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Association Between Immunosuppressive Treatment and Outcomes of Cerebral Amyloid Angiopathy–Related Inflammation

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IMPORTANCE Cerebral amyloid angiopathy–related inflammation (CAA-ri), a distinct subtype of cerebral amyloid angiopathy, is characterized by an autoimmune reaction to cerebrovascular β-amyloid deposits. Outcomes and response to immunosuppressive therapy for CAA-ri are poorly understood.

OBJECTIVE To identify clinical, neuroimaging, laboratory, pathologic, or treatment-related associations with outcomes after an episode of CAA-ri.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study of prospectively identified individuals who presented from July 3, 1998, to November 27, 2017, with a median follow-up of 2.7 years (interquartile range, 1.0-5.5 years). The study included 48 consecutive patients with CAA-ri meeting diagnostic criteria who had at least 1 disease episode and subsequent outcome data. No patients refused or were excluded.

EXPOSURES Prespecified candidate variables were immunosuppressive therapies, cerebrospinal fluid pleocytosis, magnetic resonance imaging findings of recent infarcts or contrast enhancement, and histopathologic evidence of vessel wall inflammation.

MAIN OUTCOMES AND MEASURES Clinical improvement and worsening were defined by persistent changes in signs or symptoms, radiographic improvement by decreased subcortical foci of T2 hyperintensity or T1 enhancement, and radiographic worsening by increased subcortical T2 hyperintensity, T1 enhancement, or infarcts. Disease recurrence was defined as new-onset clinical symptoms associated with new imaging findings.

RESULTS The 48 individuals in the study included 29 women and had a mean (SD) age of 68.9 (9.9) years. Results of presenting magnetic resonance imaging revealed that 10 of 29 patients with CAA-ri (34%) had T1 contrast enhancement, 30 of 32 (94%) had subcortical T2 hyperintensity (22 of 30 [73%] asymmetric), 7 of 32 (22%) had acute or subacute punctate infarcts, and 27 of 31 (87%) had microbleeds. Immunosuppressive treatments after first episodes included corticosteroids (33 [69%]), cyclophosphamide (6 [13%]), and mycophenolate (2 [4%]); 14 patients (29%) received no treatment. Clinical improvement and radiographic improvement were each more likely in individuals treated with an immunosuppressive agent than with no treatment (clinical improvement: 32 of 34 [94%] vs 7 of 14 [50%]; odds ratio, 16.0; 95% CI, 2.72-94.1; radiographic improvement: 24 of 28 [86%] vs 4 of 14 [29%]; odds ratio, 15.0; 95% CI, 3.12-72.1). Recurrence was less likely if CAA-ri was treated with any immunosuppressant agent than not (9 of 34 [26%] vs 10 of 14 [71%]; hazard ratio, 0.19; 95% CI, 0.07-0.48). When controlling for treatment, no variables were associated with outcomes aside from an association between *APOE* ε4 and radiographic improvement (odds ratio, 4.49; 95% CI, 1.11-18.2).

CONCLUSIONS AND RELEVANCE These results from a relatively large series of patients with CAA-ri support the effectiveness of immunosuppressive treatment and suggest that early treatment may both improve the initial disease course and reduce the likelihood of recurrence. These results raise the possibility that early blunting of CAA-ri and the autoimmune response may have long-term benefits for the subsequent disease course.

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Supplemental content

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Cerebral amyloid angiopathy–related inflammation (CAA-ri), also referred to as *inflammatory cerebral amyloid angiopathy* and *Aß-related angiitis*, is a distinct subset of cerebral amyloid angiopathy (CAA) characterized by an autoimmune reaction to cerebrovascular β-amyloid deposits.[1-6] It differs from more common noninflammatory forms of CAA in its clinical presentation, with subacute cognitive changes and vasogenic edema rather than acute intracerebral hemorrhage.[7-10] Neuroimaging results often show multiple lobar microhemorrhages characteristic of CAA as well as patchy or confluent asymmetric white matter hyperintensities (WMHs) suggestive of subcortical edema, which may regress in response to treatment, as reported in small case studies.[4,11] Neuropathologic examination of brain biopsy samples has shown a spectrum of inflammatory changes associated with amyloid-laden blood vessel segments, ranging from perivascular accumulation of inflammatory cells[1] to true vasculitis with transmural vessel wall destructive changes.[12] Clinical and imaging criteria have been described for the diagnosis of probable CAA-ri, demonstrating high sensitivity (82%) and specificity (97%) in a small validation study.[11] Disease flares are associated with elevated cerebrospinal fluid (CSF) titers of anti-β-amyloid autoantibodies,[3] but assays for the CSF autoantibodies are not commercially available and have not been validated as a diagnostic test for this disorder.

