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CLINICAL RESEARCH

Role of C5 inhibition in Idiopathic Inflammatory Myopathies and Scleroderma Renal Crisis–Induced Thrombotic Microangiopathies

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Introduction: Connective tissue diseases, including systemic sclerosis and idiopathic inflammatory myopathies (IIMs), are a very rare cause of thrombotic microangiopathies (TMAs). Whether dysregulation of the complement pathways underlies these secondary forms of TMA and may be targeted by complement blocking agents remains elusive.

Methods: Kidney pathology and outcomes of 18 critically ill patients with TMA related to inflammatory myopathy flare-up (IIM, n=7) or scleroderma renal crisis (SRC, n=11; biopsy n=9) are assessed.

Results: IIM-TMA is characterized by acute thrombotic lesions only, whereas SRC-TMA patients also harbored chronic vascular lesions and more interstitial fibrosis. C5b9 deposits, a marker of complement component 5 (C5) cleavage, were observed in the 2 subgroups at the junction of media and intima of arterioles, colocalizing with subendothelial edema. Thus, kidney biopsy distinguished between acute and chronic renal phenotypes that may help to individualize treatment. Treatment of IIM-TMA patients with combined full-code organ support, corticosteroids, B-cell depletion, and complement C5 blocking led to 1-year survival of 72%, compared with 19% in historical cohorts. Treatment of SRC-TMA was more heterogenous and relied on conversion enzyme inhibitor only or with eculizumab (n=6) and immunosuppressor (n=5). One-year survival of SRC-TMA patients was 52%, a result similar to historical cohorts. Eculizumab was followed by a rapid dramatic improvement of TMA in all the treated patients.

Conclusion: C5 blocking may reverse hematologic abnormalities in IIM- and SRC-TMA, and adding an early and aggressive immunosuppressive regimen may improve the survival of IIM-TMA. Underlying chronic vascular and interstitial lesions mitigate renal response in SRC-TMA.

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Thrombotic microangiopathies (TMAs) are rare, heterogeneous, and life-threatening diseases.[1] TMA can be divided into immune thrombotic thrombocytopenic purpura (TTP) and primary or secondary hemolytic and uremic syndromes (HUSs). Whereas immune TTP is related to deficiency of A disintegrin and metalloprotease with thrombospondin type I repeats-13 (ADAMTS13), and typical HUS is observed in patients developing infection by Shiga toxin–producing enterobacteria, inherited or acquired abnormalities of the alternative complement pathway with subsequent uncontrolled complement C5 cleavage and C5b9 membranous attack complex formation were identified in many patients with atypical HUS.[2]

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However, the role of complement in secondary HUS remains elusive.[3]

Connective tissue diseases (CTDs) are a group of heterogeneous autoimmune diseases characterized by overlapping clinical symptoms, and include systemic sclerosis (SSc), IIM, Sharp syndrome and antisynthetase syndrome. In patients with SSc, standard immunosuppressive regimens often give disappointing results with the exception of autologous hematopoietic stem cells transplantation. Some success has also been reported for intravenous pulses of cyclophosphamide that may improve organ outcomes in a subset of patients.[4] In contrast, most mildly to moderately ill IIM patients respond to immune modulation with corticosteroids, intravenous immunoglobulin, methotrexate, rituximab or cyclophosphamide, but frequently with a delayed response.[5,6]

CTD is the cause of 1% to 2% of TMA/HUS,[7] but accurate description of this very rare association remains scarce precluding individualized and optimal management. Among CTD-related TMA, SRC was the most frequently described. SRC is characterized by severe hypertension with features of TMA and rapidly progressive renal failure related to vascular lesions (fibrointimal sclerosis with lumen narrowing). In SRC, converting enzyme inhibitors may halt the progression of renal failure but no immunosuppressive regimen significantly alters the prognosis.[8] Steroids can even induce or worsen the prognosis of SRC patients. The role of complement in scleroderma is still elusive but eculizumab, a C5-blocking agent, has emerged as a potential treatment of refractory SRC-TMA.[9–12]

We and others also previously reported single cases in whom eculizumab reversed IIM-TMA,[13,14] suggesting that targeting complement may improve the otherwise poor prognosis of this disease.[15] However, because CTD flare-up can lead to concomitant TMA and disease-specific systemic disorders (for instance, interstitial lung disease–related respiratory failure and myocarditis), their management in the setting of intensive care unit remains challenging and deserves further attention.

