Is the Clinical Application of CXCR4 Imaging in the Diagnosis and Management of Primary Aldosteronism Really Happening?

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Primary aldosteronism (PA), a condition marked by the excessive production of aldosterone, represents a significant subset of secondary hypertension. It has been historically underdiagnosed because of its complex clinical presentation and the limitations of traditional diagnostic methods. Recent advancements in nuclear medicine, particularly C-X-C chemokine receptor type 4 (CXCR4) imaging, have shown promising potential in transforming the diagnostic and therapeutic landscape of PA. This editorial explores whether the clinical application of CXCR4 imaging is truly under way, delving into its mechanisms, current status, and future prospects.

BACKGROUND ON PA

PA, also known as Conn syndrome, is characterized by the autonomous secretion of aldosterone by the adrenal cortex, independent of renin. This condition manifests primarily through hypertension, often accompanied by hypokalemia. PA is classified into unilateral forms, such as aldosterone-producing adenoma (APA) and unilateral adrenal hyperplasia, and bilateral forms, including idiopathic hyperaldosteronism or bilateral adrenal hyperplasia. The latter two account for approximately 35% and 60%, respectively, of all cases of PA. Unilateral forms are typically treated with surgery, whereas bilateral forms are managed medically (Fig. 1).

Traditional diagnostic approaches for PA involve adrenal imaging and adrenal vein sampling (AVS). CT is commonly used to identify adrenal lesions but falls short in distinguishing between functional and nonfunctional adenomas. AVS, regarded as the gold standard, provides definitive localization of aldosterone secretion but is invasive, technically challenging, high in cost, and not universally available. These limitations underscore the need for more precise, noninvasive diagnostic methods.

Received Jun. 5, 2024; revision accepted Aug. 2, 2024.
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Published online Sep. 19, 2024.

DOI: 10.2967/jnumed.124.268145

CXCR4 IMAGING: MECHANISM AND CLINICAL UTILITY

CXCR4, a G-protein–coupled receptor, plays a critical role in various physiologic processes, including hematopoiesis, immune response, and tumor progression. Recent research has identified robust expression of CXCR4 in APA cells, correlating strongly with aldosterone synthase (CYP11B2) expression (*1–3*). This finding has paved the way for using [^{68}Ga]Ga-pentixafor, a radiolabeled ligand for CXCR4, in PET/CT imaging to visualize aldosterone-producing tissues.

The clinical potential of [^{68}Ga]Ga-pentixafor PET/CT in PA has been appreciated. The procedure involves administering [^{68}Ga]Ga-pentixafor and performing PET/CT scans focused on the adrenal region. The interpretation of results includes both visual assessment and semiquantitative analysis, such as calculating the lesion-to-liver and lesion-to-adrenal ratios. These metrics significantly enhance diagnostic accuracy, allowing for better differentiation between functional and nonfunctional lesions (Fig. 2) (*2–8*).

INDICATIONS

There are specific clinical scenarios in which CXCR4 imaging is particularly beneficial.

Confirmed PA Diagnosis

When adrenal CT shows unilateral nodules or hyperplasia, especially when AVS is unavailable or inconclusive, CXCR4 imaging can help confirm the presence of APA.

Inconclusive Diagnostic Tests

For patients with high clinical suspicion of PA but inconclusive diagnostic results, CXCR4 imaging can determine the functionality of adrenal nodules observed on CT.

Postoperative Recurrence

CXCR4 imaging is recommended for evaluating recurrence in patients who have undergone surgery for PA.

CURRENT CLINICAL EVIDENCE AND RESEARCH

The [^{68}Ga]Ga-pentixafor PET/CT imaging procedure involves injecting the radiotracer and conducting scans 40–60 min afterward.

