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PlA1/A2 Polymorphism of the Platelet Glycoprotein Receptor IIIa and Risk of Cranial Ischemic Complications in Giant Cell Arteritis

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Objective. **To investigate potential associations of the PlA1/A2 polymorphism of the platelet glycoprotein IIIa (GPIIIa) gene with susceptibility to, and clinical expression of, giant cell arteritis (GCA).**

Methods. **One hundred forty patients with biopsy-proven GCA who were residents of Reggio Emilia, Italy, and 241 population-based healthy controls from the same geographic area were genotyped for the PlA1/A2 polymorphism of the platelet GPIIIa gene by molecular methods. The patients were divided into subgroups according to the presence or absence of polymyalgia rheumatica and cranial ischemic complications. The distribution of the PlA1/A2 genotype was investigated, and odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.**

Results. **The distribution of the PlA1/A2 genotype differed significantly between GCA patients with and those without visual loss caused by anterior ischemic optic neuritis ($P = 0.016$, corrected P [P_{corr}] $= 0.048$). The PlA2 allele was found significantly more frequently in GCA patients with anterior ischemic optic neuritis than in those without anterior ischemic optic neuritis ($P = 0.023$, $P_{corr} = 0.046$, OR 2.4 [95% CI 1.2–4.8]). Homozygosity for the PlA2 allele was significantly more frequent among GCA patients with anterior ischemic optic neuritis than among those without ($P = 0.019$, $P_{corr} = 0.038$, OR 7.1 [95% CI 1.64–30.6]). Cranial ischemic complications occurred in 8 of 19 patients (42.1%) receiving antiplatelet therapy, compared with 22 of 118 patients (18.6%) not receiving such therapy ($P = 0.03$, OR 3.2 [95% CI 1.1–8.8]).**

Conclusion. **Our findings show that A2/A2 homozygosity is associated with an increased risk of visual loss due to anterior ischemic optic neuritis in GCA patients. Antiplatelet therapy, however, was not effective in reducing the risk of ischemic events in this population of GCA patients.**

Acute visual loss, attributable mostly to anterior ischemic optic neuritis, and cerebrovascular accidents (CVAs) are among the leading causes of giant cell arteritis (GCA)–related morbidity (1–6). Permanent partial or complete loss of vision in one or both eyes occurs in up to 20% of patients with GCA and is often an early manifestation of the disease (2–4). Although ischemic damage in GCA is usually attributed to occlusive vasculopathy caused by intimal proliferation, a possible role of thrombosis in causing cranial ischemic complications cannot be excluded (7,8). Low-dose aspirin or anticoagulant therapy has been shown to reduce the risk of visual loss and CVAs in patients with GCA (9,10). The benefits of low-dose aspirin in GCA could derive from the antiplatelet effect of aspirin, although its antiinflammatory action may also be involved (11).

Glycoprotein IIb-IIIa (GPIIb-IIIa) is a platelet receptor which binds fibrinogen and von Willebrand factor (vWF). It plays a key role in platelet aggregation and in thrombus formation on the injured vessel wall (12,13). The genes encoding GPIIb-IIIa are located on chromosome 17q21, and genetic variants can potentially

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influence both activation of the GP complexes and aggregation itself (14). The PlA1/A2 polymorphism of platelet GPIIIa has been widely studied in cardiovascular disease, and presence of the PlA2 allele has been associated in vitro with increased platelet aggregation and in vivo with ischemic cardiovascular disease (15–19).

This study was undertaken to assess the role of the PlA1/A2 polymorphism in susceptibility to, and clinical expression of, GCA. Allele frequencies were investigated in patients with versus those without cranial ischemic complications, such as acute visual loss and/or CVAs.

PATIENTS AND METHODS

Study population. We reviewed the computerized register maintained by the pathology laboratory of Arcispedale S. Maria Nuova, which contains information on all temporal artery biopsies performed in Reggio Emilia between 1986 and 2004. Specimens with positive results were reviewed by a pathologist, and 166 patients residing in the Reggio Emilia area were identified. Of these, 140 patients could be contacted and were willing to participate in the present study.