Given the appearance of an underlying autoimmune inflammatory response in CAA-ri, various immunosuppressive agents are often implemented, with small observational studies suggesting clinical and radiographic improvement.[1,2,6,7,13] However, the optimal agents and regimens have not been identified, and some individuals with CAA-ri appear to improve spontaneously in the absence of immunosuppressive treatment.[2] Furthermore, it is unclear whether particular markers of CAA-ri, such as pathologic evidence of vessel wall inflammation, pleocytosis in the CSF, or neuroimaging appearance of recent infarcts and abnormal contrast enhancement, are associated with a more severe course of disease requiring more aggressive immunosuppressive treatment. We therefore sought to identify clinical, neuroimaging, laboratory, pathologic, or treatment-related associations with outcomes after an episode of CAA-ri.

Key Points

Question What are the clinical, neuroimaging, laboratory, pathologic, or treatment-related associations with outcomes after an episode of cerebral amyloid angiopathy–related inflammation?

Findings In this cohort study of 48 patients with cerebral amyloid angiopathy–related inflammation, both clinical improvement and radiographic improvement were more likely to occur in individuals treated with an immunosuppressive agent than in untreated individuals; recurrence was also significantly less likely among individuals who received treatment than those who did not. When controlling for treatment, no other variables were associated with outcomes aside from an association between *APOE* ε4 and radiographic improvement.

Meaning Early immunosuppressive treatment may improve the disease course of cerebral amyloid angiopathy–related inflammation and reduce the likelihood of recurrence.

Methods

Individuals with CAA-ri, diagnosed by clinical presentation, validated imaging criteria,[11] and/or pathologic findings, were identified from a prospective cohort of consecutive patients with CAA seen at Massachusetts General Hospital under Massachusetts General Hospital Institutional Review Board approval with waived informed consent (based on minimal patient risk and practical inability to perform the study without the waiver) as described.[14,15] This systematic prospective cohort includes demographic, genetic, and pathologic data. We systematically reviewed the records of those who presented from July 3, 1998, to November 27, 2017, for additional detailed clinical, laboratory, imaging, treatment, and outcomes data. Diagnostic criteria for probable CAA-ri, with interrater reliability κ = 0.81, were used.[11] Clinical inflammatory episodes were defined as new or atypical or worsened headache, acute or subacute cognitive decline, seizures, or focal deficits. Radiographic inflammatory episodes were based on acute magnetic resonance imaging (MRI) findings defined as (1) subcortical T2 WMH, often asymmetric and suggestive of cerebral edema rather than typical periventricular or subcortical white matter lesions[16]; (2) T1 enhancement; or (3) diffusion-weighted imaging restricted diffusion lesions.[11] We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Clinical improvement and worsening were defined by persistent changes in neurologic signs or symptoms based on medical record review of clinical care documentation. Clinical symptoms were classified while blinded to MRI images, although in some cases descriptions of MRI findings may have been present in the clinical notes. Radiographic improvement was defined as decreased or disappearance of subcortical T2 WMH or T1 enhancement, while radiographic worsening was defined as increased or new subcortical T2 WMH, T1 enhancement, or diffusion-weighted imaging lesions. Disease recurrence was defined as new-onset symptoms, including new or atypical or worsened headache, cognitive changes, seizures, or focal deficits, associated with new or worsening imaging findings consistent with CAA-ri.[11] For recurrence analyses, participants were censored at the time of their last neurology clinic appointment or primary clinician appointment if they were instructed to follow up on an as-needed basis.

Magnetic resonance imaging was performed on a 1.5-T imaging system (Signa; GE Medical Systems) using previously reported parameters[17,18] and evaluated without knowledge of other clinical data. Lesions detected on MRI were recorded for side, symmetry, lobar vs deep location, and number. T1 postgadolinium sequences were assessed for regions of enhancement. T2 sequences were assessed for hyperintensity suggestive of edema associated with CAA-ri. T2 sequences were also assessed for chronic WMH using the Fazekas score.[19] Recent small subcortical infarcts, lacunes, and cerebral microbleeds

were identified using STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) criteria.[20,21] Focal and disseminated cortical superficial siderosis and acute convexity subarachnoid hemorrhage were defined as in previous studies.[22]

Surgical specimens and autopsy specimens were processed and stained using standard protocols.[11] *APOE* (OMIM 107741) genotype was also determined as described previously.[1]

Statistical Analysis

Median and interquartile range were reported for continuous variables, and percentage and number were reported for categorical variables. *APOE* ε4 was analyzed according to number of alleles (0 for absent, 1 for heterozygous, and 2 for homozygous) based on prior studies showing high risk associated with the homozygous ε4/ε4 genotype.[1] Associations were assessed by univariate logistic regression. Candidate variables (immunosuppressive treatment, age, *APOE* ε4 genotype, pathologic vessel wall inflammation, CSF nucleated cells, T1 contrast enhancement, Fazekas score, acute infarcts, lacunes, and microbleeds) were selected a priori and were included in multivariate logistic regression if univariate $P < .10$. Analyses of recurrence were performed with the Kaplan-Meier estimator and Cox proportional hazards regression for calculating multivariable hazard ratio. Two-tailed $P < .05$ and 95% CIs that did not include unity were interpreted as statistically significant. Analyses were performed with Prism, version 6.01 (GraphPad) and SPSS, version 23.0 (IBM Corp).

