

## SHORT REPORT

Prevalence and risk factors of  
osteonecrosis of the femoral head in  
patients with ANCA-associated  
vasculitis: a multicentre cohort study

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## ABSTRACT

**Objective** We aimed to determine the prevalence and risk factors for osteonecrosis of the femoral head (ONFH) in a multicentre cohort of patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

**Methods** One hundred and eighty-six AAV patients who underwent radiographs and MRI screening of bilateral hip joints at more than 6 months after initial remission induction therapy (RIT) were retrospectively assessed for the presence of ONFH.

**Results** Among 186 AAV patients, 33 (18%) were diagnosed with ONFH. Among the patients with ONFH, 55% were asymptomatic and 64% had bilateral ONFH. Seventy-six per cent of ONFH joints were in precollapse stages (stage  $\leq 2$ ), whereas 24% of ONFH joints were in collapse stages (stage  $\geq 3$ ). Moreover, 56% of the precollapse stage joints were already at risk of future collapse (type  $\geq C-1$ ). Even in asymptomatic ONFH patients, 39% of the precollapse stage joints were type  $\geq C-1$ . Prednisolone dose of  $\geq 20$  mg/day on day 90 of RIT was an independent risk factor for ONFH in AAV patients (OR 1.072, 95% CI 1.017 to 1.130,  $p=0.009$ ). Rituximab use was a significant beneficial factor against ONFH ( $p=0.019$ ), but the multivariate analysis rejected its significance ( $p=0.257$ ).

**Conclusion** Eighteen per cent of AAV patients developed ONFH, and two-thirds of the ONFH joints were already in collapse stages or at risk of future collapse. Prednisolone dose of  $\geq 20$  mg/day on day 90 of RIT was an independent risk factor for ONFH. A rapid reduction of glucocorticoids in RIT and early detection of precollapse ONFH by MRI may decrease and intervene ONFH development in AAV patients.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ No data are available yet about the prevalence and risk factors of osteonecrosis of the femoral head (ONFH) in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV), although neutrophil extracellular traps formation and vasculitis have been implicated in the pathophysiology of ONFH.

## WHAT THIS STUDY ADDS

⇒ Eighteen per cent of AAV patients developed ONFH after the remission induction therapy (RIT), indicating that not a few AAV patients develop ONFH.  
⇒ Seventy-six per cent of ONFH joints were in precollapse stages (stage  $\leq 2$ ), whereas 24% of ONFH joints were in collapse stages (stage  $\geq 3$ ). Moreover, 56% of the precollapse stage joints were already at risk of future collapse (large necrotic lesions; type  $\geq C-1$ ).  
⇒ Prednisolone dose of  $\geq 20$  mg/day on day 90 of RIT was identified as an independent risk factor for ONFH in AAV patients.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A rapid reduction of glucocorticoids in 90 days after RIT and early detection of precollapse ONFH by MRI screening are important for decreasing and intervening ONFH development in AAV patients.

## INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a

systemic small-vessel vasculitis frequently affecting kidneys and respiratory tracts<sup>1</sup> and is characterised by the production of autoantibodies to the neutrophil proteins such as myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA).<sup>2</sup> The current standard protocol of remission induction therapy (RIT) with the combination of glucocorticoids with either rituximab or cyclophosphamide has improved survival,<sup>3</sup> whereas comorbidities, both from the disease itself and its treatment, remain to be improved.<sup>1,4,5</sup>

Osteonecrosis of the femoral head (ONFH) is characterised by the necrosis of osteocytes due to ischemia of the femoral head.<sup>6,7</sup> ONFH causes collapse of the femoral head and dysfunction of the hip joint, resulting in a decline in the quality of life. At present, no proven prophylaxis for ONFH exists and non-operative treatments are generally ineffective,<sup>7</sup> but recent studies suggest that core decompression combined with autologous bone marrow cell transplantation in the precollapse stage of ONFH may delay the hip joint collapse and prevent total hip arthroplasty.<sup>7</sup> Vasculitis, especially in systemic lupus erythematosus (SLE), and glucocorticoid administration are well-known risk factors for ONFH.<sup>6,8</sup> Furthermore, a recent study has shown an essential role of neutrophil extracellular traps (NETs) formation in the pathogenesis of ONFH.<sup>9</sup> However, although AAV has some clinical similarities to SLE, that is, small-vessel vasculitis, involvement of NETs formation in the pathogenesis and glucocorticoid use,<sup>1,10</sup> no data are available yet about the prevalence and risk factors of ONFH in patients with AAV. Therefore, we aimed to determine the prevalence and risk factors for ONFH and seek its possible prophylaxis in patients with AAV.