Patients were diagnosed as having biopsy-proven GCA if histologic examination of the temporal artery biopsy showed disruption of the internal elastic lamina with infiltration of mononuclear cells into the arterial wall, with or without giant cells. Temporal artery biopsy procedures in Reggio Emilia have been described previously (20,21). Temporal artery biopsy was routinely performed in all patients with clinical manifestations of GCA. Segments >2 cm long were generally obtained.

Clinical findings at diagnosis and during followup, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level at diagnosis, initial prednisone dosage, and information on other medications taken by the patient were obtained through interviews and a review of medical records. All patients with permanent visual loss were examined by an ophthalmologist (LC) at diagnosis and during the course of treatment. Visual acuity was measured using a Snellen chart, and visual field was tested with a Goldmann perimeter. Information was obtained on the numbers of patients with ischemic complications (visual loss, jaw claudication, CVAs, and/or aortic arch syndrome). Visual loss and CVAs were considered cranial ischemic complications. Patients were divided into subgroups according to the presence or absence of polymyalgia rheumatica (PMR; marked bilateral aching and stiffness without other apparent cause in at least 2 of the 3 following regions: neck, shoulder girdle, or hip girdle), visual loss (anterior ischemic optic neuritis and/or central retinal artery occlusion), and cranial ischemic complications.

Control subjects were randomly recruited from lists of patients under the care of medical practitioners in the same public health service. Stratification of the group by age and sex was used to approximately match the controls with the cases. At the end of this selection process, 241 control subjects were identified. The median age of the controls was 69 years (range 50–80 years).

All study subjects were white, of Italian descent, and had resided in Italy for at least one generation. No ethnic differences were found between the patients and the controls. None of the study participants had a Jewish background. The study was approved by the Ethics Committee of Reggio Emilia Hospital, and informed consent was obtained from all patients or their relatives.

DNA extraction and genotyping. DNA was isolated from venous blood samples by standard 3-step phenol–chloroform proteinase K extraction and stored at 4°C until further analysis. Primers were designed according to the sequence described by Tanaka et al (22). A 247-bp fragment of exon 2 of the GPIIIa gene was amplified with 1 unit of AmpliTaq (PerkinElmer, Weiterstadt, Germany), 0.2 mmoles/liter deoxynucleotides, 20 pmoles downstream primer 5′-CTGCAGGAGGTAGAGAGTCGCCATAG, 20 pmoles upstream primer 5′-GTGCAATCCTCTGGGGACTGACTTG, and 1.5 mmoles/liter magnesium chloride in a final volume of 25 μl. Polymerase chain reaction (PCR) conditions were 35 cycles of 20 seconds at 94°C, 20 seconds at 68°C, and 20 seconds at 72°C in a PerkinElmer 9600 Thermal Cycler (PerkinElmer, Foster City, CA). PCR efficiency was checked on a 2% agarose gel for 20 minutes at 120V. Fifteen microliters of the amplified product was digested overnight at 37°C with 5 units of *Bsm* I (Fermentas, Vilnius, Lithuania) in a final volume of 20 μl. Fragments were separated on a 2.5% agarose gel for 60 minutes at 80V.

Statistical analysis. Statistical analysis was conducted using the SPSS statistical package (SPSS, Chicago, IL). Continuous variables were compared by Student's 2-tailed *t*-test, and categorical variables were compared by chi-square test. The frequencies of the alleles and genotypes among the patients and the controls were determined and were compared by chi-square test with the values predicted by the assumption of Hardy-Weinberg equilibrium in the sample. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Corrected *P* values (P_{corr}) were calculated by multiplying *P* by the number of alleles compared. We performed power calculations for an unmatched case–control study and estimated relative risk (RR) using Power and Sample Size software, version 2.1.31.

RESULTS

Table 1 shows the demographic and clinical characteristics of the 140 patients with GCA. PMR was present in 63 patients. Ischemic complications occurred in 81 patients, with some patients experiencing more than one type of complication. Twenty-eight patients experienced visual loss (25 had anterior ischemic optic neuritis, and 6 had central retinal artery occlusion), 67 had jaw claudication, 4 experienced CVAs, and 4 had aortic arch syndrome. Cranial ischemic complications (visual loss and/or CVAs) occurred in 31 patients. ESR and CRP values at diagnosis were significantly higher in patients who did not experience ocular and cerebrovascular ischemic events compared with those who did