Results

Of 56 consecutive patients with a diagnosis of CAA-ri, 48 had at least 1 clinical or radiographic inflammatory episode with available treatment and outcomes data, with a median follow-up of 2.7 years (interquartile range, 1.0-5.5 years). Patient demographic features are summarized in **Table 1**.[23-25] Of the 24 individuals with pathologic data available, 7 (29%) had at least 1 focus of transmural vessel wall inflammation, 14 (58%) had only perivascular inflammation, and 3 (13%) had no inflammation in the biopsy sample, but clinical and imaging data supported probable CAA-ri. First episodes included headache (present in 20 individuals [42%]), cognitive or behavioral change (28 [58%]), focal deficit (9 [19%]), seizure (20 [42%]), and other symptoms (6 [13%]; atypical but additional symptoms or imaging results were consistent with CAA-ri) including presyncope, gait instability, incoordination, and fever. Analyses of CSF after the first episodes showed 26% of patients (6 of 23) with elevated nucleated cells (>5/μL, all with lymphocytic predominance [to convert to $\times 10^9$ per liter, multiply by 0.001]), 92% (24 of 26) with elevated CSF protein (>45 mg/dL), none with low glucose (<50 mg/dL; median, 66 mg/dL; interquartile range, 61-70 mg/dL [to convert to millimoles per liter, multiply by 0.0555]), and 4% (1 of 23) with no abnormality. Similar frequencies of clinical presentations and laboratory data were noted in analyses of recurrent episodes (eTable 1 in the Supplement).

Magnetic resonance imaging with results available for review were performed a median of 1 day (interquartile range, 0-5 days) after the first episode (Table 1[23-25]). T2 sequences showed that 30 of 32 participants (94%) had subcortical foci of WMH characteristic of CAA-ri, of which 22 of 30 participants (73%) showed asymmetry. All individuals also showed some degree of chronic T2 WMH distinct from the subcortical foci. T1 postgadolinium sequences showed enhancement in 10 of 29 participants (34%), of which 8 of 10 (80%) were asymmetric and 10 (100%) involved meninges (**Figure 1**). T2 sequences also showed chronic lacunes in 4 of 32 participants (13%), and diffusion-weighted imaging sequences showed punctate acute or subacute infarcts in 7 of 32 participants (22%), all less than 10 mm in the largest in-plane dimension (Table 1[23-25]). T2*-weighted sequences found 27 of 31 individuals (87%) had microbleeds and 13 individuals had more than 50 microbleeds. A total of 5 of 31 participants (16%) had macrobleeds or evidence of past intracerebral hemorrhage. Cortical superficial siderosis was present in 6 of 31 individuals (19%) and acute sulcal subarachnoid hemorrhage in 6 of 31 individuals (19%).

Treatments after first episodes included corticosteroids (33 of 48 [69%]), cyclophosphamide (6 of 48 [13%]; 5 of 6 also treated with corticosteroids), and mycophenolate (2 of 48 [4%]); 14 patients (29%) received no treatment. For recurrent episodes of CAA-ri, treatments included corticosteroids (54 of 82 [66%]), cyclophosphamide (12 of 82 [15%]; 11 of 12 also treated with corticosteroids), mycophenolate (4 of 82 [5%]), and rituximab (1 of 82 [1%]); 27 of 82 patients (33%) received no treatment. Of the 33 patients treated with corticosteroids after the first episode, treatment was started during the acute admission for 30 and within 2 months of clinical presentation for 2, while initiation of corticosteroids was unknown for 1 patient. Of the 6 patients treated with cyclophosphamide after the first episode, treatment was started during the acute admission for 4 and within 2 months of clinical presentation for 2. Both cases of mycophenolate treatment after the first episode were delayed (7.5 and 9 months). Corticosteroid doses and tapering regimens varied but most commonly involved intravenous methylprednisolone, 1 g, daily for 3 to 5 days followed by oral prednisone, 60 mg, daily that then tapered to discontinuation over several months. Cyclophosphamide was administered intravenously at 2- to 4-week intervals in 4 individuals, as 500 mg orally daily for 10 days in 1 patient, and as 100 mg orally daily for 6 months followed by a 4-month tapering regimen in 1 patient. Mycophenolate doses ranged from 500 to 1500 mg orally twice daily.

Among potential factors associated with receiving immunosuppressive treatment at first episodes, presenting with cognitive or behavioral changes (odds ratio [OR], 3.76; 95% CI, 1.02-13.9) and focal deficits (OR, 0.13; 95% CI, 0.03-0.63) were significant; *APOE* ε4 number demonstrated a nonsignificant association (OR, 2.53; 95% CI, 0.95-6.76). Only cognitive or behavioral change remained independently associated with receiving treatment in a multivariate model (OR, 10.3; 95% CI, 1.19-88.6), and no other associations, including vessel wall inflammation or imaging characteristics, were identified (eTable 2 in the Supplement).

