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FULL PAPER

MRI parametric monitoring of biological therapies in primary large vessel vasculitides: a pilot study

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Objective: To evaluate the development of characteristic MRI changes in patients with primary large-vessel vasculitis (LVV) when treated with biological therapies.

Methods: 12 patients with primary LVV (8 patients with Takayasu arteritis and 4 patients with giant-cell arteritis) received biological therapy with tumour necrosis factor- α blockers ($n=9$) or an interleukin-6 inhibitor ($n=3$). MRI investigations were performed at baseline (pre-treatment) and follow-up. All patients underwent the same MRI/MR angiography (MRA) protocol. Laboratory parameters (C-reactive protein and erythrocyte sedimentation rate) and clinical response (Birmingham Vasculitis Activity Score) were assessed.

Results: Wall thickness was 4.2 ± 0.3 mm pre-treatment and significantly decreased to 3.2 ± 0.3 mm post treatment in 9/12 patients. Mural enhancement was increased in all 12/12 patients with LVV, and subsided with therapy in 5/12 patients. Mural oedema or ill-defined contour were

less prevalent but also improved with biological treatment. C-reactive protein and erythrocyte sedimentation rate levels decreased, and clinical assessment revealed a significant improvement from pre-treatment to post-treatment. However, the course of imaging characteristics often did not parallel that of laboratory or clinical parameters. In all three patients receiving interleukin-6 blockade, laboratory markers and clinical scores normalized despite persistent vascular inflammation in one patient which was disclosed by MRI.

Conclusion: Contrast-enhanced MRI/MRA may be useful when evaluating the development of disease activity in primary LVV under biological therapies. A high degree of suspicion and regular imaging follow-up is needed to detect persistent inflammation.

Advances in knowledge: This is the first study investigating the applicability of different MRI/MRA parameters for monitoring biological therapy in patients with primary LVV.

INTRODUCTION

Inflammatory changes of large vessels can be due to sarcoidosis, infections and radiation exposure or may be imitated by vascular neoplasias and ergotism—all of which need to be carefully excluded in order to establish the diagnosis of a primary large-vessel vasculitis (LVV). Primary LVV occurs in two main types, giant-cell arteritis (GCA) and Takayasu arteritis (TA).¹ Both GCA and TA are characterized histologically by granulomatous infiltrates in the wall of large- and medium-sized arteries. GCA usually presents in persons older than 50 years—predominantly in females.² TA also has a marked preference for females but occurs at a younger age, in the second or third decades of life, and shows its highest incidence in Eastern Asia. In North America, it was reported to be 2.6 million per year.³

Most patients with primary LVV initially respond to glucocorticoid (GC) therapy;⁴ however, up to 48% of patients with GCA and up to 84% of patients with TA require additional immunosuppression in the disease course to achieve remission or taper GC administration. Methotrexate showed some benefit as second-line treatment, decreasing the number of relapses and the amount of GC application to some extent.⁵ Nevertheless, further treatment options are eagerly searched for and biological agents such as tumour necrosis factor- α blockers (e.g. infliximab, adalimumab and etanercept) or interleukin-6 (IL-6) antibodies [tocilizumab (TOC)] are currently discussed as alternate agents.⁴

Therapy response monitoring constitutes a fundamental challenge in the evaluation of LVV. Serological tests

including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tissue factor or von Willebrand factor cannot reliably distinguish florid from dormant LVV.^{6,7} Besides laboratory markers, imaging is indispensable to diagnose and monitor LVV. MRI combined with MR angiography (MRA) does not rely on radiation and nicely demonstrates vascular anatomy and inflammatory changes of the vessel wall.⁸ However, no studies exist in the current literature investigating the applicability of different MRI/MRA parameters for monitoring biological therapy in patients with primary LVV.

We therefore set out to evaluate the development of characteristic MRI changes in patients with primary LVV when treated with biological therapies.

METHODS AND MATERIALS

Population and clinical history

This retrospective study was approved by our local institutional review board which waived informed consent. 12 female patients (age range 19–72 years; mean 43.1 years) with confirmed primary LVV (8 patients with TA and 4 with GCA) received off-label biological therapy with tumour necrosis factor- α blockers adalimumab (3 patients) and infliximab (6 patients) and the IL-6 inhibitor TOC (3 patients). Table 1 demonstrates each patient's LVV type, prior anti-inflammatory medication, the applied biological therapy, interval between pre- and post-treatment MRI and vascular sites of LVV involvement. An MRI and MRA according to a standardized protocol were performed directly before treatment beginning and during ongoing therapy. Thus, all patients received at least one MRI/MRA follow-up examination according to our standardized protocol. At the time these new therapy regimens were initiated, all patients had clinical and laboratory signs of active disease.

