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ORIGINAL ARTICLE

Combination therapy for Sneddon syndrome to reduce the incidence of cerebrovascular complications

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Summary

Background: Sneddon syndrome is an occlusive vasculopathy that presents clinically with generalized livedo racemosa on the skin and transient ischemic attacks, strokes, and cognitive or motor deficits in the central nervous system. Antiplatelet or anticoagulant therapy is recommended. Due to the limited therapeutic efficacy and the resulting serious complications, we propose combination therapy with additional infusion cycles of alprostadil and captopril and report initial long-term results.

Patients and methods: We performed a systematic retrospective analysis of all patients with primary Sneddon syndrome who received combination therapy in our clinic between 1995 and 2020. Therapeutic outcomes were evaluated using descriptive statistics compared to historical controls receiving monotherapy. We also analyzed the event rate of complications when combination therapy was discontinued.

Results: During the 99.7 patient-years of follow-up, there were no transient ischemic attacks and the stroke rate dropped to 0.02 per patient-year. In comparison, the rates of transient ischemic attacks and strokes in the historical controls ranged from 0.08 to 0.035 per patient-year. After discontinuation of alprostadil therapy, eight events occurred in three patients.

Conclusions: Combination therapy reduces the long-term incidence of ischemic events in patients with primary Sneddon syndrome.

KEYWORDS
alprostadil, antiplatelet drugs, livedo racemosa, occlusive vasculopathy, prostanoids, Sneddon syndrome

INTRODUCTION

Sneddon syndrome (SS) is a rare disease with an estimated annual incidence of approximately 1/250,000 (ORPHA:820). SS is understood to be a clinical form of thrombotic and thus occlusive microangiopathy, which manifests in the clinical phenotype on the skin as a non-thermoreactive, generalized livedo racemosa (Figure 1). The pathogenesis of SS remains unclear, but it is thought to involve processes in the arterial wall structure, including increased myocyte proliferation in the intima, and thrombophilic processes in areas of slow blood flow (Figure 2).[1,2] It is unclear whether histologically described inflammatory processes in the vessel wall are causally relevant.[3] Thrombotic events can also result in functional disorders in the central nervous system, presenting as motor deficits, cognitive impairment, transient ischemic attacks (TIAs), and polyneuropathy in the peripheral nervous system.[4] SS is usually sporadic,

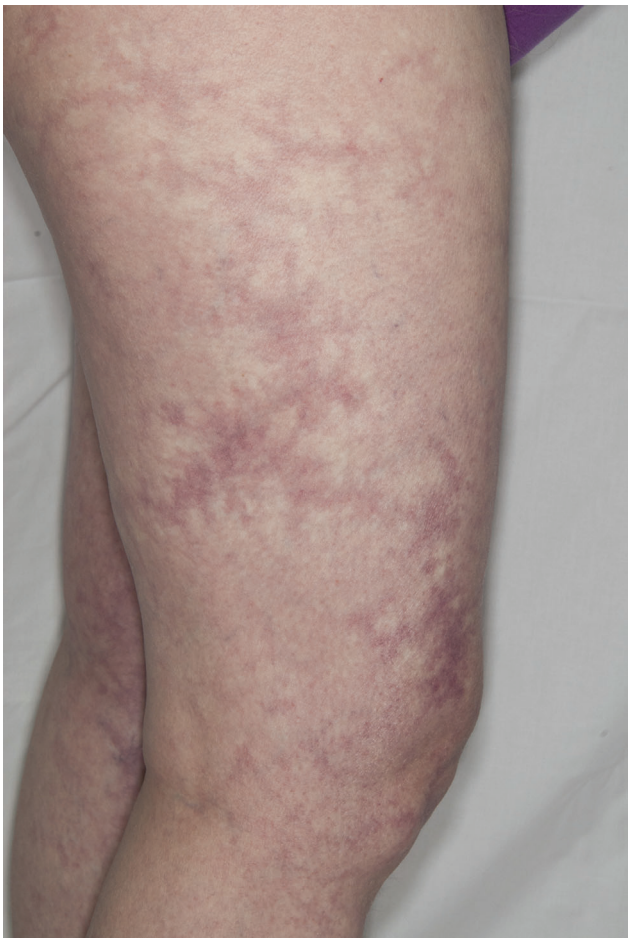

FIGURE 1 Typical clinical findings of livedo racemosa in primary Sneddon syndrome.