We examined clinical course, neuroimaging course, and recurrence after the first CAA-ri episode (**Table 2**). A total of 39 patients (81%) had a clinically improving course after

Table 1. Patient Demographic Characteristics, Genotype, Pathologic Findings, Clinical Presentation, and MRI Assessment After First Episode of Cerebral Amyloid Angiopathy–Related Inflammation

Characteristic	No./total No. (%) with available information
Age, first episode, mean (SD), y/No.	68.9 (9.9)/48
Female sex	29/48 (60)
Race/ethnicity	
White	46/48 (96)
Black	1/48 (2)
Asian	1/48 (2)
Diagnosis of cerebral amyloid angiopathy[23]	
Definite by autopsy	3/48 (6)
Probable by biopsy	25/48 (52)
Probable by MRI	20/48 (42)
APOE genotype	
ε2/-	0/33 (0)
ε3/ε3	8/33 (24)
ε3/ε4	10/33 (30)
ε4/ε4	15/33 (45)
Pathologic findings	
Any vessel wall inflammation	7/24 (29)
Only perivascular inflammation	14/24 (58)
No inflammation	3/24 (13)
Clinical presentation, first episode[a]	
Headache	20/48 (42)
Cognitive or behavioral change	28/48 (58)
Focal deficit	9/48 (19)
Seizure	20/48 (42)
Other[b]	6/48 (13)
Cerebrospinal fluid, first episode	
Nucleated cells >5/μL	6/23 (26)
CSF protein >45 mg/dL	24/26 (92)
Glucose <50 mg/dL	0/23 (0)
Normal cell count and protein	1/23 (4)
MRI, first episode	
Contrast enhancement	10/29 (34)
Asymmetric	8/10 (80)
Meninges involved	10/10 (100)
Subcortical T2 hyperintensity	30/32 (94)
Asymmetric	22/30 (73)
Fazekas score[24]	
1	5/32 (16)
2	9/32 (28)
3	18/32 (56)
Lacunes	4/32 (13)
Acute or subacute infarcts	7/32 (22)
Microbleeds	27/31 (87)
>50	13/27 (48)
Past intracerebral hemorrhage	5/31 (16)
Cortical superficial siderosis[25]	6/31 (19)
Focal	4/6 (67)
Disseminated	2/6 (33)
Acute subarachnoid hemorrhage	6/31 (19)

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

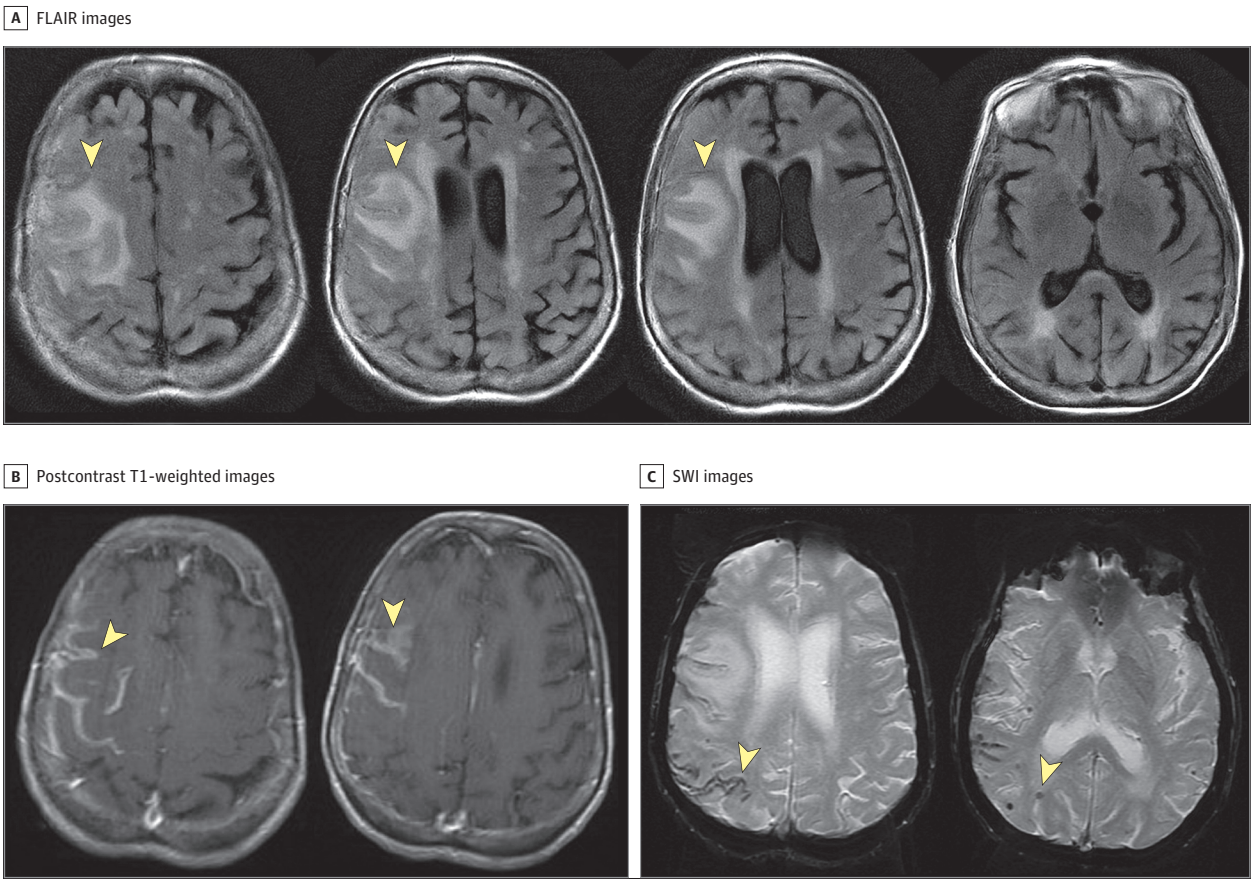
SI conversion factors: To convert nucleated cells to $\times 10^9$ per liter, multiply by 0.001; glucose to millimoles per liter, multiply by 0.0555.