In this study, we aimed to characterize the presentation and outcome of CTD-related TMA and to highlight the role of complement activation and the validity of the use of complement-blocking agents in this rare and life-threatening association.

METHODS

In this retrospective study, we included all the adult patients with CTD referred to the Department of Nephrology and Organ Transplantation for TMA between January 2013 and June 2020. Patients with immune TTP or Shiga toxin–dependent HUS were excluded. The investigation conforms to the principles outlined in the Declaration of Helsinki. According to French law on ethics and the Institutional Review Board of the Toulouse University Hospital (Direction de la Recherche Clinique et de l'Investigation), patients were informed that their codified data will be used for the study.

Diagnosis of TMA relied on the association of mechanical hemolytic anemia (undetectable haptoglobin, more than 1% of schistocytes, and elevated serum levels of lactate dehydrogenase), peripheric thrombocytopenia, and negative Coombs test. Because some patients did not have tissue biopsy, meeting the histologic criteria for TMA was not mandatory.

Diagnostic criteria for CTD relied on the 2017 (IIM) and 2013 (SSc) EULAR/ACR classifications. Clinical data included demographic profile and routine clinical and laboratory findings that were obtained from medical records.

Processing of renal biopsies included light microscopy and immunofluorescence. For light microscopy, all cases were stained with hematoxylin and eosin, periodic acid-Schiff, Masson trichrome, and Jones methenamine silver. For immunofluorescence, 0.3-μm cryostat sections were stained with polyclonal antibodies to IgG, IgM, IgA, C3, C1q, C5b9, kappa, lambda, fibrinogen and albumin-FITC (rabbit, polyclonal; Agilent, Santa Clara, CA).

Continuous variables are expressed as medians and ranges and compared with the Mann-Whitney test. Discontinuous variables are expressed as numbers and percentages and compared with the Fisher exact test.

RESULTS

Over the 7 years of inclusion period, 18 patients with a diagnosis of IIM or SRC-TMA were referred to our intensive care renal unit: 7 had IIM (antisynthetase syndrome, n=4; overlap syndrome, n=1; dermatomyositis, n=2) and 11 had SSc (Table 1). Diagnosis of the CTD preceded TMA in 8 (44%) patients. Acute organ involvement included myocarditis (n=7, 39%) or pericardial effusion (n=2, 11%), interstitial lung disease (n=11, 61%), or acute kidney injury KDIGO stages 2-3 (n=18, 100%). Renal replacement therapy and mechanical ventilation were required in 10 (61%) and 6 (28%) patients, respectively. At the admission, the median simplified acute physiology score SAPS2 was 30 (interquartile range [IQR] 19–50) (no difference between IIM and SSc patients). Systolic pulmonary artery pressure was measured in 17 patients (cardiac ultrasonography) and was higher than 30 mm Hg in 7 patients, including 5 who subsequently received eculizumab (median 70 mm Hg [IQR 35–77]).

Table 1. Characteristics and outcomes of 18 critically ill patients with scleroderma renal crisis– or idiopathic inflammatory myopathies–thrombotic microangiopathy