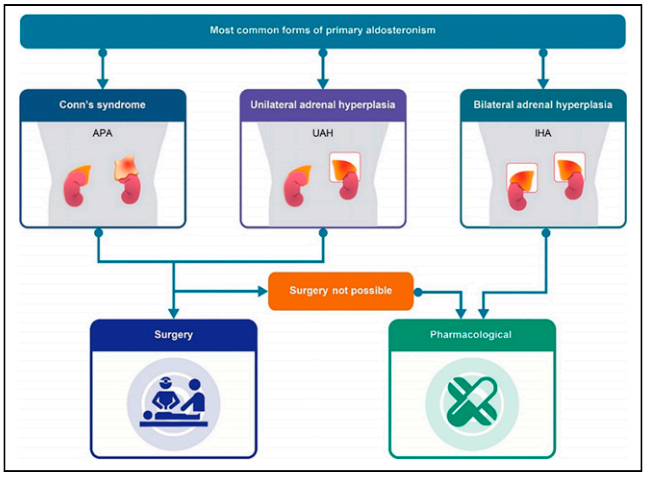

FIGURE 1. Classification and treatment protocol for most common forms of PA. IHA = idiopathic hyperaldosteronism; UAH = unilateral adrenal hyperplasia.

Visual assessment and semiquantitative analysis are performed, comparing uptake in adrenal lesions with uptake in adjacent normal tissues. Positive lesions exhibit higher uptake than surrounding tissues, whereas negative lesions show similar or lower uptake. Semiquantitative parameters including SUV_{max}, lesion-to-liver ratio, and lesion-to-adrenal ratio are calculated to support visual assessment. For instance, an SUV_{max} threshold of 7.1 or more, a lesion-to-liver ratio of 2.5 or more, and a lesion-to-adrenal ratio of 2.4 or more are indicative of functional adenomas (*6*).

Incorporating semiquantitative analysis can enhance the specificity of subtype diagnosis. Table 1 outlines these statistics, derived from a metaanalysis of current studies, to provide a clear understanding of the diagnostic accuracy of CXCR4 imaging. Several studies have demonstrated the effectiveness of CXCR4 imaging in PA. For example, Ding et al. (*4*) reported a sensitivity of 97.8% and specificity of 87.5% for visual assessment using [^{68}Ga]Ga-pentixafor PET/CT in PA patients. Semiquantitative analysis further improved diagnostic accuracy, with thresholds for SUV_{max}, lesion-to-liver ratio, and lesion-to-adrenal ratio providing robust differentiation between APA and nonfunctional adenomas, with the sensitivity improved up to 95.5% (lesion-to-liver ratio) and specificity to 91.8% (lesion-to-contralateral ratio). These semiquantitative values can provide valuable information for clinical decision-making, but it is important to consider the potential variability across different scanners and imaging protocols.

The CASTUS trial (NL9625), a 2-step randomized controlled study, aims to compare the diagnostic accuracy and clinical outcomes of [^{68}Ga]Ga-pentixafor PET/CT with AVS in PA patients. First, the study assesses the concordance between PET/CT and AVS in identifying and localizing APAs, and second, it examines the impact on hypertension management, comparing the quantity of antihypertensive medication based on diagnoses from PET/CT or AVS. This trial's results are expected to solidify the role of CXCR4 imaging as a noninvasive alternative to AVS, potentially offering safer and more accessible diagnostic options.

CXCR4 imaging offers several advantages over traditional diagnostic methods even in patients with adrenal micronodules. Its noninvasive nature both makes it more patient-friendly and reduces the risk of complications associated with invasive procedures such as AVS. Additionally, it provides both morphologic and functional information, improving diagnostic accuracy and helping to better stratify patients for appropriate treatments. Furthermore, the ability of CXCR4 imaging to identify functional adenomas even in the presence of small or bilateral lesions represents a significant leap forward. This capability is particularly valuable when CT findings are inconclusive or when multiple nodules complicate the diagnostic picture.