[a] Clinical presentation sum to greater than 100% as patients could have multiple symptoms.

[b] Other symptoms, including presyncope, gait instability, incoordination, and fever, were atypical, but additional symptoms or imaging were consistent with cerebral amyloid angiopathy–related inflammation.

presentation, 6 (13%) remained clinically stable, and 3 (6%) had clinical worsening. Clinical improvement was more likely if treated with any immunosuppressive agent than not (32 of 34 [94%] vs 7 of 14 [50%]; OR, 16.0; 95% CI, 2.72-94.1). In addition, a secondary analysis showed that clinical improvement was more likely if treated with corticosteroids only vs no treatment (26 of 27 [96%] vs 7 of 14 [50%]; OR, 26.0; 95% CI, 2.73-248). A total of 28 of 42 patients (67%) had radiographic improvement after presentation, 1 of 42 (2%) had radiographic stability, and 3 of 42 (31%) had radiographic worsening. Radiographic improvement was also more likely if treated than not (24 of 28 [86%] vs 4 of 14 [29%]; OR, 15.0; 95% CI, 3.12-

Figure 1. Magnetic Resonance Imaging Findings of Cerebral Amyloid Angiopathy–Related Inflammation



Magnetic resonance imaging images are shown for a 79-year-old woman who presented with seizure. A, Fluid-attenuated inversion recovery (FLAIR) images show right-sided asymmetric subcortical regions of hyperintensity suggestive of subcortical edema. B, Postcontrast T1-weighted images show right-sided, primarily leptomeningeal contrast enhancement. C, The same right-sided predilection was also noted for foci of cortical superficial siderosis and microbleeds seen on susceptibility-weighted imaging (SWI) images.

Table 2. Outcomes After the First Episode of Cerebral Amyloid Angiopathy–Related Inflammation According to Treatment With Immunosuppressive Agent

Outcome	No./total No. with available information			OR (95% CI)	*P* value
	Total	No immunosuppression	Any immunosuppression		
Clinical course					
Improvement	39/48 (81)	7/14 (50)	32/34 (94)	16.0 (2.72-94.1)	.002
Stability	6/48 (13)	5/14 (36)	1/34 (3)	0.06 (0.01-0.53)	.01
Worsening	3/48 (6)	2/14 (14)	1/34 (3)	0.18 (0.02-2.19)	.18
Radiographic course					
Improvement	28/42 (67)	4/14 (29)	24/28 (86)	15.0 (3.12-72.1)	.001
Stability	1/42 (2)	0/14 (0)	1/28 (4)	NA	NA
Worsening	13/42 (31)	10/14 (71)	3/28 (11)	0.05 (0.01-0.25)	<.001
Recurrence	19/48 (40)	10/14 (71)	9/34 (26)	0.19 (0.07-0.48)[a]	<.001

Abbreviations: NA, not applicable; OR, odds ratio.

[a] Hazard ratio (95% CI).

72.1). Radiographic worsening similarly was less likely if patients were treated than not (3 of 28 [11%] vs 10 of 14 [71%]; OR, 0.05; 95% CI, 0.01-0.25). In univariate logistic regression analyses for other possible associations with clinical improvement (**Table 3**), a nonsignificant association was found for number of *APOE* ε4 alleles (OR, 2.68; 95% CI, 0.89-8.08). No other associations were found with clinical improvement. In univariate logistic regression analyses for associations with radiographic improvement, an association was found for *APOE* ε4 number (OR, 6.19; 95% CI, 1.62-23.6), which remained significant in a multivariate model controlling for immunosuppressive treatment (OR, 4.49; 95% CI, 1.11-18.2).

