Therapy response evaluation in large vessel vasculitis

Slart, Riemer H J A; Glaudemans, Andor W J M; Brouwer, Elisabeth; van der Geest, Kornelis S M

Published in:
Rheumatology

DOI:
10.1093/rheumatology/keab375

RHEUMATOLOGY

Rheumatology 2021;60:3494–3495
doi:10.1093/rheumatology/keab375
Advance Access publication 28 April 2021

Editorial

EDITORIAL

Therapy response evaluation in large-vessel vasculitis: a new role for [18F]FDG-PET/CT?

[18F]Fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT) is recommended as a first-line investigation in the diagnosis of large-vessel GCA (LV-GCA) [1]. Accumulating evidence indicates that [18F]FDG-PET/CT may also aid treatment monitoring in LV-GCA [2]. In the present issue of *Rheumatology*, Schönau *et al.* report data from the RIGA study providing important insight into the impact of distinct treatments on serial [18F]FDG-PET/CT in LV-GCA [3].

The authors included 88 patients with new-onset LV-GCA, who were treated with either prednisolone monotherapy (PRED; $n = 27$) or prednisolone in combination with MTX ($n = 42$) or tocilizumab (TOC; $n = 19$). The PET vascular activity score (PETVAS) decreased significantly during follow-up irrespective of the treatment regimen. PETVAS showed an excellent accuracy for detecting ongoing vasculitis on the follow-up scan as defined by the nuclear medicine specialist judgement. However, PETVAS provided poor accuracy for distinguishing clinically active disease from remission, as strictly defined by the presence or absence of GCA-related symptoms. The cumulative prednisolone dosages were 5637, 4478 and 2984 mg in the PRED, MTX and TOC groups ($P = 0.002$), respectively. These results are relevant, but various aspects of the study should be kept in mind.

Both the decision to perform the baseline [18F]FDG-PET/CT and the selection of treatment were guided by the physician's judgement. Evaluation of Table 2 suggests that patients in the TOC group, likely recruited in recent years, slightly differed from those in the other groups. The prevalence of jaw claudication differed substantially between the groups ($P = 0.0003$ by χ^2 test) and was highest in the TOC group. The presence of other cranial symptoms and polymyalgia rheumatica also tended to be higher in the TOC group. This could reflect the increased awareness of large-vessel involvement in patients with cranial GCA or PMR.

The low glucocorticoid requirements in the TOC group were reassuring. However, the RIGA study does not allow to compare the glucocorticoid-sparing effect of TOC to that of MTX. While the RIGA study covered a long period of time (2008–2020), only recently the GiACTA trial suggested that glucocorticoids might be tapered within 26 weeks if TOC is added to the treatment [4]. Such a quick tapering of glucocorticoids was likely not attempted in the earlier patients who were treated with either PRED monotherapy or MTX. It would also have been interesting to know the exact doses of MTX and PRED that were used during the follow-up scan. Paucity of efficacy of MTX in earlier trials might have been related to relatively low doses applied [5].

Lack of a perfect reference standard for LV-GCA disease activity remains a challenge. Disease activity in the RIGA study was defined by the presence or absence of clinical manifestations attributable to GCA. However, most symptoms in GCA are not specific [6]. This is exactly why imaging tools are increasingly applied for the treatment monitoring of GCA [7]. The poor relationship between [18F]FDG-PET/CT findings and the clinical judgement should not be considered as evidence against the use of [18F]FDG-PET/CT in the monitoring of GCA. The main role of [18F]FDG-PET/CT is to complement the clinical assessment rather than to replace it.

The timing of [18F]FDG-PET/CT is important. Baseline, arterial [18F]FDG uptake might have been influenced by treatment. [18F]FDG uptake can be affected after 3 days of glucocorticoid intake [8, 9]. The series by Schönau *et al.* may have included some patients under early/chronic glucocorticoid therapy at the baseline scan (this point was not well specified by the authors). Follow-up scans were performed at 3–63 months of treatment. It would have been interesting to learn the disease course preceding the follow-up scan as well as the exact indication, such as suspected relapse.

Various [18F]FDG-PET/CT outcomes may be used in the monitoring of LV-GCA. Schönau *et al.* applied the PETVAS score, but quantitative metrics (i.e. standardized uptake values) might also be of interest. Incorporating more objective measures such as vascular [18F]FDG-PET activity into clinical trial designs in LV-GCA may provide a more nuanced understanding of treatment of inflammation at the vascular level and may enable the conduct of more efficient trials that require smaller sample sizes to demonstrate drug efficacy.