MRI protocol

MRI investigations were performed in all patients at baseline (pre-treatment) and follow-up. All patients underwent the same MRI protocol, including axial T_2 weighted FatSat images, gadolinium (Gd)-enhanced MRA and axial post-contrast imaging of the entire aorta and outgoing branches. All scans were performed on the same 1.5-T whole-body unit (MAGNETOM® Avanto; Siemens Medical Solutions, Erlangen, Germany). The body coil was used for radiofrequency transmission and the flexible matrix body coil in combination with the spine matrix was used for signal detection. For the MRA and contrast-enhanced MRI, gadobutrol 0.1 mmol kg⁻¹ body weight (Gadovist®; Bayer, Leverkusen, Germany) was administered as an intravenous bolus injection (0.1 mmol kg⁻¹ body weight) at 2 ml s⁻¹, followed by a saline flush. T_2 weighted FatSat images were acquired using a fast spin-echo sequence [repetition time (TR) 4880 ms, echo time (TE) 95 ms, echo spacing 7.2 ms and echo-train length 13; fast spin-echo factor 13 and slice thickness 6 mm; and flip angle 150°]. Chemical-shift selective fat suppression was used; field of view (FoV) was 220 × 300 mm² and matrix size was 320 × 180, resulting in a voxel size of 1.5 × 1.1 × 5.0 mm³. T_1 weighted images were acquired before and after contrast media administration with a standard spin-echo sequence. Sequence parameters were: TR 796 ms and TE 24 ms. Chemical-shift selective fat suppression and black-blood technique were used. Slice thickness was 5 mm, FoV was 220 × 300 mm² and matrix size was 256 × 113, resulting in a voxel size of 2.0 × 1.4 × 5.0 mm³. For this sequence, a double-inversion (black-blood) technique was used. Sequence parameters for the Flash three-dimensional MRA were as follows: TR 2.66 ms and TE 0.98 ms. Chemical-shift selective fat suppression was used. Slice thickness was 1.5 mm, flip angle was 25°, FoV was 343 × 500 mm² and matrix size was 256 × 146, resulting in a voxel size of 1.9 × 1.3 × 2.0 mm³.

Table 1. Population and clinical history

Med	LVV	Patients	Age (years)	Prior therapy	Interval (months)	Initial involvement
ADA	TA	1	41	GC, MTX, CYC	6	TDA
		2	30	GC, CYC, IFX	7	TDA
		3	20	GC, CYC, MTX, MMF, CSA, IFX	40	TDA
IFX		4	28	GC, CYC	15	TAA, TDA, AA
		5	50	GC, MTX, CYC	49	TAA
		6	19	GC, CYC	12	AA
	GCA	7	72	GC, CYC	15	TDA, AA
		8	71	GC, MTX, LEF, AZA, CYC	16	TDA, AA
		9	61	GC, MTX, CYC	48	TDA, AA
	TOC	10	61	–	1	TAA, TDA, AA
TA		11	20	GC, CYC, IFX	4	AA
		12	44	GC, MTX, CYC, ADA	3	TDA

AA, abdominal aorta; ADA, adalimumab; AZA, azathioprine; CSA, cyclosporine A; CYC, cyclophosphamide; GC, glucocorticoid; GCA, giant-cell arteritis; IFX, infliximab; LEF, leflunomide; LVV, large-vessel vasculitis; Med, medication; MMF, mycophenolate mofetil; MTX, methotrexate; TA, Takayasu arteritis; TAA, thoracic ascending aorta; TDA, thoracic descending aorta; TOC, tocilizumab.