Table 3. Associations of Clinical and Imaging Variables With Outcomes After First Episode of Cerebral Amyloid Angiopathy–Related Inflammation[a]

Variable	OR (95% CI)	*P* value
Clinical improvement		
Univariate		
Immunosuppression treatment	16.0 (2.72-94.1)	.002
Age	1.06 (0.98-1.14)	.15
Female sex	1.28 (0.30-5.54)	.74
APOE ε4	2.68 (0.89-8.08)	.08
Any vessel wall inflammation	2.18 (0.20-24.2)	.53
CSF nucleated cells >5/μL	0.31 (0.02-5.96)	.44
T1 contrast enhancement	0.47 (0.06-3.97)	.49
Fazekas total	0.63 (0.15-2.71)	.53
Acute infarcts	1.14 (0.11-12.2)	.91
Lacunes	0.52 (0.04-6.36)	.61
Microbleeds >50	2.40 (0.22-26.1)	.47
Multivariate		
Immunosuppression treatment	26.4 (2.36-296)	.008
APOE ε4	1.67 (0.46-6.05)	.44
Radiographic improvement		
Univariate		
Immunosuppression treatment	15.0 (3.12-72.1)	.001
Age	0.97 (0.90-1.03)	.30
Female sex	0.32 (0.07-1.38)	.13
APOE ε4	6.19 (1.62-23.6)	.008
Any vessel wall inflammation	1.14 (0.18-7.28)	.89
CSF nucleated cells >5/μL	0.27 (0.03-2.83)	.28
T1 contrast enhancement	1.00 (0.17-5.77)	>.99
Fazekas total	0.64 (0.20-2.08)	.46
Acute infarcts	0.40 (0.06-2.57)	.33
Lacunes	0.47 (0.05-4.03)	.49
Microbleeds >50	8.75 (0.88-86.6)	.06
Multivariate		
Immunosuppression treatment	8.85 (1.00-78.4)	.05
APOE ε4	4.49 (1.11-18.2)	.04
Multivariate		
Immunosuppression treatment	56.6 (3.39-947)	.005
Microbleeds >50	8.93 (0.41-194)	.16
Recurrence[b]		
Univariate		
Immunosuppression treatment	0.19 (0.07-0.48)	<.001
Age	0.99 (0.95-1.03)	.61
Female sex	1.01 (0.40-2.57)	.77
APOE ε4	0.81 (0.39-1.66)	.56
Any vessel wall inflammation	0.66 (0.17-2.49)	.54
CSF nucleated cells >5/μL	4.15 (0.58-29.7)	.16
T1 contrast enhancement	1.45 (0.41-5.14)	.57
Fazekas total	1.00 (0.46-2.19)	>.99
Acute infarcts	0.98 (0.21-4.54)	.98
Lacunes	2.87 (0.76-10.9)	.12
Microbleeds >50	0.47 (0.12-1.77)	.26

Abbreviations: CSF, cerebrospinal fluid; OR, odds ratio.

SI conversion factor: To convert nucleated cells to $\times 10^9$ per liter, multiply by 0.001.

[a] Variables with $P < .10$ in univariate analyses were included in multivariate analyses.

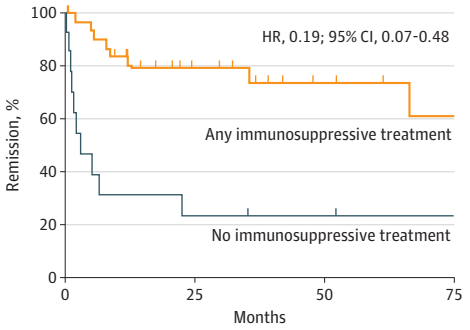
[b] Harzard ratios (95% CIs) are given for all variables associated with recurrence.

A total of 19 of 48 patients (40%) had at least 1 recurrence and 10 of 48 (21%) had multiple recurrences. The median time to recurrence was 5.2 months (interquartile range, 1.8-8.4 months; range, 0.3-66.5 months). Recurrence was less likely if treated with any immunosuppressive agent than not (9 of 34 [26%] vs 10 of 14 [71%]; hazard ratio, 0.19; 95% CI, 0.07-0.48) (**Figure 2**). In addition, a secondary analysis showed recurrence was less likely if treated with corticosteroids only vs no treatment (7 of 27 [26%] vs 10 of 14 [71%]; hazard ratio, 0.18; 95% CI, 0.06-0.49). No variables other than immunosuppressive therapy were identified in Cox proportional hazards regression analyses to have an association with recurrence. To explore the possibility that some episodes classified as distinct CAA-ri recurrences were in fact fluctuations of the pre-

senting episode, we performed a sensitivity analysis excluding the 6 individuals who had CAA-ri recurrence within 2 months of their initial presentation (eTable 3 in the Supplement). This analysis again showed reduced risk of CAA-ri recurrence among individuals treated with immunosuppressive therapy (hazard ratio, 0.27; 95% CI, 0.09-0.86).

