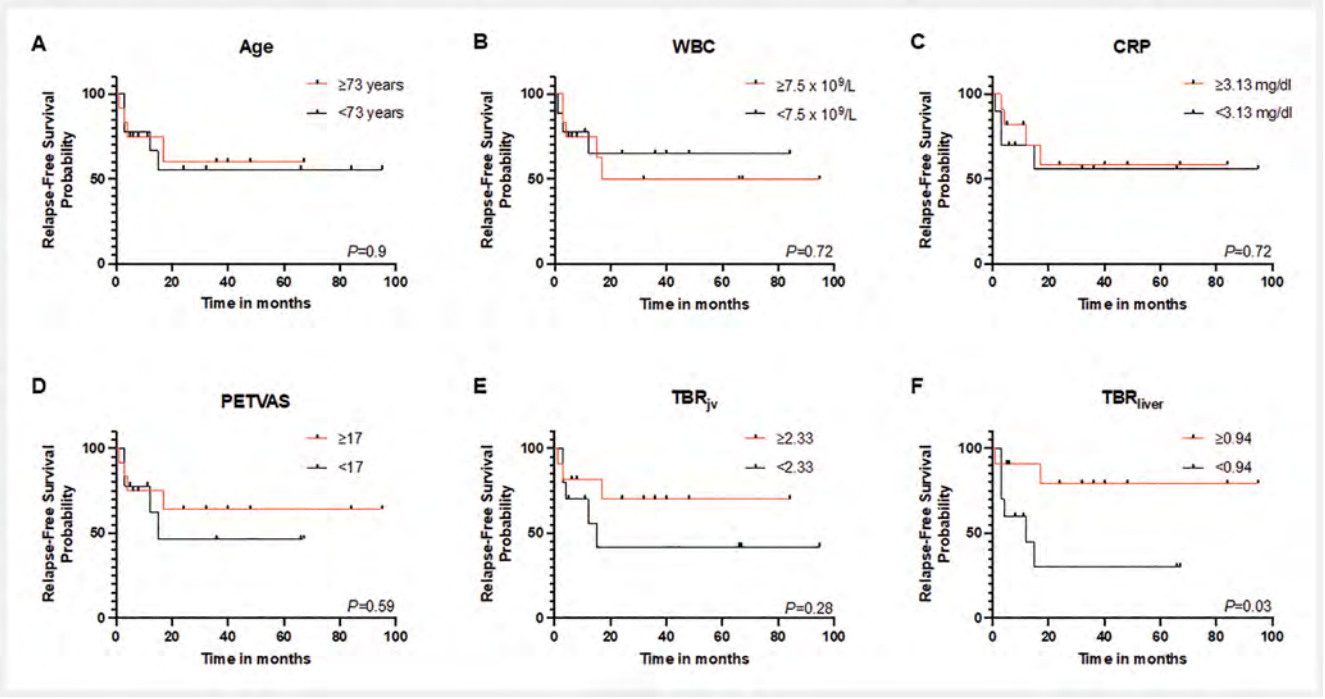
PET-based Quantification identified Individuals with Increased Risk for Relapse

On a quantitative level, TBR_{jv}-derived median of 2.33 failed to differentiate between patients with relapse vs. no relapse (HR = 0.47, 95 % CI = 0.12–1.91, p = 0.28). For TBR_{liver}, however, we observed a significant separation between individuals with and without relapse (median, 0.94; HR = 0.22, 95 % CI = 0.05–0.91; p = 0.03). Non-relapsed subjects exhibited higher baseline TBR_{liver} values (▶ **Fig. 1**), supporting the notion of better response to treatment in subjects with higher disease activity at baseline.

Discussion

Investigating 21 GCA subjects without treatment at time of scan, inflammatory laboratory biomarkers could not identify patients prone to relapse after commencing guideline-compatible treatment. Analyzing [^{18}F]FDG-PET/CT, however, visual-based PETVAS failed to segregate between high- vs. low-risk individuals. On a quantitative level, TBR_{jv} demonstrated a trend to identify subjects prone to relapse, while TBR_{liver} then reached significance. Of note, subjects with increased TBR_{liver} at time of scan demonstrated prolonged relapse-free survival, supporting the notion that patients with more extensive inflammatory burden at baseline may also better respond to anti-inflammatory therapy. Our feasibility study may therefore trigger future investigations, e. g., by testing [^{18}F]FDG-PET/CT-based quantification by other statistical tests in a larger number of treatment-naïve GCA patients, including multivariate analyses to determine whether those PET-based parameters may also serve as independent predictors [17].