				Organ support		Kidney biopsy		Treatments		Follow-up		
Gender	Age, yr	Immune disease (antibodies)	Organ involvements	MV	RRT	Acute/chronic vascular lesions	C5b9 deposits	Specific	Additional	Length, d	RRT	Alive
F	42	Antisynthetase (anti-PMScl)	Lung, heart, joints, skin	No	No	Yes/No	Yes	Eculi, Cst	—	75	No	No
F	62	Antisynthetase (anti-PMScl)	Lung, PHT, joints, skin, muscles	No	No	Yes/No	Yes	RTX, Eculi, Cst, CEI	—	500	No	Yes
F	64	Antisynthetase (anti-PL12)	Lung, PHT, Raynaud	No	Yes	Yes/No	NA	RTX, Eculi, Cst	10 PEx	1425	Yes	Yes
M	59	Antisynthetase (anti-PMScl, anti-DNA, anti-SSA, anti-CCP)	Lung, heart, joints, muscles, skin	Yes	Yes	Yes/No	NA	RTX, CYC, Cst	17 PEx, IVIg TCZ (MAS)	2389	Yes	Yes
F	59	Dermatomyositis (paraneoplastic; seronegative)	Muscles, skin	No	Yes	Yes/No	Yes	RTX, Eculi, Cst	7 PEx	473	Yes	Yes
F	19	Dermatomyositis (seronegative)	Heart, joints, muscles, skin	Yes	Yes	Yes/No	None	RTX, Eculi, Cst	4 PEx	905	No	Yes
F	67	Sharp syndrome (anti-U1-RNP)	Lung, muscle, skin	Yes	Yes	Yes/No	None	RTX, Eculi, Cst	2 PEx TCZ (MAS)	37	Yes	No
F	73	Scleroderma (anti-TRIM21, anti-RNAPol3)	Lung, heart, muscle	Yes	Yes	NA	NA	RTX, Eculi, Cst	2 PEx	19	Yes	No
M	57	Scleroderma (antitopoisomerase)	Skin, joints	No	Yes	NA	NA	Bosentan, CEI	—	195	Yes	No
M	80	Scleroderma (anti-RNAPol3)	Lung, skin, gut	Yes	Yes	Yes/Yes	NA	RTX, Eculi	—	29	Yes	No
F	44	Scleroderma (anti-RNAPol3)	Heart, skin, joints	Yes	No	Yes/No	Yes (mild)	Eculi, CEI	—	58	Yes	No
F	38	Scleroderma (anticentromeres, anti-RNAPol3)	Liver, skin	No	No	Yes/Yes	NA	CEI	—	1022	No	Yes
F	76	Scleroderma (antitopoisomerase)	Lung, heart, joints	No	Yes	Yes/No	NA	CEI	PEx, Cst, Etop. (MAS)	33	Yes	Yes
M	47	Scleroderma (anti-RNAPol3)	Lung, joints, skin	No	No	Yes/No	NA	CEI	—	2513	No	Yes
M	69	Scleroderma (anti-RNAPol3)	Skin	No	No	No/Yes	Yes	CEI	—	60	Yes	Yes
F	64	Scleroderma (anti-RNAPol3)	Lung, heart, skin	No	No	Yes/Yes	Yes	CYC, Eculi, CEI	—	210	No	Yes
F	80	Scleroderma (anti-RNA-Pol3)	Heart, skin	No	Yes	Yes/Yes	Yes (mild)	RTX, Eculi, CEI	4 PEx	300	Yes	Yes
F	43	Scleroderma (antifilaggrin)	Heart, skin	No	No	Yes/No	NA	CYC, Eculi, CEI	—	30	No	Yes

CEI, converting enzyme inhibitor; Cst, corticosteroids; CYC, cyclophosphamide; Eculi, eculizumab; Etop., etoposide; F, female; M, male; MAS, macrophage activation syndrome; MV, mechanical ventilation; PEx, plasma exchange; PHT, pulmonary hypertension; IVIg, intravenous immunoglobulin; RRT, renal replacement therapy; RTX, rituximab; TCZ, tocilizumab.

Median hemoglobin level and platelet counts were 94 (IQR 7–13.9) g/l and 99 × 10^3 (IQR 49–221)/mm^3, respectively. All patients had undetectable haptoglobin and schistocyte counts greater than 1%. No patient had ADAMTS13 deficiency and neither circulating anti-ADAMTS13 IgG, ruling out immune TTP. Search for anti–factor H antibodies was negative and, in 2 patients, molecular screening by next-generation sequencing ruled out pathogenic variations in the genes coding for proteins regulating the alternative complement pathway (*C3*, *CFI*, and *CFH* genes). At admission, serum levels of complement C3, C4, or both were decreased in 4 patients. Serum level of C1q was not available.

Kidney Pathology

A kidney biopsy was obtained in 16 patients (IIM-TMA n = 7/7, SRC-TMA n = 9/11; Figure 1 and Table 1) and showed common features but also striking differences between IIM- and SRC-TMA. Moderate to severe arteriolosclerosis was observed in 5 of 9 SRC-TMA cases (55%), compared with 0 of 7 in IIM-TMA (0%) (P = 0.04). Proliferative endarteritis with narrowing of the vascular lumen was observed in only 1 SRC patient. In contrast, acute thrombosis in small and medium-size arteries were observed in 8 of 9 SRC (89%) and 7 of 7 IIM-TMA patients (100%). Mild to frank C5b9 deposits were observed within the arterioles of 7 of the 9 tested patients (78%) (Figure 1). C5b9 deposits were located at the junction of media and intima (SRC 4/5, IIM 3/4), where optical examination showed fibro-intimal edema. C3 deposits were also observed within the vascular wall in 5 biopsies and within vascular thrombosis in 4.

