



# Molecular imaging in large vessel vasculitis has come to stay

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*Comment on:* Quinn KA, Ahlman MA, Malayeri AA, *et al.* Comparison of magnetic resonance angiography and <sup>18</sup>F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. *Ann Rheum Dis* 2018;77:1165-71.

Submitted Aug 14, 2018. Accepted for publication Aug 18, 2018.

doi: 10.21037/atm.2018.08.26

**View this article at:** <http://dx.doi.org/10.21037/atm.2018.08.26>

The field of medical imaging has experienced an awesome advance in the last decades, far above other areas, both in oncological and non-oncological diseases. This technological development has resulted in the expansion of the molecular imaging. Molecular imaging combines elements of medicine, molecular biology, immunology, biochemistry, radiochemistry, pharmacology, nanotechnology and computing, allowing the “*in vivo*” visualization, characterization and quantification of biological processes at cellular and molecular level in its own pathophysiological environment, and includes magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasonography, optical imaging, fluorescence and bioluminescence.

Until a decade ago, the diagnosis of large vessel vasculitis (LVV), especially its cranial form, has been based on clinical criteria, biochemical data and temporal artery biopsy. Nevertheless, these criteria were established for classification purposes and they are not suitable for assessing the extracranial involvement. In recent years, we have witnessed the increasing use of multimodal molecular imaging in clinical practice for the study of different inflammatory and infectious diseases, including vasculitis, polymyalgia rheumatica, endocarditis and vascular grafts infections (1-4). <sup>18</sup>F-FDG PET/CT has shown good performance both for the early diagnosis of LVV, even before the development of oedema and structural changes of the vessel wall depicted by MRI, and for the evaluation of the extent of the disease (5-7). The pooled sensitivity

and specificity described in several meta-analysis published ranged between 80–89% and 89–98% respectively for giant cell arteritis (GCA), with a lower sensitivity of around 84% in patients with Takayasu arteritis (TA) (8,9). On the other hand, a relationship between aortic <sup>18</sup>F-FDG uptake and a subsequent development of complications such as aneurysms has been described (10).

MRI has been also applied in the diagnosis of LVV, both for the study of cranial and extracranial arteries such as the aorta and its branches, with high diagnostic accuracy, although the published works are scarce and many of them limited by their retrospective nature (5,11). While PET provides relevant functional metabolic information, MRI offers anatomical data about the late development of aneurysms and stenosis. In addition, new specific sequences and procedures on MRI have provided superior soft-tissues resolution, allowing the detection of abnormalities related to the inflammatory process in early phases of the disease including intramural vessel wall oedema, thickness and contrast enhancement (12,13).

Apart from the early diagnosis, another important aspect is the long-term monitoring of disease activity given the treatment-related adverse events and the risk of vascular complications. Although the few published works have shown promising results in the follow-up of the patients using <sup>18</sup>F-FDG PET/CT, generally in correlation with clinical and biochemical improvement (5,14,15), and also for MRI, the role of the different imaging techniques in this context remains unclear and more studies are necessary.

Quinn *et al.* (16) have recently published a very interesting prospective observational study aimed to compare  $^{18}\text{F}$ -FDG PET/CT and magnetic resonance angiography (MRA) performance in the follow-up of LVV and to identify MRA features associated with PET findings and clinical activity of the disease. The study included a total of 133 MRA/PET paired scans performed in 84 patients (35 with GCA, 30 with TA and 19 as a control group with non-inflammatory large-vessel vasculopathies), evaluating 966 vascular territories (4 segments of the aorta and 11 branch arteries including innominate, carotids, subclavians, axillaries, iliacs and femorals). A relevant aspect of this work is the elevated number of patients especially with TA, in whom identifying disease activity is usually more challenging, and also the sizeable number of vascular regions analyzed. Clinical assessment and PET/CT and MRA follow-up were performed at 6 months intervals. Wall thickness, oedema, stenosis, occlusion and aneurysm were the features analyzed by MRA and for PET/CT a visual analysis of  $^{18}\text{F}$ -FDG vascular uptake in comparison with liver uptake was applied.

Regarding the presence of active disease, the authors have found agreement between PET/CT and MRA findings in 68% of the examinations, being slightly higher in GCA than in TA (72% *vs.* 64%, respectively). On the other hand, when the extent of the disease was considered, PET/CT and MRA agreed in 60% of the arterial territories evaluated and when both examinations disagreed territories were more likely to be involved on MRA. These results differ from those previously described by Meller *et al.* who reported that, although PET and MRI showed comparable results in the diagnosis of LVV, PET identified more vascular regions involved and was more reliable than MRI in monitoring disease activity during immunosuppressive therapy. Meller *et al.* also described a good correlation between PET findings, clinical improvement and normalization of acute-phase reactants, although it should be considered that the number of patients included was lower and, more important, the inclusion criteria was the presence of pathological  $^{18}\text{F}$ -FDG uptake in the aorta (5).

Quinn *et al.* found that the presence of oedema on MRA, but not the detection of wall thickness and stenosis, was associated with MRA interpretation of activity. Patients with active disease by both PET/CT and MRA had the highest number of territories showing oedema and increased wall thickness. Clinical status of the patients was associated with PET/CT activity but not with MRI activity (16). In the same line, Eshet *et al.* found no correlation between clinical

activity and MRI findings of activity in patients with TA (17). Although the clinical usefulness of PET/CT and MRI in the primary diagnosis is well established, the role in the follow-up of those patients is more controversial (5,17).