## PATIENTS AND METHODS

### Study design and patients

This is a multicentre, retrospective cross-sectional observational study, recruiting 186 patients diagnosed with AAV between March 2007 and April 2021 at Chiba University Hospital and 11 affiliated hospitals. The diagnosis of AAV and the classification of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) were made according to previously described criteria.<sup>2,11</sup> These AAV patients agreed to undergo radiographs and MRI of bilateral hip screening at more than 6 months after initial RIT, regardless of the absence or presence of hip symptoms, and were cross-sectionally enrolled between April 2020 and November 2021 in this study. None of the recruited patients had any hip symptoms at the time of AAV diagnosis.

### Initial RIT regimen for AAV

Median initial dose of prednisolone was 40 mg/day (corresponding to 0.7–0.8 mg/kg/day in our cohort) (table 1). The dose of prednisolone was usually tapered every 2 weeks by 10%–15% reduction and after around 20 mg/day (corresponding to around 0.35 mg/kg/day in

our cohort) of prednisolone, was reduced every 4 weeks. However, the actual tapering speed of prednisolone and the maintenance dose was determined depending on disease severity by the local investigators. The use of methylprednisolone pulse, rituximab, and cyclophosphamide was also determined depending on disease severity by the local investigators.

### Clinical and laboratory data collection

Baseline data at the diagnosis of AAV, dose of alcohol intake and history of smoking, presence/absence of a new-onset hip pain after AAV diagnosis, and comorbidities related to ONFH or vascular occlusion were collected. The baseline organ manifestations associated with AAV were assessed, and baseline disease activity of AAV was scored according to the Birmingham Vasculitis Activity Score (BVAS).<sup>12</sup> Treatment information for AAV, including the initial and cumulative doses of glucocorticoids, methylprednisolone pulse therapy, immunosuppressants and biologics, was also collected.

### Detection and staging and type classification of ONFH

The median period between the diagnosis of AAV and the hip joint MRI screening for ONFH was 2.6 (1.3–4.8) years. All radiographs and MRIs of the bilateral hip joints were reviewed again for this study by an orthopedist, an expert in hip joint disease. The diagnosis of ONFH was made according to the Japanese Orthopaedic Association diagnostic criteria for ONFH as described previously.<sup>13</sup> The severity of ONFH was evaluated by the staging and type classification for ONFH.<sup>13</sup>

### Statistical analysis

Statistical analysis was performed using the SPSS software (V.28). Continuous variables were expressed as medians and IQR and compared by Mann-Whitney U test. Categorical variables were described as numbers and percentages and compared by  $\chi^2$  test or Fisher's exact test. Cut-off value was calculated by receiver operating characteristic (ROC) analysis. Logistic regression analysis was used to detect independent factors for ONFH with ORs and 95% CIs. Variables that were significant (p values <0.05) in univariate analysis were analysed by logistic regression (forced entry method) and p values <0.05 were considered significant.

## RESULTS

### Prevalence of ONFH in AAV patients and their baseline characteristics

During the enrollment period, 525 patients with AAV were eligible for this study. Among them, 284 AAV patients were informed by the local investigators for this study of ONFH detection, and 186 AAV patients agreed to participate in this study (online supplemental figure S1).

Among 186 AAV patients, 33 (17.7%) were diagnosed with ONFH (table 1). Among the 33 patients with ONFH,

**Table 1** Comparison of characteristics between ANCA-associated vasculitis patients with and without osteonecrosis of the femoral head