Identifying patients prone to relapse would be essential for a tailored and risk-adapted therapy in patients with GCA. In this study, we observed a better segregation of quantitative metrics obtained by an inflammatory-targeted [^{18}F]FDG-PET/CT when



▶ **Fig. 1** Kaplan-Meier curves of all patients affected with Giant Cell Arteritis divided in 2 subgroups with or without relapse. As cut-offs, median of each parameter was used. For clinical parameters, **A** Age, **B** white blood cell count (WBC), and **C** C-reactive protein (CRP) were investigated. For PET, we investigated the PET vascular activity score (PETVAS, **D**) and quantitative parameters, including target-to-background ratios of the blood pool provided by the jugular vein (TBR_{jv}, **E**) and the liver (TBR_{liver}, **F**). Only TBR_{liver} reached significance, with higher values at baseline linked to prolonged relapse-free survival probability.

compared to other established markers used in the clinic or a visual PET read-out. Following current guidelines [12], we applied a TBR with healthy liver serving as background, which then allowed us to determine subjects with elevated inflammation in the vessels, that respond well to treatment. Although our initial findings have to be interpreted with extreme caution, the number of patients included in this investigation in the context of relapse prediction may still be substantial, in particular in a treatment-naïve setting using [^{18}F]FDG-PET/CT. For instance, a recent study reported on 4 subjects with relapse and did not demonstrate a relevant association between TBR_{liver} and risk of recurrence [18]. Those discrepant findings relative to our study may then be partially explained by the low number of relapsed subjects of the previous investigation and the more balanced subgroups in our study. So far, quantitative analyses based on [^{18}F]FDG-PET/CT examinations in GCA have played a rather negligible role in clinical routine, mainly due their time-consuming nature and the need to acquire a relatively large amount of data for reliable test results [7]. On the other hand, they provide objective measurements, unlike the purely visual assessments such as the total visual score (TVS) [19] or PETVAS [10], thereby minimizing the risk of observer dependence and improving reproducibility [20, 21]. For instance, Blockmans et al also enrolled a treatment-naïve cohort and could not establish an association between relapse and visual assessment using the total vascular score (TVS) [19]. This observation is in line with the results of several studies that have shown only moderate significance for the PETVAS score for relapse prediction [22, 23]. Of note, Blockmans and coworkers reported on a substantial decrease of TVS under treatment [19]. In the present study, we did not analyze follow-up [^{18}F]FDG-PET/CTs, as we aimed to determine baseline parameters to segregate between high- vs low-risk patients prior to treatment onset. Nonetheless, the finding of decrease in delta TVS upon restaging is also in line with our finding of patients less likely experiencing relapse when TBR is higher at baseline, as those patients may then also be more likely to exhibit a relevant drop in their TBR_{jv} and/or $_{liver}$ during follow-up [19]. Taken together, our and previous findings may indicate that [^{18}F]FDG-PET/CT may provide a valuable diagnostic tool to monitor disease activity in patients affected with LVV prior to and under anti-inflammatory treatment. Our quantitative analysis also demonstrated significant benefit with respect to relapse probability only for the liver as background for TBR assessment, but not for the vena jugularis, i. e., with blood pool serving as reference. This is also in line with a study conducted by Dashora et al [21], which compared different backgrounds that can be used for TBR calculation (including unaffected blood pool, lung, and liver). In this study, hepatic parenchyma corrected uptake then achieved the highest area under the curve in terms of reader interpretation and physician assessment of disease activity [21], also indicating that TBR_{liver} may be more useful for quantitative scan interpretation.

Our study has several limitations. The present retrospective study included only a small number of patients and thus, we relied on the median of every parameter. A larger cohort may then allow to apply more sophisticated tests including receiver operating characteristics and multivariate analyses, which would then pro-

vide independent predictors [17]. Nevertheless, we focused on a homogenous cohort, which was treatment-naïve at time of scan. Moreover, only patients with predominantly LV-GCA were included, but not with Takayasu arteritis or cranial GCA. For the latter, [^{18}F]FDG-PET/CT may rather not be useful, as cranial involvement may be missed due to the partial volume effect [24]. Nonetheless, the herein performed risk assessment in particular for LV-GCA, however, may be of importance, as the latter subtype is often more challenging to diagnose, mainly due to rather unspecific symptoms when compared to cranial GCA [16].

Conclusions

Investigating treatment-naïve GCA patients at time of scan, a significant separation of high- vs low-risk individuals prone to relapse was observed for [^{18}F]FDG-PET/CT-based TBR_{liver}. Other parameters, including PETVAS or inflammatory blood-based biomarkers failed to discriminate between respective subgroups, supporting the notion that a local quantitative read-out of the inflammatory disease activity in vessel segments may provide superior predictive performance. In addition, in those treatment-naïve individuals, higher TBR_{liver} was also linked to better outcome, indicating that patients with increasing inflammatory burden at baseline may respond better to immunosuppressive therapy. Further investigations in a prospective study design including more patients are warranted, in particular to determine whether [^{18}F]FDG-PET/CT-based quantification is also an independent predictor for identifying patients prone to relapse under anti-inflammatory treatment.

Author Contribution

Conceptualization, M.F., K.V.G., and R.A.W.; methodology, M.F., K.V.G., and R.A.W.; software, M.F. and K.V.G.; validation, A.K.B., and T.A.B.; formal analysis, M.F. and K.V.G.; investigation, M.F. and K.V.G.; resources, M.S. and A.K.B.; writing – original draft preparation, M.F., and R.A.W..; writing – review and editing, A.K.B., T. A.B. and M.S.; visualization, R.A.W., and M.F.; supervision, R.A.W. and T.A.B.; project administration, R.A.W. and T.A.B. All authors have read and agreed to the published version of the manuscript.

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Declarations

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest

The authors declare that they have no conflict of interest.

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