Studies evaluating the role of the emerging new biological therapies are very scarce. Spira *et al.* evaluated retrospectively the usefulness of different contrast-enhanced MRI/MRA parameters for therapy monitoring in 8 patients with TA and 4 patients with GCA, 9 of them treated with tumor necrosis factor- $\alpha$  blockers and 3 with an interleukin-6 inhibitor (tocilizumab). Although they found a decrease of wall thickness and mural enhancement after treatment, imaging findings often did not correlate well with clinical or laboratory parameters (18).

Quinn *et al.* have also noted that more than half of patients in clinical remission had active disease by PET/CT and MRA, hypothesizing that a certain degree of inflammatory activity remains in the vessel walls (16). Persistent vascular  $^{18}\text{F}$ -FDG uptake in the follow-up of asymptomatic patients has been previously described and has been also related to vascular remodeling or resistance, although the etiology remains unknown (14,19).

Lower sensitivities both for PET/CT (6) and MRA (12,20) after glucocorticoid intake have been widely reported. Nielsen *et al.* described that, although  $^{18}\text{F}$ -FDG uptake decreased after 3 days of high-dose glucocorticoid treatment, LVV was accurately diagnosed. Diagnostic accuracy of PET/CT decreased significantly after 10 days of treatment (21). The general recommendation is that both studies, PET/CT and MRI, should be performed prior to initiation or after immunosuppressive therapy withdrawal (22,23).

In daily clinical practice we have witnessed a growing demand by clinicians of imaging techniques for the management of LVV and also for the enrolment in clinical trials. As a result of this interest and very recently, the European League Against Rheumatism (EULAR) have published for the first time a guideline of evidence-based recommendations specifically focused on the role of imaging for the early diagnosis and monitoring of patients with LVV in clinical practice (23). Thus, an imaging test (depending on the local expertise and availability) for early diagnosis is recommended in patients with suspected GCA to complement the clinical criteria. Panel experts also consider that in patients with high clinical suspicion of GCA the diagnosis may be established by a positive imaging scan without an additional test. The first recommended technique in patients with suspicion of TA is MRA, being

PET/CT useful as an alternative procedure. Regarding long-term monitoring of the disease, EULAR task force recommends the use of MRI, CT angiography and/or ultrasonography in order to detect structural damage including stenosis, occlusion, dilatation or aneurysms. There is not a recommendation for the frequency of follow-up studies.

The main advantages of MRI compared to PET/CT are the usefulness for temporal arteries examination, an increased soft-tissue contrast with high resolution, a better discrimination between vasculitis and atherosclerosis, and finally but not least, the absence of radiation. Consecutive radiation exposure related to PET/CT examination is a remarkable disadvantage in the long-term therapy monitoring and follow-up of LVV, especially in young patients with TA, making a priori MRI the ideal technique in this scenario. A relevant contribution of imaging in the study of LVV not available by other methods is that it allows the knowledge of the real extent of vascular inflammation and the more frequently involved vessels in a non-invasive way.

In summary, there is still not enough scientific evidence about the usefulness of imaging for monitoring vascular inflammatory activity and it also remains unclear the role of these techniques in the context of new biologic therapeutic agents, such as IL-6 receptor  $\alpha$  inhibitors. Many outstanding issues should be clarified before its use in the clinical setting such as the standardization of MRI and PET/CT images interpretation, the definition of imaging disease activity criteria, the timing and frequency of examinations, the usefulness for outcome prediction, cost-effectiveness and clinical impact (22,23). More randomized prospective comparative PET/CT and MRA studies with larger number of patients are necessary in order to establish evidence-based recommendations.

The near future for multimodal imaging in LVV will probably come hand in hand with the expansion of hybrid PET/MR scanners, currently limited to a few centers. Integrated PET/MR equipment combines “the best of each word” in a whole-body single examination: a sensitive early evaluation of inflammation in multiple vascular beds and a high contrast soft-tissues resolution with an absolute match between the functional and anatomical information under the same physiological conditions. Other additional advantages come from a substantial reduction in motion artifacts, more accurate quantification of PET data and the improvement in cranial arteries evaluation. Finally, avoiding the radiation derived from the CT component of PET/CT technology allows a lower exposure to ionizing radiation,

especially relevant in young patients, as in the case of TA, and in long-term follow-up of patients. Preliminary studies reported very promising results for hybrid PET/MR, highly comparable to PET/CT, both in the evaluation of vascular inflammatory activity and in the extent of the disease (24). Another interesting line of research has focused in the development of new more specific inflammation radiotracers such as  $^{11}\text{C}$ -PK11195, a selective ligand of membrane receptors of activated macrophages. Promising preliminary results in a limited number of patients have been obtained (25).

In conclusion, the study published by Quinn *et al.* (16) is a new step on the way that contributes to increase the knowledge of the natural history of LVV and, although there are numerous questions waiting for an answer, it seems clear that in the near future imaging techniques will play a relevant role in the diagnosis and follow-up of patients with LVV and that the world of image has come to stay.

## Acknowledgments

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Martínez-Rodríguez I, González-Gay MA, Prieto-Peña D, Banzo I. Molecular imaging in large vessel vasculitis has come to stay. *Ann Transl Med* 2018;6(Suppl 1):S2. doi: 10.21037/atm.2018.08.26