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Editorial

Contrast-Enhanced Ultrasound for Monitoring Takayasu Arteritis

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In this issue of *The Journal of Rheumatology*, the retrospective study by Ding and co-authors investigated follow-up contrast-enhanced ultrasound (CEUS) of both common carotid arteries and its correlation with clinical variables in patients with Takayasu arteritis (TAK).[1] The authors analyzed the data of 106 patients who had at least 2 CEUS examinations. The vascularization of the artery walls detected by CEUS was associated with the Kerr criteria, which describe the disease activity in TAK. The presence, recent occurrence, or deterioration of at least 2 criteria correlates with active disease: (1) systemic features like fever and arthralgia that cannot be explained by other reasons; (2) elevated erythrocyte sedimentation rate (ESR); (3) findings of vascular ischemia and inflammation; and (4) typical angiographic findings.[2] CEUS also correlated separately with ESR and C-reactive protein. In most patients, the vessel wall vascularization detected by CEUS decreased with treatment over time. CEUS found more patients who had not achieved remission as opposed to the clinical evaluation. This study shows that CEUS of carotid arteries may be a potential monitoring tool for patients with TAK in addition to clinical variables both in clinical practice and in future studies,[1] and perhaps in addition to measurements of the intima-media thickness (IMT).

TAK is a rather rare though very important primary vasculitis of the aorta and its branches. At disease onset, patients are young, most commonly under 40 years. Ischemic and other complications are common. Long-term treatment and monitoring are necessary over decades in most patients.

A suspected diagnosis of large-vessel vasculitis (LVV) needs to be confirmed either histologically or with imaging. Imaging may include magnetic resonance imaging (MRI), ultrasound (US), computed tomography (CT), or positron emission tomography (PET). PET is often combined with CT (PET/CT). Particularly in TAK, an overview of affected arteries should be available through imaging at least at the time of diagnosis. This information may be of interest also at follow-up. Histology is most commonly unavailable in TAK unless vascular surgery has been performed. The European Alliance of Associations for Rheumatology (EULAR) recommendations on imaging in LVV support MRI as the first imaging method based on expert opinion, as MRI provides a good overview without radiation.[3] PET/CT is an alternative. The main disadvantage of PET/CT is its radiation exposure, which can be as high as 25 mSV for a whole-body PET/CT.[4] The lifetime risk for malignancy is significantly increased, particularly when PET/CT is performed in the mainly young females with TAK and when using it as a monitoring tool. Radiation can be lowered by applying low-dose CT or by combining PET with MRI instead.[5]

A metaanalysis found 57 mostly small retrospective studies on imaging in TAK. The pooled sensitivities for the diagnosis of TAK by clinical criteria and/or conventional angiography for US, MRI, and PET were 81%, 92%, and 81%, respectively. The respective pooled specificities were > 90% for US and MRI, and 74% for PET.[6] US is often the first imaging tool to confirm the diagnosis of TAK in clinical practice, even in nonstenotic disease.[7] Nearly all arteries are well accessible with US, except the thoracic descending aorta. Reliability of experienced sonographers is good even when tested with patient-based reliability exercises in giant cell arteritis (GCA).[8]

Monitoring disease activity in LVV is important. Particularly in TAK, but also in extracranial GCA, symptoms may be nonspecific, and progression of stenoses may occur without high laboratory inflammation markers, especially in patients treated with tocilizumab.[9,10]

With US, MRI, and CT, wall thickness can be measured. Wall thickness decreases with treatment, and patients with TAK with greater IMT of carotid arteries are more likely to develop progressive disease.[11] An IMT cut-off of 2.2 mm has been proposed for

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differentiating aortitis from a normal aorta.[12] Likewise, IMT cut-offs of 1.0 mm have been found for carotid, subclavian, and axillary arteries in GCA.[13,14] Several recent studies with US in GCA could show a decrease of initially increased IMT with treatment[15-17] and an increase of IMT in case of relapse.[18] An Outcome Measures in Rheumatology (OMERACT) score for monitoring the IMT of temporal and axillary arteries with US in GCA is currently being developed. For monitoring TAK or extracranial GCA with PET, the PET Vascular Activity Score (PETVAS) has been developed. It decreases faster in GCA than in TAK. Correlations between clinical, laboratory, and imaging findings are complex.[19]

It was shown that PET/CT correlated well with CEUS of carotid arteries for determining the inflammatory activity in patients with TAK and GCA.[20] In contrast to synovitis, vessel wall perfusion with slow blood flow cannot be detected by color or power Doppler US without using contrast agent, even in patients with abnormal IMT because of vasculitis. This is possible when applying CEUS through a contrast medium that usually contains microbubbles and needs to be injected intravenously. Once the medium passes the area in which US is performed, the sound waves are reflected from interfaces between the substances.

The need for placing the needle and applying the contrast agent increases both the time for performing the examination and the costs. US contrast agents are regarded as safe; however, several products are not approved worldwide. As the contrast agent remains in the blood for a short time, only 2 arteries can be evaluated in relation to an injection of US contrast agent. Likewise, Ding at al examined only both common carotid arteries.[1] Thus, deterioration of other arterial segments may be missed. Follow-up would be available only for patients with carotid artery involvement. Most data for CEUS in LVV have been collected at the carotid arteries. Further studies are warranted, particularly on subclavian arteries, which are also frequently involved in TAK. It seems to be more difficult, or even so far impossible, to use CEUS for smaller arteries, particularly for the temporal arteries. The advantages and disadvantages of the different imaging methods for TAK are shown (Table).

The EULAR recommendations on imaging in LVV included in their future research agenda that further studies are needed for developing tools for the assessment of disease activity in LVV and to agree on definitions of remission and relapse in order to better investigate the role of imaging for monitoring of LVV.[3] CEUS is a promising potential tool in centers with the ability, time, and expertise to apply US contrast agent. Further studies are needed to study how CEUS performs in other arteries.

The following points should be addressed in future studies on CEUS in TAK and in extracranial GCA:

- The performance of CEUS should be assessed on arteries other than the carotid arteries.
- The possibility of assessing more than 2 arteries in a single examination should be explored.
- Definitions of key elementary lesions should be developed.
- An agreement should be found on how to grade the severity of lesions.
- Agreement should be also reached on arteries that need be examined.
- Then, a scoring system should be developed.
- This scoring system should be tested for reliability, sensitivity to change, and convergent construct validity.
- A score should be then tested in further cohorts as well as in prospective randomized controlled pharmacological trials, which are warranted for developing future therapies for TAK.
- This process should ideally follow the methodology stipulated by the OMERACT Instrument Selection Algorithm.[21]

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Table. Advantages and disadvantages of imaging modalities as a monitoring tool in Takayasu arteritis.

	CEUS	US	MRI	CT	PET/CT
Availability	0	++	0	+	-
Patient comfort	+	++	0	0	-
Low cost	+	++	-	0	--
No radiation	++	++	++	-	--
Study data on monitoring	+	+	0	-	+
Anatomical overview	--	0	++	++	++

+: good; ++: excellent; -: poor; --: very poor. CEUS: contrast-enhanced ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound.

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