Table 2. MRI parametric monitoring of biological therapies in large-cell vasculitis (LVV)

Med	LVV	Patients	T ₂ signal		Enhancement		Thickness (mm)		Contour		Stenosis	
			Pre-treatment	Post treatment	Pre-treatment	Post treatment	Pre-treatment	Post treatment	Pre-treatment	Post treatment	Pre-treatment	Post treatment
ADA	TA	1	→	→	↑	→	5.5	2.0	Well	Well	S	S
		2	→	→	↑	↑	5.5	5.5	Well	Well	S, A	S, A
		3	→	→	↑	↑	2.5	4.0	Well	Well	S, C	S, C
		4	→	→	↑	↑	4.5	2.5	Well	Well	S, A	S, A
		5	→	→	↑	→	4.0	2.0	Ill	Well	S	S
		6	→	→	↑	↑	4.0	3.5	Ill	Well	A	A
IFX	GCA	7	↑	↑	↑	↑	5.0	4.0	Ill	Ill	S	S
		8	→	→	↑	→	2.5	2.0	Well	Well	S	S
		9	↑	→	↑	→	3.0	2.0	Well	Well	–	–
		10	↑	→	↑	→	4.5	2.5	Ill	Well	–	–
TOC	TA	11	→	↑	↑	↑	3.5	4.5	Well	Well	A	A
		12	↑	→	↑	↑	5.5	3.5	Ill	Well	–	–

↑, increased; →, normal; A, aorta; ADA, adalimumab; C, common carotid arteries; GCA, giant-cell arteritis; IFX, infliximab; Med, medication; S, subclavian arteries; TA, Takayasu arteritis; TOC, tocilizumab.

A relevant diminution of parameters has been italicized.

Figure 1. A 41-year-old female patient with Takayasu arteritis (Patient 1). At pre-treatment MRI, (a) thickening and prominent enhancement of the aortic wall was observed on contrast-enhanced black-blood T_1 fat saturated (FatSat) sequences. After 6-month biological therapy with the tumour necrosis factor- α blocker adalimumab, mural thickening and enhancement subsided (b). However, 3 years later, aortic wall inflammation recurred (c) and was illustrated by mural thickening and enhancement on contrast-enhanced black-blood T_1 FatSat sequences.

Image analysis

Images were assessed for T_2 hyperintense signal intensity, increased Gd enhancement, contour and maximum thickness of vessel walls as well as vascular stenoses. The degree of T_2 signal intensity and enhancement was evaluated by comparing mural signal intensity with that of the myocardium.⁹ To verify investigator observations in an unbiased manner, an independent evaluation of every MRI/MRA scan was performed retrospectively by two radiologists (MH and DS). Both readers were blinded to laboratory results and clinical response. Discrepant results were solved by consecutive consensus reading.

Laboratory and clinical follow-up

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were assessed at baseline (pre-treatment) and after treatment with biological medication (post treatment). For additional clinical response monitoring, the Birmingham Vasculitis

Activity Score (BVAS) was used.^{10,11} Patients were evaluated accordingly, pre-treatment and post treatment.

Statistics

All data are reported as arithmetic mean $\pm$ Standard error. Statistical analysis was performed with STATA® v. 10.0 (StataCorp LP, College Station, TX). Shapiro–Wilk test revealed a non-normal distribution of our data. Therefore, the Wilcoxon signed-ranks test was used for comparisons between groups. For all tests, p -values <0.05 were considered as statistically significant.

RESULTS

MRI parametric monitoring of biological therapies in large-vessel vasculitis

Oedema of the aortic wall was observed as T_2 hyperintensity in 4/12 (33%) patients before treatment (Table 2). In three of those patients, the T_2 hyperintensity resolved with biological

Table 3. Clinical and laboratory markers for monitoring biological therapies in large-vessel vasculitis (LVV)

Med	LVV	Patients	CRP (mg dl ^{−1})		ESR (mm h ^{−1})		BVAS	
			Pre-treatment	Post treatment	Pre-treatment	Post treatment	Pre-treatment	Post treatment
ADA	TA	1	0.52	0.59	35	17	2	0
		2	0.04	0.01	13	5	0	0
		3	0.36	0.25	–	17	2	0
IFX		4	1.62	0.12	14	7	0	0
		5	1.86	1.99	13	11	3	0
		6	7.75	1.38	38	8	8	8
	GCA	7	0.35	0.50	5	11	2	0
		8	1.32	–	13	–	0	–
		9	3.09	0.11	28	32	2	0
TOC	TA	10	23.7	0.01	105	8	3	0
		11	0.09	0.55	4	4	8	0
		12	3.59	0.01	88	6	3	0

ADA, adalimumab; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant-cell arteritis; IFX, infliximab; Med, medication; TA, Takayasu arteritis; TOC, tocilizumab.