but familial clustering has been reported, suggesting a genetic predisposition, and candidate genes have been identified.[5,6] According to Schellong, in addition to primary idiopathic SS, there are secondary forms associated with antiphospholipid antibody syndrome (APS) or other thrombophilic diseases.[7] In general, and without adequate therapy, the prognosis *quoad vitam* and *quoad functionem* is poor. Mortality is reported to be 9.5% at 6.2 years and 23% at 9 years.[8,9] In addition, half of those affected suffer from relevant neurological impairments and 15% become dependent on care during the course of their illness.

To date, there are no prospective, randomized, controlled trials on the treatment of SS. Some retrospective cohort studies show a reduction in central ischemic events with antiplatelet or anticoagulant therapy.[10–12] Due to presumed equal efficacy with a more favorable safety profile, platelet aggregation inhibitors are preferred in APS-negative patients with SS.[10–13] The use of immunosuppressive therapies, on the other hand, shows no efficacy and notably fails to objectively prevent strokes.[13–16]

Against this background, the concept of a combination therapy consisting of inhibition of platelet aggregation by clopidogrel, improvement of hemorheology by alprostadil and inhibition of myocyte proliferation by captopril was developed as early as 2001.[17–21] With this combination therapy, no increase in cutaneous symptoms and no new onset of neurological deficits were observed in a total of five patients over a period of up to 5 years.[17] This prompted us to retrospectively analyze this combination therapy in a larger patient population and over a longer observation period.

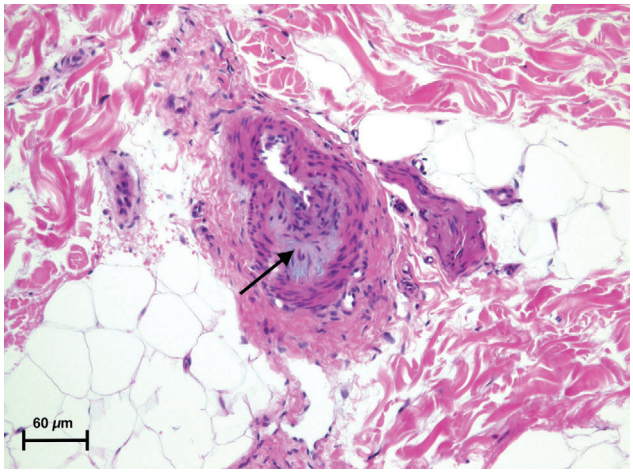

FIGURE 2 Hematoxylin-eosin stain. Histologic findings in a skin biopsy showing cushion-like subendothelial proliferation of smooth muscle cells and formation of an occluding arteriole.

PATIENTS AND METHODS

For a structured retrospective analysis of treatment outcomes in patients diagnosed with primary SS who were treated with combination therapy at the Department of Dermatology and Venerology at the Martin Luther University Halle-Wittenberg between 1995 and 2020, all diagnostic and treatment data were first recorded. The following parameters were defined as inclusion criteria for the analysis: *(1)* confirmation of the diagnosis of SS by the presence of livedo racemosa generalisata (LR), *(2)* presence of a history of TIA or stroke or MRI findings of cerebral occlusive microangiopathy (infarcts, microbleeds, changes in white matter, or atrophy), *(3)* presence of skin biopsy with evidence of arteriolar occlusion or intimal proliferation and exclusion of relevant differential diagnoses, *(4)* absence of antiphospholipid (aPL) antibodies, *(5)* exclusion of collagenosis (SLICC criteria).[22] In addition, a combination therapy concept (triple therapy) with a platelet aggregation inhibitor (ticlopidine 2 x 250 mg/d, acetylsalicylic acid 100 mg or clopidogrel 1 x 75 mg/d or anticoagulation with Marcumar), hemorheological therapy by infusion cycles with alprostadil 60 µg in 250 mL physiological saline solution (0.9% NaCl) once a day for 4 weeks per cycle (at least once a year) and myocyte proliferation inhibition with captopril 1 x 50 mg (alternatively an angiotensin II receptor subtype 1 antagonist [sartans] in case of intolerance[23]).