	Total (n=186)†	ONFH – (n=153)	ONFH + (n=33)	P value*
Age of onset, median (IQR), y	70.5 (63.9–76.0)	71.1 (64.6–76.3)	68.7 (61.4–72.6)	0.133
Female, n (%)	122 (65.6)	98 (64.1)	24 (72.7)	0.341
Body weight, mean±SD, kg	55.0±11.1	55.0±11.0	54.8±11.7	0.896
BMI, median (IQR), kg/m <sup>2</sup>	21.6 (19.6–23.8)	21.6 (19.6–23.8)	21.8 (19.5–24.4)	0.829
Alcohol (ethanol intake ≥320 g/week), n (%)‡	19 (10.2)	17 (11.1)	2 (6.1)	0.385
History of smoking, n (%)	59 (31.7)	48 (31.4)	11 (33.3)	0.826
Diagnosis, n (%)				
MPA	123 (66.1)	103 (67.3)	20 (60.6)	0.435
GPA	32 (17.2)	27 (17.6)	5 (15.2)	
EGPA	31 (16.7)	23 (15.0)	8 (24.2)	
BVAS domain, n (%)				
General	135 (72.6)	114 (74.5)	21 (63.6)	0.204
Cutaneous	35 (18.8)	31 (20.3)	4 (12.1)	0.278
Mucous membranes/eyes	18 (9.7)	17 (11.1)	1 (3.0)	0.154
Ear/nose/throat	53 (28.5)	46 (30.1)	7 (21.2)	0.307
Respiratory	129 (69.4)	108 (70.6)	21 (63.6)	0.432
Cardiovascular	10 (5.4)	8 (5.3)	2 (6.1)	0.848
Abdominal	4 (2.2)	4 (2.6)	0 (0)	0.348
Renal	107 (57.5)	92 (60.1)	15 (45.5)	0.122
Nervous system	75 (40.3)	63 (41.2)	12 (36.4)	0.609
BVAS, median (IQR)	16 (10–20)	16 (12–20)	14 (6–19)	0.070
ANCA positivity, n (%)				
MPO-ANCA	147 (79.0)	124 (81.0)	23 (69.7)	0.146
PR3-ANCA	24 (12.9)	20 (13.1)	4 (12.1)	0.883
eGFR, median (IQR), mL/min	67.1 (42.8–88.7)	67 (43–87)	69 (48–95)	0.409
CRP, median (IQR), mg/dL	8.0 (2.4–13.0)	8.1 (3.1–12.9)	6.1 (0.9–13.4)	0.389
aPL positivity, n (%)	31 (18.6) /n=167	25 (18.1) /n=138	6 (20.7) /n=29	0.746
Induction treatments				
Methylprednisolone pulse, n (%)	35 (18.8)	26 (17.0)	9 (27.3)	0.171
Initial prednisolone dose, median (IQR), mg/day	40 (30–50)	40 (30–50)	40 (33–50)	0.694
Prednisolone dose on day 90, median (IQR), mg/day	15 (13–20) /n=183	15 (12.5–20) /n=150	20 (15–25) /n=33	0.009
Cumulative prednisolone dose§ on day 90, median (IQR), mg	2700 (1933–3725) /n=183	2628 (1833–3532) /n=150	2767 (2204–4879) /n=33	0.192
Rituximab, n (%)	85 (45.7)	76 (49.7)	9 (27.3)	0.019
Cyclophosphamide, n (%)	61 (32.8)	47 (30.7)	14 (42.4)	0.194
Osteoporosis treatment, n (%)	173 (93.0)	141 (92.2)	32 (97.0)	0.325
Bisphosphonates, n (%)	133 (71.5)	106 (69.3)	27 (81.8)	0.202
Denosumab, n (%)	12 (6.5)	11 (7.2)	1 (3.0)	0.696
Vitamin D/Ca, n (%)	65 (34.9)	55 (35.9)	10 (30.3)	0.688
Comorbidities				
Hypertension, n (%)	49 (26.3)	41 (26.8)	8 (24.2)	0.763
Dyslipidaemia, n (%)	114 (61.3)	93 (60.8)	21 (63.6)	0.760

Continued

**Table 1** Continued

	Total (n=186)†	ONFH – (n=153)	ONFH + (n=33)	P value*
Diabetes mellitus, n (%)	34 (18.5)	30 (19.6)	4 (12.1)	0.313
Atrial fibrillation, n (%)	10 (5.4)	8 (5.2)	2 (6.1)	0.848
Malignancy, n (%)	11 (5.9)	10 (6.5)	1 (3.0)	0.439

\*P values were calculated with  $\chi^2$  test, Fisher's exact test or Mann-Whitney U test. P values <0.05 were considered significant.

†This study was conducted on 186 patients, unless otherwise noted.

‡Ethanol intake of more than 320 g/week was defined as a risk factor for ONFH.<sup>19</sup>

§Methylprednisolone and other glucocorticoids were converted to an equivalent dose of prednisolone and included in the cumulative prednisolone dose.

ANCA, antineutrophil cytoplasmic antibody; aPL, antiphospholipid antibodies; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; CRP, C reactive protein level; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic GPA; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; ONFH, osteonecrosis of the femoral head; PR3, proteinase 3.

18 (54.5%) were asymptomatic and 21 (63.6%) had bilateral ONFH.

In addition, radiographic hip osteoarthritis (OA) (Kellgren/Lawrence radiographic severity grade  $\geq 1$ ) was found in 10 hip joints from 10 participants (5.4%) at the time of radiographs and MRI screening for ONFH. Seven patients had grades 1 and 3 patients had grade 3 hip OA, but none of them had hip pain at the time of AAV diagnosis.