Table 1. Demographic and clinical features of the 140 patients with biopsy-proven GCA*

Male/female	30 (21.4)/110 (78.6)
Age at disease onset, mean ± SD years	74 ± 7
Headache	117 (83.6)
Abnormalities of temporal arteries†	93 (66.9)
Scalp tenderness	58 (42.3)
Jaw claudication	67 (47.9)
Visual manifestations	43 (30.7)
Visual loss	28 (20.0)
Anterior ischemic optic neuritis	25 (17.9)
Arterial retinal occlusion	6 (4.3)
Cerebrovascular accidents	4 (2.9)
Aortic arch syndrome	4 (2.9)
Cranial ischemic complications‡	31 (22.1)
Systemic symptoms and/or signs§	109 (77.9)
Polymyalgia rheumatica	63 (45.0)
Duration of therapy, mean ± SD months	21 ± 15
Duration of followup, mean ± SD months	26 ± 21
ESR at diagnosis, mean ± SD mm/hour	91 ± 30
CRP level at diagnosis, mean ± SD mg/dl	10 ± 7
Platelet count at diagnosis, mean ± SD/mm^3	392,029 ± 116,494

* Except where indicated otherwise, values are the number (%) of patients. Information on abnormalities of temporal arteries and on scalp tenderness was available on 139 and 137 patients, respectively. GCA = giant cell arteritis; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
† Artery tenderness and/or decreased or absent temporal artery pulsation.
‡ Visual loss and/or cerebrovascular accidents.
§ Presence of at least 1 of the following: asthma, anorexia, weight loss ≥4 kg, or fever.

experience such events (95 ± 30 mm/hour versus 85 ± 28 mm/hour [$P = 0.05$], and 10.5 ± 6.6 mg/dl versus 6.6 ± 4.4 mg/dl [$P = 0.02$], respectively).

The use of antiplatelet or anticoagulant therapy was investigated in 137 of the 140 patients. For 3 patients, there was no clear information about the dates of onset of therapy in relation to the diagnosis of GCA, and those patients were excluded from the analysis. At the time of diagnosis, 19 of 137 patients (13.9%) had already been receiving long-term treatment with either low-dose aspirin (16 patients) or ticlopidine (3 patients) for previous ischemic events (mainly ischemic heart disease and carotid stenosis). None of the patients were receiving anticoagulant therapy. Cranial ischemic complications were present in 30 patients at diagnosis. Eight of 19 patients (42.1%) receiving antiplatelet therapy presented with cranial ischemic complications, compared with 22 of 118 patients (18.6%) who were not receiving antiplatelet therapy ($P = 0.03$, OR 3.2 [95% CI 1.1–8.8]).

Allele and genotype frequencies of the PlA1/A2 polymorphism were not significantly different in GCA patients versus controls, as shown in Table 2. Given the sample sizes (140 patients with GCA and 241 controls) and the allele frequencies of the polymorphism examined, a genetic RR of 1.9 for GCA with the PlA1/A2 polymorphism could be excluded with 80% certainty. Similarly, the distribution of genotype and carriage rates of the PlA1/A2 polymorphism did not differ significantly when comparing patients with and those without PMR and those with and without ischemic complications (visual loss, jaw claudication, CVAs, and/or aortic arch syndrome) (data not shown). Given the sample sizes (63 GCA patients with PMR and 77 GCA patients without PMR and 81 GCA patients with ischemic complications and 59 GCA patients without ischemic complications) and the allele frequencies of the polymorphism examined, a genetic RR of 2.4 for GCA with the PlA1/A2 polymorphism could be excluded with 80% certainty.

The distribution of the PlA1/A2 genotype differed significantly between GCA patients with and those without cranial ischemic complications (anterior ischemic optic neuritis, central retinal artery occlusion, and/or CVAs) ($P = 0.05$, $P_{corr} = 0.15$) (Table 3). The PlA2 allele occurred significantly more frequently in the GCA patients with cranial ischemic complications than in those without ($P = 0.037$, $P_{corr} = 0.074$, OR 2.1 [95% CI 1.1–4.1]). Homozygosity for the PlA2 allele was significantly more frequent among GCA patients with cranial ischemic complications than among those without ($P = 0.043$, $P_{corr} = 0.086$, OR 5.2 [95% CI 1.1–24.8]). However, the significance was lost after the correction of P values. Given the sample sizes (31 GCA patients with cranial ischemic complications and 109 GCA patients without cranial ischemic complications) and the allele frequencies of the polymorphism exam-