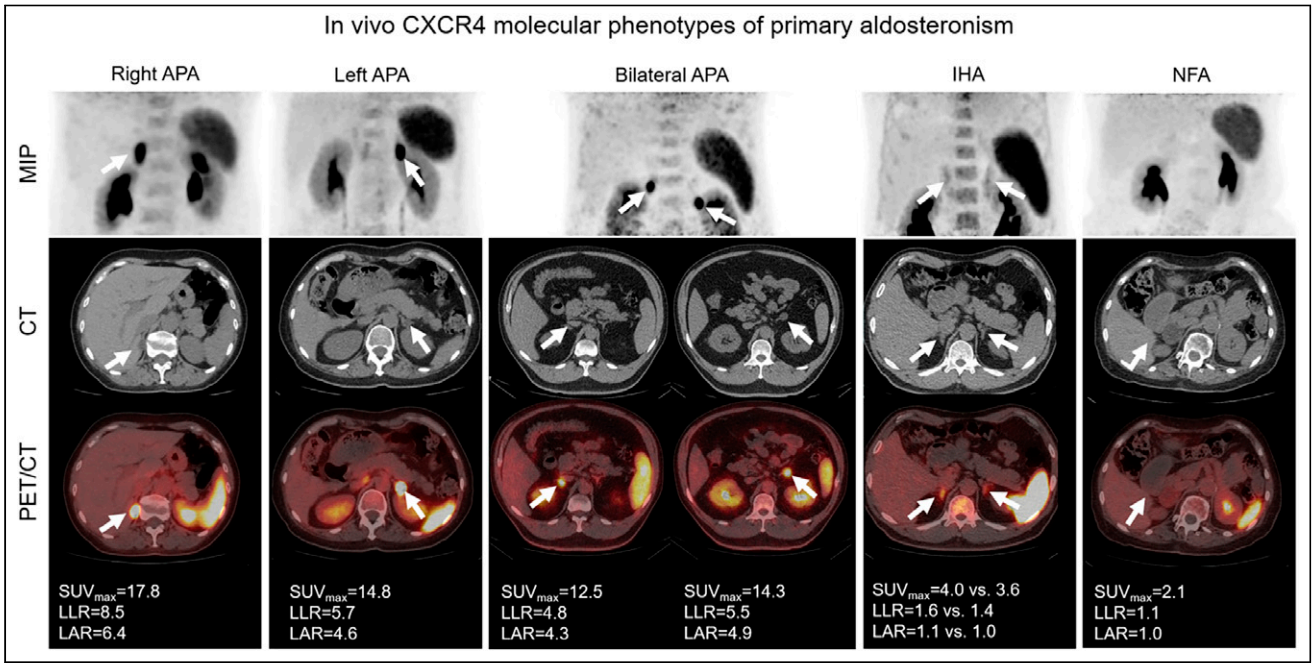

FIGURE 2. Representative CXCR4 PET/CT imaging of major forms of PA. IHA = idiopathic hyperaldosteronism; LAR = lesion-to-adrenal ratio; LLR = lesion-to-liver ratio; MIP = maximum-intensity projection; NFA = nonfunctional adenoma.

TABLE 1
Summary of Representative Studies

Study	Patient cohort	Diagnostic performance (visual)	Semiquantitation	Diagnostic performance (semiquantification)
Ding (*2*)	26 PA and 10 NFA patients	Sensitivity (100%), specificity (78.6%), accuracy (92.3%)	SUV_{max}, lesion-to-liver and lesion-to-contralateral ratios	$SUV_{max} \geq 11.18$: sensitivity (88.0%), specificity (100%), accuracy (92.3%); lesion-to-liver ratio ≥ 2.36: sensitivity (100%), specificity (100%), accuracy (100%); lesion-to-contralateral ratio ≥ 2.12: sensitivity (100%), specificity (92.9%), accuracy (97.4%)
Ding (*3*)	64 patients who had benign adrenal masses (including 51 PA patients)	Sensitivity (97.8%), specificity (87.5%), accuracy (95.2%)	SUV_{max}, lesion-to-liver and lesion-to-contralateral ratios	$SUV_{max} \geq 7.1$: sensitivity (90.0%), specificity (85.3%); lesion-to-liver ratio ≥ 2.5: sensitivity (95.5%), specificity (88.2%); lesion-to-contralateral ratio ≥ 2.4: sensitivity (88.6%), specificity (91.8%)
Gao (*5*)	50 PA and 10 NFA patients	Sensitivity (93.0%), specificity (84.6%), accuracy (91.1%)	SUV_{max}	$SUV_{max} \geq 8.95$: sensitivity (76.7%), specificity (92.3%), accuracy (80.4%)
Hu (*8*)	100 PA patients		LI based on SUV_{max} at 10 and 40 min	LI (10 min) ≥ 1.65: sensitivity (77.0%), specificity (100%); LI (40 min) ≥ 1.57: sensitivity (86.0%), specificity (91.0%)
Zheng (*9*)	99 PA and 21 NFA patients	Sensitivity (92.4%), specificity (94.4%), accuracy (93.3%)	SUV_{max}	$SUV_{max} \geq 7.3$: sensitivity (83.7%), specificity (100%)

NFA = nonfunctional adrenal adenoma; LI = lateralization index.