We then compared the baseline characteristics of AAV patients with and without ONFH. AAV diagnosis (MPA, GPA or EGPA) and MPO-ANCA or PR3-ANCA positivity were not significantly different between patients with and without ONFH (table 1). Regarding the organ involvements, each BVAS domain was not significantly different between patients with and without ONFH (table 1).

Between-group differences were not observed regarding commonly known risk factors of ONFH such as alcohol intake and history of smoking<sup>6</sup> and general risk factors of vascular interruption or thrombosis such as hypertension, diabetes mellitus and antiphospholipid antibody status (table 1).

### Stages and types of ONFH in AAV patients

Thirty-three AAV patients with ONFH had 54 necrotic joints in their femoral head. Among the 54 ONFH joints, 41 (75.9%) joints were in precollapse stages (stage  $\leq 2$ ) and the remaining 13 (24.1%) joints were in collapse stages (stage  $\geq 3$ ) (table 2A). Twenty-three out of the 41 precollapse stage joints (56.1%) were at risk of future collapse (large necrotic lesions; type  $\geq C-1$ ) (table 2A). In 18 asymptomatic ONFH patients, 28 of 29 ONFH joints (96.6%) were in precollapse stages. However, 11 of the 28 precollapse stage joints (39.3%) were already at risk of future collapse (table 2B). ONFH patients in collapse stages or at risk of future collapse were significantly associated with a new-onset hip pain after the initiation of RIT (p<0.001 and p<0.01, respectively) (table 2C,D).

### Risk factors for ONFH development in AAV

Regarding RIT, all patients with AAV received glucocorticoid treatment, and the median initial prednisolone dose was 40 mg/day. Thirty-five (18.8 %) patients received

methylprednisolone pulse therapy. Only the prednisolone dose on day 90 of RIT was significantly higher in patients who developed ONFH than in those who did not (p=0.009, table 1). The history of methylprednisolone pulse therapy, initial prednisolone dose and cumulative prednisolone dose showed no significant differences between patients with and without ONFH (table 1). On the other hand, patients treated with rituximab had a significantly lower ONFH prevalence rate than those not treated with rituximab (p=0.019, table 1).

Logistic regression analysis detected the prednisolone dose on day 90 of RIT as an independent risk factor for ONFH in AAV patients (OR 1.072, 95% CI 1.017 to 1.130 for prednisolone one mg/day increase, p=0.009) (table 3). ROC analysis determined a prednisolone dose of  $\geq 20$  mg/day on day 90 as a cut-off value associated with ONFH (p<0.05, data not shown). Rituximab use was not a significant independent beneficial factor against ONFH in AAV patients (OR 0.592, 95% CI 0.239 to 1.465, p=0.257) (table 3). However, prednisolone dose on day 90 of RIT was significantly lower in patients with rituximab use than patients without rituximab use (14 mg/day (7.5–15), n=85 vs 20 mg/day (15–22.5), n=98, median (IQR), p<0.0001).

### DISCUSSION

To our knowledge, this is the first study to investigate the prevalence and risk factors of ONFH in AAV patients. We showed that 17.7% of AAV patients developed ONFH after RIT (table 1), which is a little lower prevalence rate compared with that of SLE patients.<sup>8 14</sup> Furthermore, we found that 75.9% of ONFH joints were in precollapse stages (stage  $\leq 2$ ) and 24.1% of ONFH joints were in collapse stages (stage  $\geq 3$ ) (table 2A). Moreover, 56.1% of the precollapse stage joints were already at risk of future collapse (type  $\geq C-1$ ) (table 2A). Thus, two-thirds of the ONFH joints were already in collapse stages or at risk of future collapse in our radiographs and MRI screening.

We also showed that the prednisolone dose of  $\geq 20$  mg/day on day 90 of RIT was an independent risk factor for ONFH development in AAV patients (table 3), suggesting that a rapid reduction in prednisolone dose