Table 2. Frequencies of alleles, genotypes, and carriage of the PIA1/A2 polymorphism in GCA patients and controls*

	GCA patients (n = 140)	Controls (n = 241)	OR (95% CI)
Allele			
A2	50 (17.9)	68 (14.1)	1.3 (0.9–2.0)
A1	230 (82.1)	414 (85.9)	
Genotype			
A2/A2	7 (5.0)	8 (3.3)	
A1/A2	36 (25.7)	52 (21.6)	
A1/A1	97 (69.3)	181 (75.1)	
Carriage rate			
A2/A2 + A1/A2	43 (30.7)	60 (24.9)	1.3 (0.8–2.1)
A1/A1	97 (69.3)	181 (75.1)	
A1/A1 + A1/A2	133 (95.0)	233 (96.7)	1.5 (0.5–4.3)
A2/A2	7 (5.0)	8 (3.3)	

* Values are the number (%) of alleles or genotypes. There were no significant differences in allele or genotype frequencies in giant cell arteritis (GCA) patients versus controls. OR = odds ratio; 95% CI = 95% confidence interval.

Table 3. Frequencies of alleles, genotypes, and carriage of the PIA1/A2 polymorphism in GCA patients with and those without cranial ischemic complications*

	Patients with cranial ischemic complications (n = 31)	Patients without cranial ischemic complications (n = 109)	*P*	Corrected *P*	OR (95% CI)
Allele					
A2	17 (27.4)	33 (15.1)	0.037	0.074	2.1 (1.1–4.1)
A1	45 (72.6)	185 (84.9)			
Genotype					
A2/A2	4 (12.9)	3 (2.8)			
A1/A2	9 (29.0)	27 (24.8)	0.050†	0.15†	
A1/A1	18 (58.1)	79 (72.5)			
Carriage rate					
A2/A2 + A1/A2	13 (41.9)	30 (27.5)	NS		1.9 (0.8–4.4)
A1/A1	18 (58.1)	79 (72.5)			
A1/A1 + A1/A2	27 (87.1)	106 (97.2)	0.043	0.086	5.2 (1.1–24.8)
A2/A2	4 (12.9)	3 (2.8)			

* Values are the number (%) of alleles or genotypes. Cranial ischemic complications comprised visual loss and/or cerebrovascular accidents. NS = not significant (see Table 2 for other definitions).
† By chi-square test for a 3 × 3 frequency table.

ined, a genetic RR of 2.8 for GCA with the PlA1/A2 polymorphism could be excluded with 80% certainty.

The distribution of the PlA1/A2 genotype differed significantly between GCA patients with and those without anterior ischemic optic neuritis ($P = 0.016$, $P_{corr} = 0.048$) (Table 4). The distribution of the PlA1/A2 genotype indicated that the difference in allele distribution was related to a higher frequency of PlA2/A2 homozygosity in the GCA patients with anterior ischemic optic neuritis compared with that in the GCA patients without anterior ischemic optic neuritis, whereas PlA1/A1 homozygosity was lower in the GCA patients with anterior ischemic optic neuritis.

The PlA2 allele was found significantly more frequently in the GCA patients with anterior ischemic optic neuritis than in those without anterior ischemic optic neuritis ($P = 0.023$, $P_{corr} = 0.046$, OR 2.4 [95% CI 1.2–4.8]). Homozygosity for the PlA2 allele was also significantly more frequent among the GCA patients with anterior ischemic optic neuritis than among those without anterior ischemic optic neuritis ($P = 0.019$, $P_{corr} = 0.038$; OR 7.1 [95% CI 1.64–30.6]). Given the

Table 4. Frequencies of alleles, genotypes, and carriage of the PIA1/A2 polymorphism in GCA patients with and those without anterior ischemic optic neuritis*