Although initial studies are promising, further research is needed to fully validate its efficacy and establish standardized protocols for widespread clinical use. The correlation between CXCR4 imaging results and histopathologic findings also needs further exploration. The Histopathology of Primary Aldosteronism (HISTALDO) classification, which uses hematoxylin and eosin staining and CYP11B2 immunohistochemistry (*7*), provides a histologic framework that could enhance the understanding and interpretation of CXCR4 imaging results. Investigating this correlation could help refine diagnostic criteria and improve the accuracy of PA subtyping.

FUTURE DIRECTIONS AND RECOMMENDATIONS

The promising results from early studies and ongoing trials highlight the potential of CXCR4 imaging in revolutionizing PA diagnosis and management. However, further research and development are warranted in several areas, which include the need for continued efforts to standardize imaging protocols and interpretation criteria across different clinical settings. Further research should explore the correlation between CXCR4 imaging outcomes and histopathologic findings, particularly using the HISTALDO classification for PA. In addition, innovations such as delayed or dual-phase imaging and the use of contrast agents during CT scans may enhance the accuracy of CXCR4 imaging, particularly in differentiating adrenal tissues from adjacent structures such as the liver. Furthermore, MRI with superior soft-tissue contrast could provide more detailed characterization of adrenal masses. More importantly, the large-scale, multicenter clinical trials are essential to validate the efficacy of CXCR4 imaging. These trials should focus on long-term outcomes, including the impact on hypertension management and patient quality of life.

In clinical future practice, the adoption of CXCR4 imaging has the potential to significantly improve patient outcomes. Current clinical evidence shows that CXCR4 imaging can enhance the accuracy of PA diagnosis, particularly in challenging cases for which traditional methods are inconclusive. This can lead to more appropriate treatment decisions, such as when selecting candidates for surgical intervention versus medical management. Furthermore, by accurately identifying the subtype of PA and the laterality of aldosterone production, CXCR4 imaging enables personalized treatment plans. Patients with unilateral disease may benefit from targeted surgical intervention, whereas those with bilateral disease can receive optimized medical therapy.

In summary, the clinical application of CXCR4 imaging in the diagnosis and management of PA is not just a possibility but an emerging reality. By providing a noninvasive, accurate, and functional assessment of adrenal lesions, [^{68}Ga]Ga-pentixafor PET/CT offers significant advantages over traditional diagnostic methods. However, the potential of completely supplanting AVS necessitates further robust clinical research data for validation. Presently, adrenal [^{68}Ga]Ga-pentixafor PET/CT imaging serves as a viable alternative in medical institutions lacking AVS capabilities. As the technology continues to advance and more robust clinical data become available, CXCR4 imaging is poised to become a cornerstone in the management of PA, ultimately leading to improved patient outcomes and streamlined clinical workflows.

CONCLUSION

The promising early results and ongoing trials of CXCR4 imaging highlight its potential to revolutionize PA diagnosis and management. However, to fully realize this potential, diagnostic criteria need to be refined and the accuracy of PA subtyping improved through standardization of imaging protocols and interpretation

criteria and exploration of the pathomechanism of CXCR4 and of the potential of the multimodal imaging approach in PA. We firmly believe that CXCR4 imaging will become a reality in the management of PA in coming years, and the integration of CXCR4 imaging into clinical practice could revolutionize the approach to diagnosing and managing PA, offering new optiond for improved patient care and outcomes in this challenging condition.

DISCLOSURE

Martin Reincke has received consulting honoraria from Damian. Constantin Lapa has engaged in prior consulting activities for Blue Earth Diagnostics Ltd. (Oxford, U.K.) and Novartis. No other potential conflict of interest relevant to this article was reported.

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