**Table 2** Stage and type distribution of osteonecrosis of the femoral head in ANCA-associated vasculitis patients†

<b>A. Overall necrotic joints</b>		<b>Type, n</b>			
<b>(Total n=54 from 33 patients with ONFH)</b>		<b>A</b>	<b>B</b>	<b>C-1</b>	<b>C-2</b>
Stage, n	1	8	7	11	4
	2	1	2	6	2
	3A	0	0	1	5
	3B	0	0	1	4
	4	0	0	0	2
<b>B. Asymptomatic necrotic joints</b>		<b>Type, n</b>			
<b>(Total n=29 from 18 asymptomatic ONFH patients)</b>		<b>A</b>	<b>B</b>	<b>C-1</b>	<b>C-2</b>
Stage, n	1	7	7	5	3
	2	1	2	1	2
	3A	0	0	0	0
	3B	0	0	1	0
	4	0	0	0	0
<b>C. Frequency of hip pain stratified by stage</b>					
		<b>New-onset hip pain -</b>	<b>New-onset hip pain +</b>	<b>P value*</b>	
<b>(Patients with ONFH, total n=33)</b>		<b>n (% total)</b>	<b>n (% total)</b>		
Stage ≤2		17 (51.5)	5 (15.2)	<0.001	
Stage ≥3		1 (3.0)	10 (30.3)		
<b>D. Frequency of hip pain stratified by type</b>					
		<b>New-onset hip pain -</b>	<b>New-onset hip pain +</b>	<b>P value*</b>	
<b>(Patients with ONFH, total n=33)</b>		<b>n (% total)</b>	<b>n (% total)</b>		
Type ≤B		8 (24.2)	0 (0.0)	<0.01	
Type ≥C-1		10 (30.3)	15 (45.5)		

\*P values <0.05 were considered significant.

†Staging and type classification of ONFH was determined by the Japanese Orthopaedic Association classification criteria<sup>13</sup> and is described in the Method section. Briefly, stage defines the degree of collapse and is classified into five stages. Stages 1 and 2 are defined as precollapse phases (no collapse on radiographic images), while stages 3A, 3B and four are considered collapse phases. Type defines the extent of necrotic lesions and is classified into four types (types A, B, C1 and C2). Large necrotic lesions (types C-1 and C-2) are considered a high risk of future collapse.<sup>13</sup>

ANCA, antineutrophil cytoplasmic antibody; ONFH, osteonecrosis of the femoral head.

to <20 mg/day in the first 90 days would decrease the incidence rate of ONFH in AAV patients. Our findings are in agreement with previous findings that ONFH developed between 2 and 5 months after the start of

high-dose glucocorticoid treatment in SLE patients<sup>15</sup> and that increased daily glucocorticoid doses contribute to osteonecrosis in SLE patients.<sup>16</sup> As shown in PEXIVAS and LoVas studies indicating that a reduced-dose/rapid

**Table 3** Independent risk factor of osteonecrosis of the femoral head in patients with ANCA-associated vasculitis

<b>Logistic regression (forced entry)</b>			
<b>Univariate predictors†</b>	<b>OR</b>	<b>95% CI for OR</b>	<b>P value*</b>
Prednisolone dose on day 90, median (IQR), mg/day	1.072	1.017 to 1.130	0.009
Rituximab use	0.592	0.239 to 1.465	0.257

\*P values <0.05 were considered significant.

†Candidate risk factors with p<0.05 were included in the multivariate analysis.

ANCA, antineutrophil cytoplasmic antibody.

reduction glucocorticoid regimen is non-inferior to a standard high-dose/gradual reduction glucocorticoid regimen with respect to the efficacy on AAV,<sup>17 18</sup> our results also suggest that a reduced-dose/rapid reduction glucocorticoid regimen would be useful in decreasing ONFH development in AAV.

The univariate analysis also detected rituximab use as a significant beneficial factor against ONFH (table 1), but multivariate analysis rejected its significance as an independent beneficial factor against ONFH (table 3). Rituximab use for treating severe AAV might have decreased glucocorticoid use and ONFH development in AAV patients.<sup>3</sup> It has recently been shown that a reduced-dose glucocorticoid plus rituximab regimen is non-inferior to a high-dose glucocorticoid plus rituximab regimen in the induction of disease remission at 6 months in AAV patients.<sup>18</sup> In this study, we also found that prednisolone dose on day 90 of RIT was significantly lower in patients with rituximab use than patients without rituximab use. Together, our results suggest that the combination of lower doses of glucocorticoids and rituximab would be useful in preventing or slowing the progression of ONFH in AAV patients.

The limitations of this study include its retrospective observational design, which cannot assess the fluctuations of variables over time. In addition, since not all AAV patients routinely underwent MRI screening, a selection bias, missing the chance to detect occult ONFH patients, might have occurred and affected the study population. On the other hand, patients with hip pain might have been more likely to participate in a study. This may have affected the prevalence rate of osteonecrosis in AAV patients.

In conclusion, we have shown that 18% of AAV patients develop ONFH after RIT and that glucocorticoid dose on day 90 of RIT is an independent risk factor for ONFH in AAV patients. Our results suggest that a rapid reduction of glucocorticoids in RIT and early MRI screening for detecting precollapse ONFH are important for decreasing and intervening ONFH development in AAV patients. Optimal time points of MRI screening (eg, 6 months and 12 months after RIT) to detect the precollapse ONFH in high-risk patients should be determined in a future prospective longitudinal study.

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