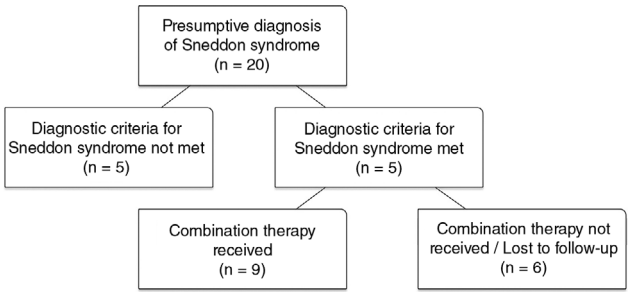

FIGURE 3 Flow chart for sample characterization of the patient population with suspected Sneddon syndrome.

As part of the treatment cycles, all patients underwent routine general medical, dermatological and neurological examinations. In addition, cranial MRI scans were performed as baseline or in cases of suspected focal cerebral symptoms and were repeated at least once for each patient during the course of treatment to monitor progress.

Data analysis was performed retrospectively with the approval of the local ethics committee (Medical Faculty of the Martin Luther University Halle-Wittenberg, vote no. 2019/139). The data were processed using descriptive statistics and defined subgroups were analyzed using Kaplan-Meier survival curves and Cox regression.[24] Events in the triple therapy periods were compared intraindividually with those in which alprostadil therapy was discontinued. The age-related white matter changes scale (ARWMC) has been used to quantify pathologic changes in the white matter of the brain. White matter lesions (WML) are considered a radioneurological risk factor for stroke, cognitive impairment, and increased mortality.[25,26] Vascular WMLs are attributed to chronic reduced blood flow, among other factors.[27,28] They typically occur bilaterally or symmetrically. As the total volume of WML increases, the risk of neurological deficits, dementia, and death increases.[29,30] The presence of arterial hypertension is considered an independent risk factor for the development of WML. White matter lesions also occur in patients with SS and are considered a possible progression parameter.[31] Therefore, the frequency of occurrence in the general population is taken into account in the evaluation of the cohort studied.[32,33] In addition, the Montreal Cognitive Assessment (MoCA) was used to record cognitive impairments and the Modified Ranking Scale (mRS) to assess the degree of disability.[34]

RESULTS

Clinical data

A total of 15 patients were identified who met our criteria for Sneddon syndrome. Of these, nine female patients received triple therapy over an extended period and thus met our inclusion criteria (Figure 3). All patients were primarily characterized by livedo racemosa. The mean age at diagnosis was 42.1 years (Table 1). The first CNS ischemic events were observed at a mean of 8 years after disease onset. The mean age at treatment initiation was 42.9 years.

All patients received rheological therapy with alprostadil (prostaglandin E1). After an initial higher frequency regimen (cycles every 4–8 weeks), subsequent cycles of 4 weeks' duration followed 1–3 times per year. The infusions were administered for 1 week during inpatient care and continued for an additional 3 weeks in our outpatient clinic, if tolerated. Individual cumulative treatment durations ranged from 3.6 to 17.2 years. For organizational reasons, one patient received 3-week cycles. In addition, all patients received antiplatelet therapy (predominantly clopidogrel, occasionally ticlopidine or acetylsalicylic acid). One patient was additionally treated with phenprocoumon temporarily due to multiple port thromboses. (This patient had a thrombophilic diathesis caused by a methylenetetrahydrofolate reductase [MTHFR] mutation [heterozygous, with normal homocysteine] and a plasminogen activator inhibitor 1 [PAI] mutation.) Additionally, either captopril or a sartan (in two patients due to intolerance) was used.