Signs of glomerular TMA (thrombosis, capillary wall thickening, and double contouring of the loop wall) were observed in 4 of 7 IIM-TMA (57%) and 3 of 8 SRC-TMA patients (38%). Ischemic glomeruli were seen in all patients. Glomerular staining for IgA, IgG, IgM, C3, and C5b9 was negative in all patients. Severity of the glomerulosclerosis was mild to moderate (median of sclerosed glomeruli 7% [0%–13%]) and similar in both groups.

Scarring interstitial fibrosis was more severe in SRC-TMA (median area 15% [0%–20%] vs. 0% [IQR 0%–5%], P = 0.10). Interstitial inflammation was mild or absent in all patients.

Treatments

Patients with IIM-TMA received a combination of rituximab (375 mg/m^2 weekly for 4 weeks) plus

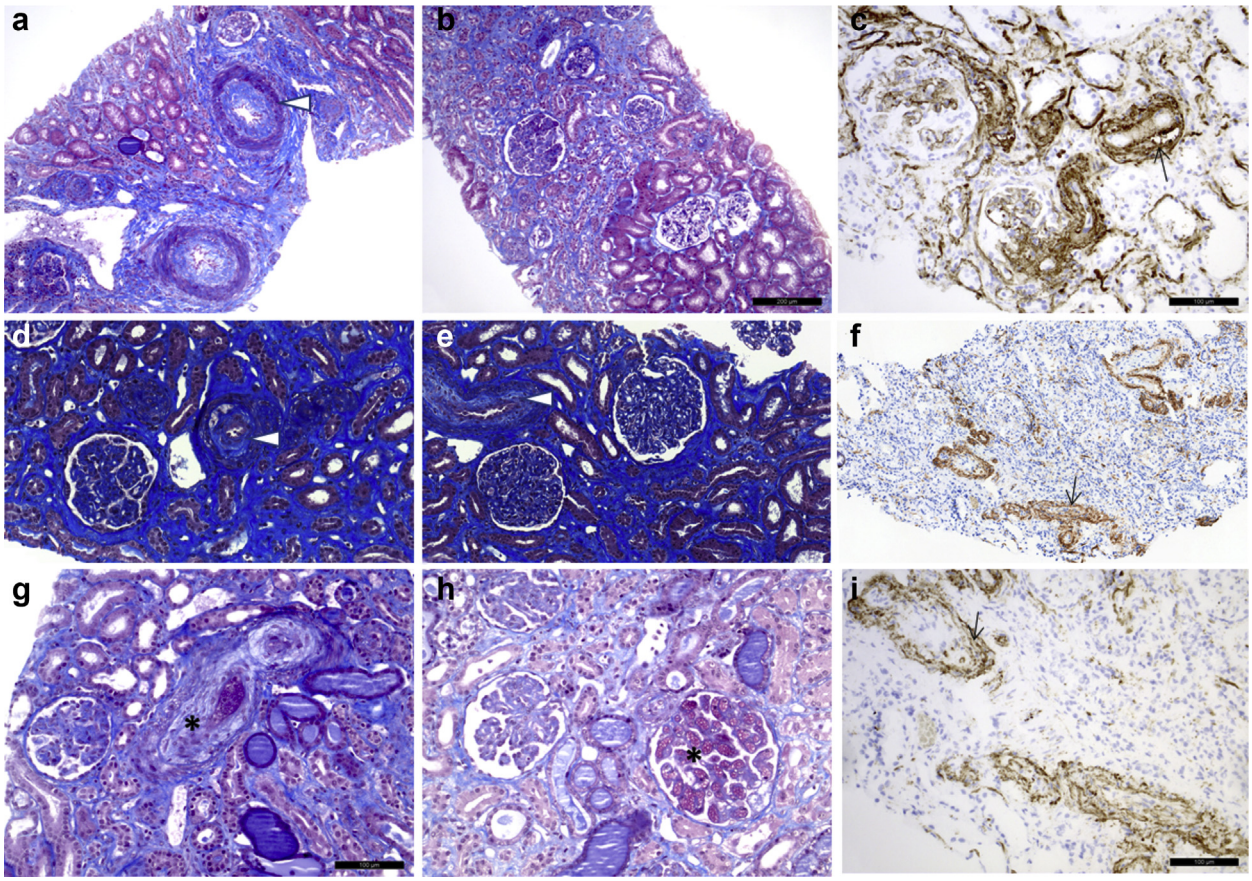

Figure 1. Kidney pathology in scleroderma renal crisis (SRC)– or idiopathic inflammatory myopathy (IIM)–thrombotic microangiopathy (TMA). (a–c) SRC-TMA: (a) Masson trichrome staining; proliferative endarteritis with narrowing of the vascular lumen (arrow). (b) Masson trichrome staining; area of interstitial fibrosis (patchy fibrosis). (c) C5b9 deposits (brown coloration) around tubules and at the intima-media junction (arrow). (d–f) SRC-TMA: (d, e) Masson trichrome staining; subendothelial edema (arrow). (f) C5b9 staining showing deposits at the intima-media junction. (g–i) IIM-TMA (seronegative dermatomyositis): (g) Masson trichrome staining. (*Arteriolar thrombosis.) (h) Masson trichrome staining; ischemic glomeruli. (i) C5b9 staining (arrow) shows deposits at the intima-media junction.