A relevant diminution of parameters has been italicized.

therapy. Gd enhancement of the aortic wall was increased in all 12/12 patients with LVV (100%), but subsided with therapy in 5/12 (42%) patients (Figure 1). The maximum wall thickness of the involved vessel sections significantly decreased from 4.2 ± 0.3 mm pre-treatment to 3.2 ± 0.3 mm post treatment ($p = 0.04$). However, in two patients (Patients 3 and 11), wall thickness increased despite biological therapy, and in another patient (Patient 2), wall thickness remained unchanged. The contour of the diseased vessels was ill defined before biological treatment in 5/12 (42%) patients and became sharply demarcated afterwards in 4 of those patients. Vascular stenoses were observed in 9/12 (75%) patients before therapy and predominated in the subclavian arteries (7/12 patients, 58%) and abdominal aorta (4/12 patients, 33%). In those nine patients, the pre-existing stenoses remained unchanged and no new stenosis occurred within the treatment interval.

Clinical and laboratory markers for monitoring biological therapies in large-vessel vasculitis

CRP levels non-significantly decreased from 3.7 ± 1.9 mg dl⁻¹ pre-treatment to 0.5 ± 0.2 mg dl⁻¹ post treatment ($p = 0.16$) (Table 3). This decrease can be considered clinically relevant in only 5/12 (42%) patients. ESR values significantly decreased from 32.4 ± 9.8 mm h⁻¹ pre-treatment to 11.5 ± 2.3 mm h⁻¹ post treatment ($p = 0.04$) with a clinically relevant diminution in only 6/12 (50%) patients. Clinical assessment of the patients according to the BVAS score revealed a significant improvement in 8/12 (67%) patients with values decreasing from 2.8 ± 0.8 pre-treatment to 0.7 ± 0.7 post treatment ($p = 0.01$).

Correlation of MRI/MR angiography with laboratory and clinical parameter

An unequivocal non-response according to MRI/MRA criteria was observed in 3/12 patients (Patients 2, 3 and 11). None of these MR-morphologic non-responses were paralleled by elevated laboratory markers (CRP and ESR) or an increased BVAS at post treatment. Indeed, a normalization of CRP/ESR occurred in all but two patients (Patients 5 and 9) at post treatment—the slightly elevated CRP of Patient 5 and the moderately increased ESR of Patient 9 were both accompanied by a good MR-morphologic response at post treatment and a stable disease course over the following 16 months. In all three patients receiving IL-6 blockade by TOC (Patients 10–12), laboratory markers and clinical scores were normalized despite changes suggesting persistent vascular inflammation of Patient 11 disclosed by MRI. In the subsequent treatment regimen of Patient 11, leflunomide was added and combined TOC/leflunomide therapy resulted in a good MR-morphologic response 4 months and 16 months later.

DISCUSSION

Assessing therapy response constitutes a fundamental challenge in the clinical management of patients with primary LVV. Laboratory markers such as ESR and CRP can only be used with caution and never as single parameters.^{6,7} Physical examination searching for bruits, absent pulses, blood pressure differences or signs and symptoms of ischaemia does not reliably indicate vasculitic activity.¹²

Against this background, imaging is an essential adjunct to monitor the disease course. Fluorine-18 fluorodeoxyglucose

positron emission tomography (PET) is a sensitive and specific tool for detecting changes suggesting vascular inflammation in LVV; however, it does not demonstrate vascular anatomy and stenoses.^{13,14} Wall thickening, luminal narrowing and mural contrast enhancement are well demonstrated by CT and MRI, and vascular stenoses are best depicted by angiography or ultrasound. MRI and MRA reveal vascular anatomy and changes compatible with mural inflammation of the entire aortic tree and outgoing branches without exposing the patient to radiation. Vessel wall oedema is illustrated by T_2 weighted MRI sequences, and the degree of wall enhancement can be assessed by contrast-enhanced MRI when comparing mural signal intensity with that of the myocardium.^{9,15} Even though these abnormalities detected on T_2 weighted and contrast-enhanced images may truly represent inflammation, it would be unjustified to use wall oedema and enhancement as proof for inflammation, because no true histopathological gold standards have been performed. It may well be that discordant cases where MRI shows persistent abnormalities in patients who responded clinically were in fact false positives. Nevertheless, mural oedema and enhancement as well as the reduction in wall thickness were reported to be associated with disease activity.^{9,15} In patients with steroid-naïve LVV, Dellavedova et al¹⁶ found evidence that PET/CT is not only a diagnostic tool but can distinguish patients with favourable disease course from those with complicated progression. First results of the upcoming PET/MRI technologies demonstrate that PET/MRI is feasible in LVV, yielding results highly comparable with that of PET/CT¹⁷, and current data suggest a role of perfusion-based assessment of disease activity *via* perfusion CT in untreated and treated aortitis and chronic periaortitis.¹⁸