SYMPTOMS AND CLINICAL SIGNS PRIOR TO INITIATION OF TREATMENT

In the cohort studied, LR initially manifested primarily in the proximal extremities (9/9 [100%] proximal femur, 7/9 [78%] proximal humerus, 3/9 [33%] trunk, 3/9 [33%] gluteal).

Before the start of combination therapy, previous ischemic insults were detected on MRI in 8/9 (89%) patients (Table 2). Territorial infarcts and cerebellar infarcts lacking a distinct emboliform character were the most common findings. The superficial territory of the middle cerebral artery and of the cerebellar vessels were mainly affected. Transient ischemic attacks (TIAs) occurred prior to therapy in 4/9 (44%) patients (a total of six events), with one case of weekly recurrent amaurosis fugax over approximately 3 months being counted only once. Six out of nine patients (67%) reported headache, and 2/9 (22%) additionally reported dizziness. One patient reported isolated dizziness. Two out of nine patients (22%) had neither headache nor dizziness.

Mild cognitive impairment was documented in only one patient. These impairments were related to short-term memory with attention deficits, as well as in planning and conceptual thinking. Due to the retrospective nature of this study, not all patients were tested at baseline, but only after diagnosis.

Only mild WMLs were found in the patients of the present case cohort. Eight out of nine patients (89%) had an ARWMC ≤ 4, and only one patient scored 14 points. The latter had independent thromboembolic risk factors (nicotine abuse, arterial hypertension).

All patients had an mRS ≤ 1 prior to treatment and therefore no relevant restrictions in daily life.

TABLE 1 Comparison of the characteristics and risk factors of patients with primary Sneddon syndrome from the analyzed cohort and the historical comparison cohorts.

	Study cohort (n = 9)	Bottin et al.[11] (n = 53)	Starmans et al.[12] (n = 53)
Demographic data			
Female	100 %	83 %	79 %
Age at the start of LR	31.1	32	–
Age at onset of first vascular event in years	39.0	43.6	36.0
Age at diagnosis in years	42.1	44.6	40.0
Age at start of therapy in years	42.9	–	–
Positive histology	8 of 9	5 of 20	29 of 43
Cardiovascular risk factors			
Hypertension	77 %	55 %	60 %
Smoker	66 %	53 %	79 %
Diabetes mellitus type 2	0 %	32 %	0 %
Obesity	44 %	55 %	39 %
Dyslipidemia	–	32 %	43 %
Hyperhomocysteinemia	11 %	–	43 %
Atrial fibrillation	0 %	4 %	0 %

TABLE 2 Clinical neurological symptoms of patients with primary Sneddon syndrome.

	Before starting therapy	Under combination therapy	After therapy interruptions
Neurological manifestation			
TIAs	6	0	2 (of which 2 are recurrences)
Clinically symptomatic strokes	7	0	4
Ischemic strokes on imaging	13	2	6
Hemorrhagic strokes	0	0	0
Other neurological symptoms			
Dizziness	3	3 (of which 2 are recurrences)	3 (of which 3 are recurrences)
Chronic tension-type headache / not otherwise specified	6	2 (of which 2 are recurrences)	0
Epilepsy	0	0	0
Cognitive impairment			
No cognitive impairment	8	–	–
Mild or moderate cognitive impairment	1	2 (1 primary)	1 (recurrence)
Progressive cognitive impairment	–	–	–

SYMPTOMS AND CLINICAL SIGNS UNDER THERAPY

Patients in the cohort studied were treated and followed up for a mean of 13.6 years. During this treatment period, no fatalities were observed. Contact was lost with three of the nine patients (33%), so their health status cannot be conclusively assessed. The follow-up research showed that all three patients were still alive after 2, 4 and 9 years, respectively.

The livedo racemosa showed no objective clinical response to treatment. In three out of nine (33%) patients, livedo developed on the trunk despite combination therapy. The livedo was subjectively symptomatic (cold allodynia) in only one out of nine (11%) patients. No patient developed ulceration in the area of the LR during combination therapy.