eculizumab ($n = 5$), eculizumab plus converting enzyme inhibitor ($n = 1$) or cyclophosphamide plus plasma exchanges ($n = 1$). Five patients who received eculizumab also had 2 to 10 plasma exchanges before infusion. In addition, all patients received glucocorticoids (1–2 mg/kg/d) and 2 patients received the IL6-R inhibitor tocilizumab (8 mg/kg once) during their hospitalization because of secondary hemophagocytic syndrome.

Treatments of the 11 patients with SRC combined converting enzyme inhibitor ($n = 9$), eculizumab ($n = 6$), plasma exchange ($n = 2$), corticosteroids ($n = 1$), rituximab ($n = 2$), cyclophosphamide ($n = 2$), or bosentan ($n = 1$). One patient also received corticosteroids and etoposide because of hemophagocytic syndrome.

Eculizumab was given at a dose of 900 mg once weekly for 4 weeks then followed by 1200 mg bimonthly.

In patients surviving to the TMA episode, eculizumab was pursued until TMA remission and for a minimal length of 4 weeks. Owing to its retrospective nature, the timing of eculizumab was not standardized (median number 6 pulses [IQR 1–14] over a median time of 2 months [IQR 0.5–5.5]). All patients receiving

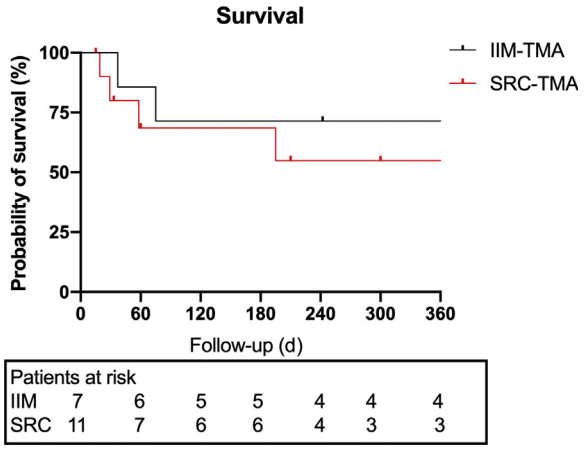

Figure 2. Survival curves in 18 patients with scleroderma renal crisis– or idiopathic inflammatory myopathy–thrombotic microangiopathy. IIM, idiopathic inflammatory myopathies; SRC, scleroderma renal crisis.

eculizumab also received prophylaxis with ceftriaxone for 1 month and antipneumococcal and antimeningococcal vaccine. Cotrimoxazole was also proposed to all patients receiving cyclophosphamide or long-term corticosteroids.