This is the first study investigating the applicability of different MRI/MRA parameters for monitoring biological therapy in patients with primary LVV. Choe et al⁹ suggest that the sensitivity of T_2 weighted imaging in the detection of active disease is inferior to Gd-enhanced T_1 weighted imaging. This notion is supported by our results. In our cohort, all patients showed increased mural Gd enhancement before treatment, whereas we found T_2 hyperintense oedema of the aortic wall in only 33% of patients before treatment. Under biological therapy, increased mural enhancement subsided in 42% of patients, and T_2 hyperintensity resolved in three of four patients. Homogeneous vessel wall thickening is described typical of arteritis when it is >2 – 3 mm in the aorta, and >1.5 mm in large supra-aortic vessels.^{19–21} In our study, wall thickness of the involved aortic sections was 4.2 mm pre-treatment and significantly decreased to 3.2 mm post treatment. This goes along nicely with the results of Muto et al¹⁹ who measured a pre-treatment aortic wall thickness of 3.8 mm and a significant reduction after glucocorticoid therapy in 10 patients with LVV using contrast-enhanced CT. Furthermore, we observed an ill-defined vessel contour before biological treatment in 42% of patients which became sharply demarcated post treatment in 33%.

However, the development of imaging characteristics often did not parallel an increase or decrease in laboratory parameters. In our study, an unequivocal non-response according to MRI/MRA criteria was observed in 25% of patients. None of these

MR-morphologic non-responses were paralleled by elevated laboratory markers or an increased BVAS at post treatment. On the other hand, those two patients in whom laboratory markers were not normalized showed a good MR-morphologic response at post treatment and a stable disease course over the following 16 months. These findings hint at possible drawbacks in the response assessment after biological therapy *via* laboratory and clinical parameters. Furthermore, in a study on rheumatoid arthritis treatment with TOC, laboratory markers ESR and especially CRP normalized despite persistent joint inflammation.²² Analogously, in our study, laboratory markers and clinical scores were normalized in all three patients receiving IL-6 blockade by TOC and did not identify the changes suggesting persistent vascular inflammation of Patient 11 disclosed by MRI. In the further treatment regimen of Patient 11, leflunomide was added and combined TOC/leflunomide therapy resulted in a good MR-morphologic response 4 months and 16 months later. Hence, laboratory and clinical markers may be hampered by false-positive and false-negative results with biological treatment. A high degree of suspicion and regular imaging follow-up is needed to detect changes suggesting persistent inflammation and progression of stenoses.

This study holds some limitations that need to be discussed. Firstly, one inherent problem with the assessment of LVV treatment response is the variable definition of disease remission. Most studies define a patient to be in remission when asymptomatic and showing normalized inflammatory markers (CRP and ESR).⁴ However, as discussed above, inflammatory markers are not reliable, and several studies have shown that

persistent inflammation disclosed by autopsy or radiographic progression was overlooked in >50% of patients.^{6,7,23} Accordingly, we observed that the development of imaging characteristics often does not parallel an increase or decrease in laboratory parameters. Secondly, owing to the sparseness of primary LVV, our patient cohort consists of only 12 patients treated with different biological agents. Nevertheless, this is the first study on biological therapies evaluating the development of several MRI parameters using a standardized MRI protocol. The goal was not to establish the gold standard in monitoring LVV under these novel agents but to disclose imaging parameters indicating treatment response. Subsequent studies focusing on long-term outcome, symptomatic relief and concomitant surveillance of laboratory and imaging parameters are needed, and large randomized studies are required to prove the benefit of an imaging-based approach as compared with conventional parameters alone.

In conclusion, contrast-enhanced MRI/MRA may be useful when evaluating the development of disease activity of primary LVV under biological therapies. A reduction in wall thickness and decrease of mural enhancement were the imaging parameters most frequently affected by biological therapy. The development of imaging characteristics often does not parallel an increase or decrease in laboratory parameters. Hence, laboratory and clinical markers may be hampered by false-positive and false-negative results with biological treatment. A high degree of suspicion and regular imaging follow-up is needed to detect changes suggesting persistent inflammation and progression of stenoses.

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