^{68}Ga-DOTATATE PET/CT for assessment of cardiac sarcoidosis

Monroy-Gonzalez, Andrea G.; Erba, Paola A.; Slart, Riemer H.J.A.

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^{68}Ga-DOTATATE PET/CT for assessment of cardiac sarcoidosis: hidden opportunities?

Andrea G. Monroy-Gonzalez, MD, PhD,[a] Paola A. Erba, MD, PhD,[a,b,c] and Riemer H. J. A. Slart, MD, PhD[a,d]

[a] Departments of Radiology and Nuclear Medicine & Molecular Imaging, Medical Imaging Center, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[b] Nuclear Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy
[c] Department of Medicine and Surgery, Bicocca University Milan, Milan, Italy
[d] Biomedical Photonic Imaging Group, Faculty of Science and Technology, University of Twente, Enschede, The Netherlands

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Diagnosis and treatment of cardiac sarcoidosis (CS) currently remain challenging with no imaging-based gold standard. MRI delineates scarring and edema but does not provide enough information about the immunological state of this granulomatous disease.[1] [^{18}F]FDG PET/CT, the gold standard for non-invasive cardiac inflammation, may be hindered by physiological myocardial uptake despite patient preparation (fasting, ketogenic diet, or heparin injection), resulting in low specificity.[1] Because somatostatin receptor has been identified in inflammatory cells, somatostatin analogues have been proposed as a potential alternative for different chronic inflammatory diseases.[2]

Lee et al. present a pilot study with 11 patients for imaging of CS by targeting the somatostatin receptor with [^{68}Ga]Ga-DOTATATE in comparison with [^{18}F]FDG PET/CT.[3] In their study, 10 patients demonstrated multifocal [^{68}Ga]Ga-DOTATATE uptake suggestive of active CS and one patient showed diffuse uptake without focal areas of uptake. Regarding [^{18}F]FDG PET, 10 patients demonstrated multifocal myocardial uptake with [^{18}F]FDG at baseline and one patient had focal on diffuse uptake. The patient-level concordance was therefore considered good (91%). However, segment level showed considerable false-positive and false-negative rates. Out of 170 evaluable segments in the ten patients with multifocal uptake, 50 segments were positive on both scans, 24 were positive only on [^{18}F]FDG, and 15 segments were only positive on [^{68}Ga]Ga-DOTATATE. The overall agreement was therefore considered suboptimal (77%). Additionally, all patients had extra-cardiac [^{18}F]FDG uptake suggestive of sarcoidosis involvement, while only 82% showed [^{68}Ga]Ga-DOTATATE extra-cardiac sarcoidosis involvement.

Follow-up with both [^{18}F]FDG and [^{68}Ga]Ga-DOTATATE was performed in seven patients (out of eleven). Based on the [^{18}F]FDG, three patients had complete response (CR) and one partial response (PR), while with [^{68}Ga]Ga-DOTATATE, one patient had CR and one PR. Major reason for response underestimation on [^{68}Ga]Ga-DOTATATE was persistence of uptake at the inferior segments due to spillover from the abdomen.

Previous studies have reported different accuracy of somatostatin analogues for the diagnosis of CS. Sharma et al. reported underestimation on [^{68}Ga]Ga-DOTATATE in four out of nine patients with complete clinical response following immunosuppressant treatment.[4] Bravo et al. reported that [^{68}Ga]Ga-DOTATATE may be less sensitive than [^{18}F]FDG for the detection of myocardial inflammation, but comparable for detecting extra-cardiac inflammation.[5] [^{68}Ga]Ga-DOTATATE PET/CT has been reported to show areas of increased

Reprint requests: Riemer H. J. A. Slart, MD, PhD, Departments of Radiology and Nuclear Medicine & Molecular Imaging, Medical Imaging Center, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; *r.h.j.a.slart@umcg.nl*
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tracer uptake to be consistent with acute inflamed myocardium.[6,7] Also, [^{68}Ga]Ga-DOTATATE showed 100% accuracy for the detection of inflammation in the form of sarcoid granulomas, while [^{18}F]FDG PET sensitivity was 33% and specificity was 88%, according to the Japanese ministry of Health and Welfare CS criteria.[8]

The study of Lee et al. is a pilot study with a small sample size, it is the first one to report baseline and follow-up imaging with [^{68}Ga]Ga-DOTATATE. As stated by the authors, time delay between [^{18}F]FDG and [^{68}Ga]Ga-DOTATATE in their study may be an important confounding factor. One more important consideration is the use of [^{18}F]FDG as the reference standard, since [^{18}F]FDG uptake is not specific, then it remains unknown the real clinical significance of [^{18}F]FDG uptake without [^{68}Ga]Ga-DOTATATE uptake. Similarly, significant uptake of [^{68}Ga]Ga-DOTATATE also may represent other inflammatory processes such as myocarditis, post-infarction, or coronary atherosclerosis. Interestingly, despite those limitations, patient-level concordance was good. Lee et al. suggested different explanations for the suboptimal concordance on the segment level and the follow-up response. However, these ''suboptimal'' results may represent different patterns of uptake not yet understood related to different physio-pathological states of CS. Imaging the contribution of different inflammatory cell subtypes will allow to phenotype the different phases of the disease, potentially providing important diagnostic and prognostic insight.[9] The use of [^{68}Ga]Ga-DOTATATE has been proposed given the high binding affinity to the G-protein-coupled receptor SST2 which is up-regulated on the surface of activated macrophages while very low levels of SSTR2 mRNA have been detected in unstimulated M0 macrophages, alternatively activated M2 macrophages as well as monocytes, T or B lymphocytes, natural killer cells, platelets, neutrophils, and endothelial cells.[10–12] Targeting proinflammatory M1 macrophages by SSTR2 with [^{68}Ga]Ga-DOTATATE has been successfully achieved in macrophage-rich carotid plaque regions with a better identification of high-risk coronary lesions by [^{68}Ga]Ga-DOTATATE vs [^{18}F]FDG which uptake is dependent on the high expression of GLUT1 and GLUT3 by all inflammatory cell subtypes, demonstrating that SSTR2 offers greater cell specificity as an inflammation imaging target than glucose metabolism.[13] Uptake of [^{68}Ga]Ga-DOTATATE in activated macrophages can be also enhanced by hypoxia as shown in the inflammatory process associated with acute ischemic injury.[14–17] Therefore, identifying the clinical relevance of uptake of somatostatin analogues tracers in terms of identification of patients at high risk for major adverse cardiac events, patients who will potentially benefit from treatment with electronic cardiac devices and prediction of treatment efficacy. It is reasonable that patients who defer primary prevention implantable cardioverter defibrillator (ICD) therapy undergo serial clinical follow-up and advanced imaging to detect cardiac disease progression, as the current ICD guidelines fail to distinguish a truly low-risk group of patients with clinically manifest CS.[18]

In conclusion, [^{68}Ga]Ga-DOTATATE PET/CT is able to identify active CS with good patient-level concordance when compared to [^{18}F]FDG PET/CT, but it is accompanied with considerable false-positive and false-negative rates on segment level with low signal-to-background ratio. Compared to [^{18}F]FDG PET/CT, [^{68}Ga]Ga-DOTATATE PET/CT tends to underestimate treatment response. Adequate further prospective randomized studies are needed to determine the diagnostic and prognostic value of [^{68}Ga]Ga-DOTATATE PET/CT.

Disclosures

The authors have no conflict of interest to declare.

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