Outcomes

At month 12, survival was 52% in SRC-TMA compared with 72% in IIM-TMA ($P = 0.43$; Figure 2). Causes of death were infection-related multiorgan failure in 2 patients and cardiac arrest related to refractory TMA or interstitial lung disease–related respiratory failure in 2 and 1, respectively. Three of the 5 patients who required mechanical ventilation at the admission ultimately died.

Median time from the admission to the first pulse of eculizumab was 5 days (IQR 1-20) in IIM-TMA patients. Eculizumab was followed by normalization of haptoglobin and dramatic rise of platelets in the 7 days following administration (Supplementary Figure S1), except in 1 patient with concomitant macrophage activation syndrome. In 2 patients, eculizumab was also followed by rapid improvement of a severe Raynaud syndrome, formerly resistant to plasma exchanges. In 1 patient, TMA relapsed 21 days after the initiation of eculizumab and subsequently led to cardiac arrest 3 weeks later. Of note, 3 of the 5 patients who survived to the episode of IIM-TMA reached end-stage kidney failure at 1 year. In the 3 patients who required mechanical ventilation and survived, length of the respiratory support was 6, 37, and 65 days. None developed progressive lung fibrosis or chronic respiratory failure.

In the 6 SRC-TMA patients who received eculizumab (median time from admission 6 days [IQR 2-14]), complete normalization of the hematologic parameters was observed following the administration. One patient among the 3 who received eculizumab and survived the SRC-TMA episode ultimately reached end-stage kidney failure at 1 year. One of the 6 patients who did not receive eculizumab died (day 195), and 3 reached end-stage kidney failure. Four SRC-TMA patients received mechanical ventilation and 3 died.

The course of pulmonary hypertension was assessed in only 5 patients: the systolic pulmonary artery pressure decreased in 2 of 2 patients who did not receive eculizumab and in 2 of 3 who received it.

DISCUSSION

In this study, we included severely ill patients with IIM or SRC and TMA. Organ dysfunction included acute respiratory failure, cardiac dysfunction or tamponade, and acute kidney injury. Despite its retrospective design, our study emphasized several key points for the management of critically ill patients with these rare and life-threatening forms of TMA. Common patterns of C5b9 deposits within arteriolar walls were also identified.

First, 1-year survival of IIM-TMA patients (72%) was significantly higher in our series compared with previous cohorts that included patients with polymyositis/dermatomyositis-TMA (19%)[16] or mixed SRC- and IIM-TMA (57%).[17] This increased survival was not observed in SRC-TMA patients. Most IIM-TMA patients received a combination of eculizumab (a C5 inhibitor) and intensive immunosuppressive regimen, including corticosteroids and B-cell depletion with rituximab. In a recent review, Moghadam-Kia *et al*. discussed the role of new biologic agents in the management of inflammatory myopathies and suggested that rituximab and eculizumab may be used as salvage therapy or corticosteroid-sparing agents.[5] For example, although in a randomized controlled trial testing rituximab in IIM the primary outcome was not met, a significant improvement was observed in patients with refractory disease.[18] The use of eculizumab in IIM also emerged owing to the identification of the role of C5 cleavage and C5b9 deposits on the endothelial cells within inflamed muscles.[19] Eculizumab may thus target both complement-dependent IIM lesions and TMA. Our findings suggest that the combination of corticosteroids, rituximab, and eculizumab is a promising therapy that could rapidly control the inflammatory and endothelial processes underlying IIM flare-up with TMA. By reducing the need of mechanical ventilation in patients with interstitial lung disease, early identification of patients with active IIM CTD (i.e., before the development of TMA) may also improve their global outcome. In SRC patients, the role of eculizumab is more controversial. When considering TMA as a primary endpoint, we observed a complete normalization of hematologic parameters following administration of eculizumab, confirming preliminary data.[9,10] Improvement started as soon as day 1 in some patients. The survival discrepancy between IIM and SRC-TMA could thus be more related to response of the CTD to immunomodulation rather than response of the TMA.