The total follow-up time for the combination therapy was 99.7 patient-years. No TIAs were observed. Patients who had frequent TIAs or amaurosis fugax before starting combination therapy reported that they no longer had these symptoms during therapy. However, one in nine (11%) patients experienced an infarction. One small distal infarct and one non-territorial cerebellar infarct were detected. The

stroke rate was 0.02 per patient-year. In contrast, historical controls on antiplatelet or anticoagulant therapy showed significantly higher event rates (stroke and TIA) of 0.08, 0.05, and 0.18 per patient-year and at least 0.625 and 0.01 per patient-year for TIA.[10–12]

Two out of nine patients (22%) on combination therapy reported a single recurrence of headache symptoms that were present before the start of therapy and were attributed to SS. Dizziness also occurred as a recurrent symptom in two of nine (12%) patients and in one of nine (6%) patients, also primarily during combination therapy. It is noteworthy that headaches and dizziness, which were present at the beginning of the therapy, disappeared during the treatment.

A total of six out of nine patients (67%) underwent MoCA prior to cycle initiation during treatment. Cognitive impairment was observed in two of six patients (33%). In one case, the symptoms (impairment of short-term memory and retentiveness) were present prior to treatment, whereas in the other patient, the symptoms developed during treatment. This second patient received further treatment at an outside facility and received alprostadil infusions for three weeks. The tests were repeated in five out of six patients (83%) after a cumulative follow-up period of a further 80 months. No relevant changes in terms of new symptoms or an increase in discrepancies were detected. The three out of nine (33%) patients who were not tested showed no signs of memory impairment before or during treatment, either in their daily lives or during interactions with doctors. The patient, who had reported mild cognitive impairment in the form of memory problems prior to treatment, showed no evidence of these issues during combination therapy. They did reemerge during a therapy break but were no longer detectable upon therapy resumption.

SYMPTOMS AND CLINICAL SIGNS DURING THERAPY INTERRUPTION

Overall, eight out of nine patients (89%) discontinued treatment between 4 and 106 months, and in eleven of these cases discontinuations were due to cost coverage denial by the health insurance company.

During these interruptions, eight events occurred in three out of nine patients (33%). During the interruptions between 6 months and 8 years, six strokes were diagnosed by MRI, most of them cerebellar infarcts. In one patient, cerebrovascular events (strokes) occurred shortly after cessation of the planned alprostadil cycle, in two other patients after 2.5 years (3 silent infarctions) and after 8 years (Figure 4).

One patient also developed recurrent TIAs during the treatment interruptions. None of the patients experienced a stroke or TIA after resuming combination therapy.

The remaining 5/9 (55%) patients were readmitted because of subjective symptoms such as dizziness (n = 3) or cold allodynia (n = 2). With combination therapy, dizziness stopped and cold allodynia improved markedly. Patients did not report recurrence or progression of headache.

The intraindividual comparison of the rates of central nervous system ischemic events with combination therapy (95% confidence interval [CI] [109.5, 173.5]) and without alprostadil infusion (95% CI [14.5, 64.8]) shows a significant difference ($p = 0.005$). No hemorrhagic strokes were diagnosed at any time.

Additional observations throughout the entire observation period

While one patient had a pre-treatment score of 14 on the ARWMC scale and eight of nine (89%) patients had a score ≤ 4, the sum of all scores showed an increase from 27 to 46, with three of nine (33%) patients having a score ≥ 8. However, no correlations were found between increased scores on the ARWMC scale and cognitive impairment.

On the Modified Ranking Scale, only one patient had a score of 3, indicating moderate impairment. Another patient had a score of 2. The remaining patients were in the ≤ 1 range and therefore showed no relevant impairment.

In addition, independent cardiovascular risk factors and their comorbidity were also recorded (Table 1).

All patients underwent thrombophilia testing to rule out congenital or acquired coagulation or fibrinolysis disorders. Heterozygous resistance to activated protein C (APC) was detected in one patient. One patient was found to have a heterozygous MTHFR mutation with normal homocysteine in combination with a PAI mutation, and two of nine patients (22%) had isolated hyperhomocysteinemia. None of the patients had a history of thromboembolic events. Only the patient with the double mutation developed multiple port thrombosis.