Associations between other variables measured during the first episode were also explored in analyses to better understand CAA-ri pathophysiology; specifically, whether particular imaging variables were associated with true vasculitis on histopathologic findings (eTable 4 in the Supplement). There was a nonsignificant association for acute infarcts on diffusion-weighted imaging with pathologically confirmed vessel wall inflammation (OR, 13.5; 95% CI, 0.88-208; $P = .06$). Cerebrospinal fluid pleocytosis and MRI T1 contrast enhancement were nominally more frequent in individuals with vessel wall inflammation, but neither association approached statistical significance. Nearly all individuals had subcortical edema on results of T2 MRI, which was asymmetric in 73% (22 of 30). Of those with asymmetric edema, microbleed count was more often asymmetrically greater (>10% the contralateral count) in the side with edema compared with being asymmetrically greater in the side with less edema (12 of 22 [55%] vs 5 of 22 [23%]; $P = .01$) (Figure 1).

Figure 2. Time to Recurrence Comparing Any Immunosuppressive Therapy With No Immunosuppressive Therapy After First Episode of Cerebral Amyloid Angiopathy–Related Inflammation



No. at risk				
Any immunosuppressive treatment	34	27	26	25
No immunosuppressive treatment	14	4	4	4

HR indicates hazard ratio.

Discussion

In this study of consecutive individuals diagnosed by validated criteria with CAA-ri, immunosuppressive treatment was independently associated with clinical and radiographic improvement of the presenting disease episode and decreased risk of subsequent recurrent disease flare. No other variable was consistently and independently associated with improvement or risk of recurrence, although there was a tendency for the presence of *APOE* ε4 to be associated with an improving course.

These results provide the strongest support to date, to our knowledge, for the effectiveness of immunosuppressive treatment for CAA-ri. Although immunosuppressive treatment is commonly used for this entity, spontaneous improvement without treatment has also been observed,[2] raising the possibility that the course of CAA-ri might often be self-limited, occurring with or without treatment. Several case reports and small series have described courses after episodes of CAA-ri.[1,2,6,7] Two small series of 3 cases each described its episodic nature and responsiveness to treatment.[2,7] Another report described 5 of 6 patients who improved clinically and radiographically after immunosuppressive treatment.[1] A further series of 12 patients treated with immunosuppressive treatment reported that 7 had a monophasic illness, 3 initially improved but relapsed, and 2 did not respond.[6] Another recent study of 28 patients found that 42% had recurrent episodes.[13] In the current study of 48 patients, we observed similar rates of 40% of individuals who experienced at least 1 recurrence and 21% who experienced multiple recurrences. Individuals who received immunosuppressive treatment demonstrated substantially more frequent clinical (94% vs 50%) and radiographic (86% vs 29%) improvement and fewer recurrent flares of CAA-ri (26% vs 71%) over the median 2.7-year follow-up period, suggesting a substantial treatment effect.

We also hypothesized that certain characteristics, such as pathologic evidence of vessel wall inflammation, neuroimaging appearance of recent infarcts and abnormal contrast enhancement, or CSF pleocytosis, might be associated with a more active vasculitic process and a more aggressive clinical course. Previous studies have identified a spectrum of autoimmune responses to CAA ranging from perivascular inflammation without actual involvement of the vessel wall[1] to a true vasculitis with transmural inflammation and vessel wall destruction,[12] with the latter sometimes designated as Aß-related angiitis. Anecdotal experience has suggested that Aß-related angiitis, like other forms of vasculitis affecting the central nervous system,[26] might have a more aggressive course and require more potent immunosuppressive treatment than CAA-ri with perivascular inflammation only. Similar to prior studies,[5,7,11,12,27] the current study showed perivascular inflammation more often than vessel wall inflammation (58% vs 29%). A total of 22% of all patients with CAA-ri had acute infarcts (all less than 5-10 mm), 34% had T1 contrast enhancement (always involving leptomeninges), and 26% had CSF pleocytosis (along with elevated CSF protein in nearly all individuals). The current data provided only weak evidence for an association of these proposed neuroimaging and CSF markers with pathologically proven vasculitis, however, and no evidence for lower likelihood of improvement or higher risk of recurrence. The failure to identify stronger associations might be owing to the relatively small sample size (nonetheless representing the largest series of CAA-ri patients to date, to our knowledge). Another possible explanation is sampling error, as neuropathologic evidence of vessel wall involvement might be patchy[28] and therefore missed in a biopsy sample. Although further studies will be required to clarify this question, the current data do not suggest that neuroimaging, laboratory, or even neuropathologic data can identify CAA-ri cases with more aggressive disease courses.