In the 11 SRC-TMA patients included in this cohort, renal outcome remains poor (7 patients received RRT at the end of follow-up), including in patients receiving eculizumab. Studying kidney biopsies, we observed that SRC-TMA was characterized by mixed acute (culminating in arterial thrombosis) and chronic (arteriolosclerosis) vascular lesions. This was in sharp contrast with the findings observed in kidney biopsies of IIM-TMA patients, in which no chronic vascular lesions were observed. This finding was unexpected because chronic vascular lesions and severe hypertension were frequently reported in a large cohort of IIM

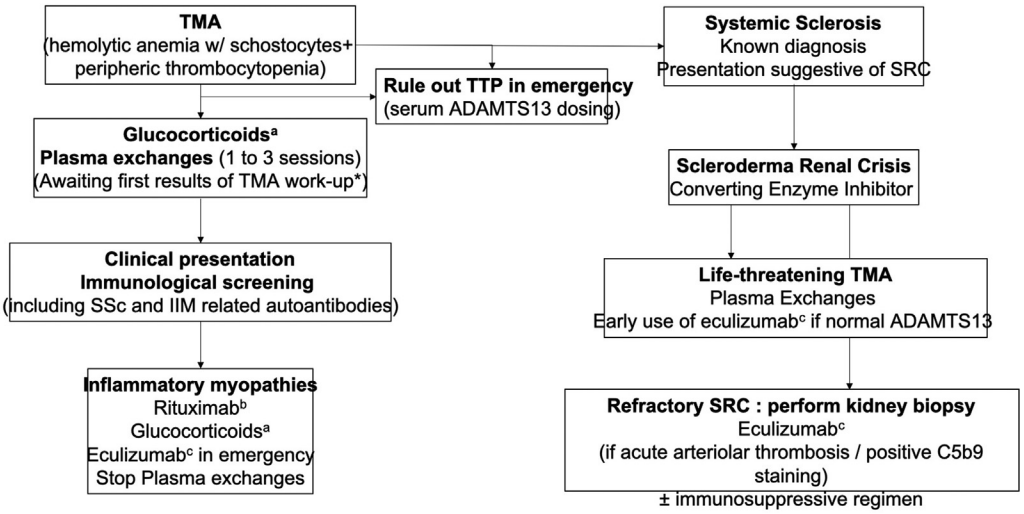

Figure 3. Proposed treatment algorithm for scleroderma renal crisis– and idiopathic inflammatory myopathy–thrombotic microangiopathy: (a) methylprednisolone 1 mg/kg/d with progressive tapering; (b) rituximab 375 mg/m^2 weekly for 4 weeks followed by biannual maintenance doses according to clinical response; (c) eculizumab 900 mg weekly for 4 weeks followed by 1200 mg bimonthly for 1 to 2 months according to hematologic and kidney responses. IIM, idiopathic inflammatory myopathies; SSc, systemic scleroderma; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

patients published in 2015.[20] In this latter study, no patient had TMA and the immune disease evolved for several months to years, suggesting that IIM-TMA may be rather secondary to a flare-up of the immune disease with subsequent endothelial dysfunction, than related to a progressive arteriolopathy. This also suggests that IIM- and SRC-TMA should be distinguished when studying renal outcomes.

Whereas current therapy may fail to reverse chronic vascular lesions, acute lesions including TMA may be targeted by specific treatments. Thereafter, SRC cases should be divided into narrowly defined SRC and SSc-associated TMA to individualize its management, as recently proposed by Yamashita *et al.*,[21] and to improve the prognosis that remained unfortunately constant over the last years.[8] In the present study, we observed a dramatic improvement of the TMA (i.e., hematologic parameters) following eculizumab (normalization of platelets count at day 7 in all but 1 patient) but inconstant renal and cardiac response, as already reported.[10] In our opinion, these findings should prompt to test in a larger cohort of SRC-TMA patients with acute lesions whether an aggressive treatment combining organ support, early eculizumab, and immunosuppression (e.g., cyclophosphamide) can target the various underlying endothelial, inflammatory, and immunologic mechanisms and improve the outcomes of the most severe patients. A treatment algorithm is proposed in Figure 3.

This study is one of the largest published in the field but has several limitations, including its retrospective nature, the small number of patients, the lack of a control group, and the confounding effects of other treatments. Response to eculizumab of pulmonary hypertension could not be adequately assessed (concomitant fluid overload, no right heart catheterization, no systematic monitoring) and will require further characterization. Especially, TMA may account for pulmonary hypertension in this setting. Last, the length of eculizumab use was not standardized in this retrospective study. Given the deposits of C5b9 within vessels, whether prolonged C5 blocking, irrespective of TMA activity, may improve organ outcomes remains to be addressed.