DISCUSSION

Although the cohort size described here is limited, compelling evidence suggests the therapeutic efficacy of combination therapy involving platelet aggregation inhibition, systemic hemorheological therapy, and inhibition of myocyte migration. This can be observed both in comparison with other retrospective cohort studies and in intraindividual comparison with patients in our cohort who discontinued treatment. Therapeutic efficacy is defined here as the ability to influence the occurrence of cerebral ischemic events (TIA or stroke) and disease-associated symptoms such as cognitive impairment, dizziness, headaches, and cold allodynia. In eight out of nine (89%) cases treated with the combination therapy, we found no clinical or MRI morphologic evidence of new cerebral ischemic events and observed a reduction or resolution of subjective symptoms and complaints. Within the cohort studied, the incidence of stroke was significantly lower with combination therapy compared to patients without combination therapy

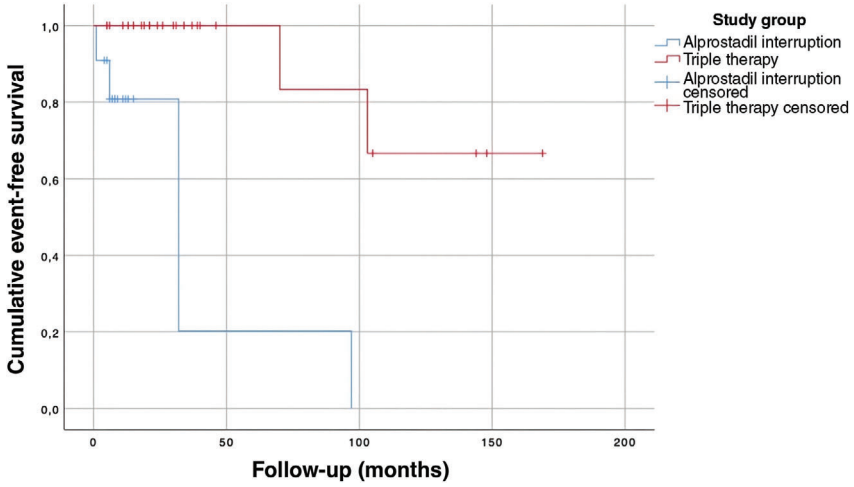

FIGURE 4 Kaplan-Meier curve comparing the frequency of ischemic complications in patients with primary Sneddon syndrome during periods of combination therapy versus periods of therapy interruption.

(p = 0.005). Interruptions in alprostadil therapy with continued platelet aggregation inhibition and myocyte proliferation inhibition resulted in an increase in the incidence of TIAs and stroke (Figure 4).

The authors attribute this primarily to iatrogenically reduced thrombogenesis. Long-term and consistent combination therapy appears to be necessary to maintain therapeutic efficacy. Therapy breaks should be avoided and are associated with an increased risk of thromboembolic events. As we were not able to demonstrate any relevant adverse effects with the combination therapy, the authors also assume that the therapy is safe and should be carried out under circulatory monitoring at least at the beginning of each therapy cycle to avoid relevant hypotensive crises.

Data from other retrospective cohort studies in which patients were treated with an antiplatelet or anticoagulant were used to compare the analyzed cohort.[11,12] The comparison of the cohorts shows similar demographic characteristics (Table 1). The mean age of our patients at onset of LR was 31.1 years; in other case series, LR was recorded on average at 28.5 years, 32 years and 29.1 years.[9–12] First neurovascular events such as stroke or TIA were reported at a mean age of 39 years. Zelger et al. describe subtle CNS symptoms in patients as young as 25 years, with a mean age of clinical manifestation of 34.5 years and mean age of lesions on brain imaging of 37.9 years.[9] Other case series have shown similar results regarding the detection of imaging findings at 43.6, 36.0, and 40.0 years of age.[10–12] The symptomatic headache observed in our cohort was also similarly common in the comparison cohorts at 47%, 51%, and 53%, respectively.[10–12]

In the comparison cohorts, the diagnosis of SS was not regularly confirmed histologically.[11] This may be due to a lack of consensus on histologic criteria and biopsy technique.[35–37] At the time of diagnosis, an average of 2.1 ischemic events per patient had occurred in our cohort; in another cohort, this value (1.26–2.4) was at a comparable level.[10–12] Table 1 shows a comparison of the study cohorts with respect to the occurrence of central vascular events over time.