We observed asymmetry in microbleed distribution, T2-hyperintense edema, and contrast enhancement, suggesting that CAA-ri tends to occur focally in an affected brain. Of the individuals with asymmetric T2 edema, microbleeds were more likely to be asymmetrically distributed in higher numbers on the side with more edema compared with the side with less edema. The mechanism for the observed focality could be focally greater vascular amyloid burdens or, alternatively, a focal predilection of the antiamyloid immune response. The mechanisms underlying the location and timing of CAA-ri, as well as the closely related process of amyloid-related imaging abnormalities observed in trials of antiamyloid immunotherapy,[29] remain active areas of ongoing research.[30]

The association between immunosuppressive therapy and decreased risk for recurrent disease flare raises questions about the determinants of CAA-ri recurrence. Previous analysis of CSF anti-β-amyloid autoantibodies showed elevated titers during active CAA-ri flares, with a return to background levels when the disease entered a remission phase.[3] Our data therefore raise the possibility that even a limited course of immunosuppressive therapy can delay or prevent recurrent elevations in anti-β-amyloid autoantibody production. We were unable to test this possibility directly, however, as most individuals did not have serial CSF samples, and anti-β-amyloid autoantibody measurements were not performed. We also considered the alternative explanation, suggested by the early separation of treated vs untreated curves on Kaplan-Meier analysis (Figure 2) that some episodes classified as CAA-ri recurrences were instead extended progression of single episodes and that immunosuppression functioned only to terminate these episodes rather than prevent future flares. Our sensitivity analysis showed essentially unchanged findings when excluding individuals with early recurrences (eTable 3 in the Supplement), however, suggesting a protective association with future independent disease flares. Formal statistical analyses of individuals whose CAA-ri recurred after a first episode despite treatment are limited given the small sample size (n = 9). Specific taper details were unavailable for 2 patients. Of the remaining 7, none experienced recurrence while treatment was being actively tapered. Two experienced recurrence within 3 months of taper completion, 3 within 3 to 6 months of taper completion, and 2 had late recurrences after being off treatment for 25.6 and 66.2 months.

Strengths and Limitations

This study has some strengths, including its relatively large sample size for this uncommon form of CAA, as well as detailed clinical, laboratory, pathology, and imaging analyses. Another strength of the data is the consistency of the association between receiving immunosuppressive treatment and multiple markers of improved disease course, including symptomatic improvement, neuroimaging improvement, and reduced risk of recurrence.

This study also has several notable limitations. Decisions about whether and how to treat with immunosuppression were at the treating physician's discretion rather than determined by a standardized protocol or randomized assignment. There is, therefore, potential confounding by indication such that individuals who were already likely to improve spontaneously might be the individuals who received treatment. We did not see evidence for systematic differences between treated and untreated individuals, however, as presentation with cognitive or behavioral symptoms was the only variable independently associated with receiving treatment. Another limitation is that relatively few individuals were treated with nonsteroidal agents, such as cyclophosphamide, mycophenolate, and rituximab, making it impossible to compare agents with each other. Individuals in our study also had various combinations of study procedures such as MRI scan, lumbar puncture, *APOE* genotyping, or neuropathologic examination (Table 1[23-25] and Table 2), reducing our ability to determine the association between results of these studies and disease course. Our data were obtained from a single referral center and a primarily white population, raising the question of generalizability to other settings. Furthermore, we cannot conclude that this cohort represents the entire CAA-ri spectrum, as milder cases may be less likely to be diagnosed and referred to our center. We finally note that blinding was implemented when possible, such as for imaging analyses, but could not be performed for all analyses given the nature of retrospective medical record review. For example, reviewing clinical notes to ascertain recurrence often unblinds the rater to treatment status. It will be important to confirm the current findings in prospective studies of standardized treatment regimens with clinical and radiographic assessments.

Given these limitations, it is premature to base firm treatment recommendations on the current data set. The data generally support a course of immunosuppressive therapy for individuals presenting with CAA-ri, however. The specific regimen used in many of the reported patients—intravenous methylprednisolone, 1 g, daily for 3 to 5 days followed by oral prednisone, 60 mg, daily tapered over months—appears reasonable. Other agents, such as cyclophosphamide or mycophenolate, can be considered as treatment for recurrent episodes, although the available data for these agents are sparse. The current data do not support use of a different immunosuppressive regimen for subsets of CAA-ri with more aggressive features in CSF or histopathologic findings. Surveillance brain MRI appears useful for detecting CAA-ri recurrences.

Conclusions

Within the limitations of the current nonrandomized data set, our study suggests that immunosuppressive treatment of patients with CAA-ri may confer not only a higher likelihood of clinical and imaging improvement but also reduced likelihood of symptomatic recurrence. Even patients receiving a short-term course of corticosteroids as their sole immunosuppressive treatment appeared to have a lower risk of CAA-ri recurrence. These results raise the possibility, to be confirmed in future prospective studies, that early blunting of CAA-related inflammation and autoimmune responses may have long-term benefits for the subsequent disease course.

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