Standardization of [18F]FDG-PET/CT scans is critical. Importantly, the authors adhered to the procedural recommendation for the use of [18F]FDG-PET/CT for LV-GCA [9]. Yet, the first baseline scans were performed on older PET/CT camera systems, and reconstructions of the scans will have changed slightly during the study. New developments in PET/CT camera systems, such as digital or total body systems, may further enhance the spatial resolution with a better signal-to-noise (i.e. vessel wall *vs* lumen) ratio. These new systems can also visualize pathologic uptake in the smaller cranial vessels (e.g. temporal arteries) [10].

Although arterial [18F]FDG uptake indicates vascular inflammation in newly diagnosed GCA, it is possible that

ongoing arterial [18F]FDG uptake during treatment reflects vascular remodelling/healing in some patients. Emergent PET tracers, for instance binding to specific macrophage subsets, could potentially be more accurate for the treatment monitoring of patients with LV-GCA [11]. These specific tracers may provide lower background radioactivity, higher diagnostic accuracy and the ability to assess treatment effectiveness. However, further understanding regarding macrophage subsets in vasculitis lesion is needed for better selection of tracers and new targets for tracer development.

In summary, despite the potential limitations, [18F]FDG-PET/CT may aid treatment monitoring in LV-GCA. The extent and severity of vascular inflammation on [18F]FDG-PET/CT is responsive to therapy [2]. The RIGA study provides valuable information by showing that PRED, MTX and TOC all improve arterial [18F]FDG uptake [3]. Given the costs and radiation exposure, follow-up [18F]FDG-PET/CT might be reserved for patients in which the disease activity remains uncertain despite thorough clinical evaluation. We encourage further research into the diagnostic yield value of [18F]FDG-PET/CT in the treatment monitoring of LV-GCA. It may soon be time to update the EULAR recommendations for the use of imaging in large-vessel vasculitis in clinical practice [1].

Funding: No specific funding was obtained for the current study.

Disclosure statement: K.v.d.G. reports grants from the Mandema Stipend and the FOREUM Foundation for Research in Rheumatology and personal fees from Roche, outside the submitted work. E.B. reports personal fees from Roche (2017 and 2018) for speaker and consulting fees, outside the submitted work.

Riemer H. J. A. Slart[1,2,3], Andor W. J. M. Glaudemans[1,3], Elisabeth Brouwer[3,4] and Kornelis S. M. van der Geest[3,4]

[1]*Department of Nuclear Medicine and Molecular Imaging, Medical Imaging Centre, University Medical Centre Groningen, University of Groningen, Groningen,* [2]*Biomedical Photonic Imaging, Faculty of Science and Technology, University of Twente, Enschede,* [3]*Vasculitis Expertise Centre Groningen and* [4]*Rheumatology and Clinical Immunology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands*

Accepted 15 April 2021

Correspondence to: Riemer H. J. A. Slart, Department of Nuclear Medicine & Molecular Imaging (EB50), University of Groningen, University Medical Centre Groningen, Medical Imaging Centre, Hanzeplein 1, PO 9700 RB, Groningen, the Netherlands. E-mail: r.h.j.a.slart@umcg.nl

References

1 Dejaco C, Ramiro S, Duftner C *et al.* EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77:636–43.

2 van der Geest KSM, Treglia G, Glaudemans AWJM *et al.* Diagnostic value of [18F]FDG-PET/CT for treatment monitoring in large vessel vasculitis: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2021; doi: 10.1007/s00259-021-05362-8. [Online ahead of print].

3 Schonau V, Roth J, Tascilar K *et al.* Resolution of vascular inflammation in patients with new-onset giant cell arteritis: data from the RIGA study. Rheumatology (Oxford) 2021.

4 Stone JH, Tuckwell K, Dimonaco S *et al.* Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317–28.

5 Brouwer E, van der Geest KSM, Sandovici M. Methotrexate in giant cell arteritis deserves a second chance – a high-dose methotrexate trial is needed. J Rheumatol 2019;46:453–4.

6 van der Geest KSM, Sandovici M, Brouwer E, Mackie SL. Diagnostic accuracy of symptoms, physical signs, and laboratory tests for giant cell arteritis: a systematic review and meta-analysis. JAMA Intern Med 2020;180:1295.

7 Hellmich B, Agueda A, Monti S *et al.* 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.

8 Nielsen BD, Gormsen LC, Hansen IT *et al.* Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. Eur J Nucl Med Mol Imaging 2018;45:1119–28.

9 Slart RHJA, Writing group *et al.* FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. Eur J Nucl Med Mol Imaging 2018;45:1250–69.

10 Nienhuis PH, Sandovici M, Glaudemans AW, Slart RH, Brouwer E. Visual and semiquantitative assessment of cranial artery inflammation with FDG-PET/CT in giant cell arteritis. Semin Arthritis Rheum 2020;50:616–23.

11 Jiemy WF, Heeringa P, Kamps JAAM *et al.* Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging of macrophages in large vessel vasculitis: current status and future prospects. Autoimmun Rev 2018;17:715–26.