For the cohort studied here, the evaluation period amounted to 99.7 patient years under treatment and an average of 11.0 (± 5.6) years per patient. This period is almost twice as long as in the comparator groups and thus provides long-term data for the first time. Bottin et al. followed 52 patients over a period of 332.8 patient years. The patients were treated with an antiplatelet or anticoagulant agent for an average of 6.4 years. Bottin et al. found 14 ischemic and three hemorrhagic events with this monotherapy.[11] This gives an incidence rate of 0.051 (95% CI: 0.032-0,082). In contrast, our data show only 2 events in 99.7 patient-years, or 0.02 events per patient-year. Since this value is outside the confidence interval, the result can be considered significant. Furthermore, a mortality rate of 4% is reported with a mean follow-up of 7.4 years, of which 6.4 years were on therapy. Although the cumulative total follow-up time in our patients is too short to expect such events, we consider the absence of such events in the long individual follow-up to be a prognostically favorable sign. In Starmans et al., 13 events occurred in 143.6 patient-years, or 0.09 events per patient-year.[12] Of the 20 patients treated with antiplatelet agents, two had a recurrent stroke within 77.6 patient-years; of the eleven patients treated with anticoagulants, two had a recurrent stroke within 66 patient-years. However, only the affected patients were counted and not the number of all events (strokes and TIAs), which means that the actual number is underestimated. The follow-up period was between 7 and 197 months, with an average of only 28 months. Frances et al. reported similar results with a follow-up period of 71 patient-years and an annual incidence of 0.08 events in aPL-negative patients with SS on antiplatelet therapy. The 18 patients were followed up for a mean of 3.9 years.[10]

The therapeutic efficacy of combination therapy is most evident in patients with prolonged interruptions of alprostadil infusion cycles. In these cases, an increase in the complication rate can be observed. From our experience, we conclude that three infusion cycles of alprostadil per year (in mild cases, one infusion cycle of alprostadil per year)

are necessary to prevent the occurrence of neurovascular defect events with a high probability.

Analysis of the ARWMS data from our cohort shows no correlation between the score value and the occurrence of stroke or cognitive impairment. Since focal WML can be observed in approximately 17.4% of the normal German population after the age of 40, the ARWMS score does not provide any additional diagnostic value.[32,33,38,39]

Our patients achieved age-appropriate results on the MoCA memory test during treatment. Of the six patients tested, four had unremarkable results. Only two patients showed abnormalities that clearly correlated with subjective short-term memory impairment. A direct comparison with the cohorts of the comparison groups is methodologically difficult. In Bottin et al., 60% had mild cognitive impairment. In the cohort of Starmans et al., 11% had mild cognitive impairment and another 13% had moderate cognitive impairment or even dementia.

Regarding quality of life, only one of our patients with an MRS score of 3 had relevant restriction in her daily life. She had a severe course, SS was diagnosed late and treated accordingly. All other patients had no or only minor daily life restrictions. In Bottin et al., 17% of patients had an mRS ≥ 3, with a slightly worse trend and shorter follow-up than in our series.[11] In the cohort of Starman et al., the index of daily activity was markedly worse in 26% (n = 7) of patients with an mRS ≥ 3.[12]

Although these studies are based on a small cohort due to the rarity of the disease, it can be concluded that the combination therapy described here can be expected to result in a significantly lower rate of complications and maintain the quality of life of patients compared to monotherapy. This is supported by the demonstrated significant benefit for patients on regular combination therapy compared to patients on interrupted alprostadil therapy. A prospective, randomized, controlled trial to validate combination therapy would be needed to prove the benefit.

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CONFLICT OF INTEREST STATEMENT

None.

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