	Patients with anterior ischemic optic neuritis (n = 25)	Patients without anterior ischemic optic neuritis (n = 115)	*P*	Corrected *P*	OR (95% CI)
Allele					
A2	15 (30.0)	35 (15.2)	0.023	0.046	2.4 (1.2–4.8)
A1	35 (70.0)	195 (84.8)			
Genotype					
A2/A2	4 (16.0)	3 (2.6)			
A1/A2	7 (28.0)	29 (25.2)	0.016†	0.048†	
A1/A1	14 (56.0)	83 (72.2)			
Carriage rate					
A2/A2 + A1/A2	11 (44.0)	32 (27.8)	NS		2.0 (0.8–5.0)
A1/A1	14 (56.0)	83 (72.2)			
A1/A1 + A1/A2	21 (84.0)	112 (97.4)	0.019	0.038	7.1 (1.6–30.6)
A2/A2	4 (16.0)	3 (2.6)			

* Values are the number (%) of alleles or genotypes. NS = not significant (see Table 2 for other definitions).
† By chi-square test for a 3 × 3 frequency table.

sample sizes (25 GCA patients with anterior ischemic optic neuritis and 115 GCA patients without anterior ischemic optic neuritis) and the allele frequencies of the polymorphism examined, a genetic RR of 2.9 for GCA with the PlA1/A2 polymorphism could be excluded with 80% certainty.

DISCUSSION

Although ischemic damage in GCA is attributed to occlusive vasculopathy caused by intimal proliferation, thrombosis may also play a role in causing cranial ischemic complications (7,8). Evidence of thrombotic occlusion has been found in the vertebral arteries in patients with GCA who experienced CVAs (8). Embolization from thrombosed vessels damaged by arteritis may also cause CVAs in GCA (23). Indirect evidence of the role of thrombosis as one of the major contributors to cranial ischemic complications in GCA is the recently demonstrated efficacy of antiplatelet agents or anticoagulant therapy in preventing visual loss or CVAs (9,10).

Gonzalez-Gay et al (24) found that the presence of risk factors for atherosclerosis at the time of GCA diagnosis significantly increased the risk of developing at least one of the severe ischemic complications of the disease. Two case–control studies have shown an increased risk of GCA in heavy smokers and in patients with previous atherosclerotic disease (cardiovascular or peripheral vascular disease) (25,26). The presence of underlying atherosclerosis seems to predispose to the development of GCA and its vascular ischemic complications.

Gonzalez-Juanatey et al (27) demonstrated that endothelial dysfunction was present in patients with active GCA and that it improved with steroid therapy. Furthermore, abnormally high levels of vWF in the circulation have been found in patients with GCA, reflecting endothelial activation that was probably induced by the inflammatory process (28).

Genetic factors may also be involved in the risk of developing ischemic complications in GCA. The vascular endothelial growth factor 634 promoter polymorphism and the CA repeat polymorphism in the first intron of the interferon-γ gene have been found to be associated with ischemic complications in GCA (29,30).

Platelets represent an important linkage between inflammation, thrombosis, and atherogenesis. Platelet adhesion to exposed endothelial cell (EC) membrane proteins, such as vWF and collagen, at the site of vascular lesions is the initial step in thrombus formation (31). However, endothelial denudation is not an absolute prerequisite for platelet attachment to the arterial wall. Although the intact, nonactivated endothelium normally prevents platelet adhesion to the EC membrane, in inflammatory conditions, ECs develop properties that render them adhesive for platelets. In vitro studies have shown that platelets are able to adhere to the intact but activated human EC monolayer (32,33).

GPIIb-IIIa is a platelet membrane receptor involved in a final step of platelet-mediated thrombus formation on the injured vessel wall. It binds fibrinogen and vWF, causing platelet aggregation (12,13). A thrombotic occlusion at the site of vascular inflammatory lesions in GCA may be facilitated by the presence of underlying atherosclerotic lesions. In addition, vascular inflammation in GCA is responsible for EC activation (27,28), which may directly facilitate thrombotic vessel obstruction and initiate accelerated atherosclerosis.

The platelet GPIIb-IIIa receptor consists of a 2-chain GPIIb subunit noncovalently associated with a single-chain GPIIIa subunit. The PlA1/A2 polymorphism of the GPIIIa gene, caused by a T-to-C nucleotide substitution at position 1565, results in a substitution of proline for leucine at position 33 of the mature GPIIIa (34). A1 is the more common allele, while A2 is the presumed variant. Approximately 25% of individuals of Northern European ancestry are PlA2 positive, and only 2% are homozygous for PlA2 (35). This polymorphism has been widely studied in cardiovascular disease, and possession of an A2 allele has been found to increase the risk of myocardial infarction, coronary artery disease, restenosis after stent placement, and stroke caused by large-vessel disease (16–19).