In summary, we showed that IIM-TMA kidney pathology differs from SCR-TMA and that a combination of B-cell depletion and C5 inhibition may improve the outcomes of IIM-TMA, even in the most critically ill individuals (Figure 2). C5 inhibition also controlled TMA in patients with SRC but the best complementary immunosuppressive regimen remains unknown.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Platelet counts before and 7 days after eculizumab.

STROBE checklist.

REFERENCES

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371:654–666.
2. Fakhouri F, Zuber J, Frémeaux-Bacchi V, Loirat C. Haemolytic uraemic syndrome. *Lancet*. 2017;390:681–696.
3. Le Clech A, Simon-Tillaux N, Provôt F, et al. Atypical and secondary hemolytic uremic syndromes have a distinct

presentation and no common genetic risk factors. *Kidney Int*. 2019;95:1443–1452.

4. Van Bijnen S, De Vries-Bouwstra J, Van Den Ende CH, et al. Predictive factors for treatment-related mortality and major adverse events after autologous haematopoietic stem cell transplantation for systemic sclerosis: Results of a long-term follow-up multicentre study. *Ann Rheum Dis*. 2020;79:1084–1089.
5. Moghadam-Kia S, Aggarwal R, Oddis CV. Biologics for idiopathic inflammatory myopathies. *Curr Opin Rheumatol*. 2017;29:645–651.
6. Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguás E, et al. Classification and management of adult inflammatory myopathies. *Lancet Neurol*. 2018;17:816–828.
7. Bayer G, Von Tokarski F, Thoreau B, et al. Etiology and outcomes of thrombotic microangiopathies. *Clin J Am Soc Nephrol*. 2019;14:557–566.
8. Woodworth TG, Suliman YA, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. *Nat Rev Nephrol*. 2016;12:678–691.
9. Uriarte MH, Larrarte C, Rey LB. Scleroderma renal crisis debute with thrombotic microangiopathy: a successful case treated with eculizumab. *Case Reports Nephrol*. 2018;2018:6051083.
10. Devresse A, Aydin S, Le Quintrec M, et al. Complement activation and effect of eculizumab in scleroderma renal crisis. *Medicine (Baltimore)*. 2016;95:e4459.
11. Okrój M, Johansson M, Saxne T, et al. Analysis of complement biomarkers in systemic sclerosis indicates a distinct pattern in scleroderma renal crisis. *Arthritis Res Ther*. 2016;18:267.
12. Benbassat C, Schlesinger M, Luderschmidt C, et al. The complement system and systemic sclerosis. *Immunol Res*. 1993;12:312–316.
13. Faguer S, Belliere J, Ribes D. Complement c5-blocking agent in refractory dermatomyositis. *J Rheumatol*. 2018;45:1710–1711.
14. Cianciolo G, Cozzolino M. Eculizumab for rescue of thrombotic microangiopathy in PM-Scl antibody-positive autoimmune overlap syndrome. *Clin Kidney J*. 2016;9:665.
15. Yamada S, Giachelli CM. Vascular calcification in CKD-MBD: roles for phosphate, FGF23, and Klotho. *Bone*. 2017;100:87–93.
16. Yamada S, Yamashita H, Nakano M, et al. Thrombotic microangiopathy with polymyositis/dermatomyositis: three case reports and a literature review. *Intern Med*. 2018;57:2259–2265.
17. Matsuyama T, Kuwana M, Matsumoto M, et al. Heterogeneous pathogenic processes of thrombotic microangiopathies in patients with connective tissue diseases. *Thromb Haemost*. 2009;102:371–378.
18. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis: A Randomized, Placebo-phase Trial. *Arthritis Rheum*. 2013;65:314–324.
19. Lahoria R, Selcen D, Engel AG. Microvascular alterations and the role of complement in dermatomyositis. *Brain*. 2016;139:1891–1903.
20. Couvrat-Desvergnes G, Masseau A, Benveniste O, et al. The spectrum of renal involvement in patients with inflammatory myopathies. *Medicine (Baltimore)*. 2014;93:33–41.
21. Yamashita H, Kamei R, Kaneko H. Review Classifications of scleroderma renal crisis and reconsideration of its pathophysiology. *Rheumatology (Oxford)*. 2019;58:2099–2106.