While the association between ischemic cardiovascular disease and A1/A2 heterozygosity remains controversial (36), A2/A2 homozygosity has been found to be associated with a 3-fold and 4-fold increased risk of ischemic cardiovascular disease and myocardial infarction, respectively, particularly in young men (17). This polymorphism has also been studied in patients with antiphospholipid antibodies (70% of the patients in a previous study had primary antiphospholipid syndrome, and 30% had antiphospholipid syndrome secondary to systemic lupus erythematosus) (37). The possession of $\geq$1 A2 allele was associated with an increased risk of arterial thrombosis. The association between arterial thrombotic events and homozygosity or heterozygosity for the A2 allele has also been confirmed in Italian patients with antiphospholipid antibodies (38).

The PlA1/A2 polymorphism influences platelet function. Several studies have shown an association between increased platelet aggregability and either A2

heterozygosity or homozygosity. Two previous studies, in which all 3 genotypes were investigated separately, demonstrated that A2 was associated with increased platelet aggregability in a gene-dose–dependent manner (15,39).

In the present study, we tested the hypothesis that Italian patients with GCA who are A1/A2 heterozygotes or A2/A2 homozygotes have an increased risk of cranial ischemic complications as compared with A1/A1 noncarriers. We found that the A2 allele occurred more frequently in GCA patients with cranial ischemic complications; the difference in frequency was significant in those with anterior ischemic optic neuritis. The significance of this association was strengthened by the finding that increased risk was related to A2/A2 homozygosity. The increased platelet aggregability induced by the A2/A2 genotype may contribute to luminal stenosis or occlusion in arteries affected by GCA, thus increasing the risk of cranial ischemic complications. Replication studies in other populations must be performed before definitive conclusions can be drawn.

Two recent studies from tertiary care centers have demonstrated that antiplatelet therapy may reduce the risk of cranial ischemic complications in patients with GCA (9,10). The present population-based study did not confirm those results. We observed that patients treated with antiplatelet therapy for ischemic events unrelated to GCA had a higher risk at diagnosis of developing GCA-related cranial ischemic complications. These results may indicate that, in spite of the protective role of antiplatelet therapy, the presence of preexisting atheromatous arterial disease is a stronger risk factor for cranial ischemic complications in GCA.

Furthermore, the reduced efficacy of aspirin in preventing CVAs in the cohort of Italian patients with GCA could be partly related to the increased frequency of the PlA2 allele in the subgroup of patients with these manifestations. Several investigators have reported that carriers of the PlA2 polymorphism appeared to be more resistant to aspirin than did noncarriers; in particular, PlA2 homozygosity has been associated with an inadequate response to aspirin (40–42). However, due to the retrospective nature of the study and the low number of patients included in the analysis, the results of the present study should be interpreted cautiously.

In conclusion, the PlA1/A2 polymorphism of the GPIIIa gene, in particular PlA2/A2 homozygosity, was found to be associated with anterior ischemic optic neuritis in GCA. Although this finding requires further confirmation, it is potentially important because the association of PlA2 with increased platelet aggregability implies that thrombosis may play a role in causing cranial ischemic complications in GCA. Our results did not confirm the previously demonstrated efficacy of antiplatelet therapy in reducing the risk of ischemic events in patients with GCA.

AUTHOR CONTRIBUTIONS

Dr. Salvarani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Salvarani, Casali, Pipitone, Boiardi.

Acquisition of data. Salvarani, Farnetti, Nicoli, Cimino, Catanoso, Restuccia, Ghinoi.

Analysis and interpretation of data. Salvarani, Farnetti, Formisano, Nicoli, Macchioni, Cimino, Bajocchi, Catanoso, Restuccia, Ghinoi, Boiardi.

Manuscript preparation. Salvarani, Casali, Pipitone, Macchioni, Bajocchi, Boiardi.

Statistical analysis. Farnetti, Formisano.

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