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CASE REPORT

Use of MLC901 in cerebral venous sinus thrombosis: Three case reports

Anita Ante Arsovska, Narayanaswamy Venketasubramanian

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Abstract

BACKGROUND

Cerebral venous sinus thrombosis (CVT) is rare cause of cerebrovascular disease. The incidence is 0.5% of all stroke. The majority of affected patients are young adults (mean age: 35-40 years) with mild to moderate disabilities. Poor outcome with severe disability is seen in 13% of cases. Early diagnosis and treatment are important for good outcomes and preventing complications. Treatment options are limited and mostly based on consensus. NeuroAiD II™ (MLC901; Moleac Pte, Ltd, Singapore) has a potential beneficial role in post-stroke recovery, by aiding the natural brain recovery process.

CASE SUMMARY

MLC901 consists of nine natural herbal ingredients. Studies have shown its safety profile and aid in post stroke recovery. The aim of this case series was to demonstrate the potential role of MLC901 in stroke recovery of patients with cerebral venous sinus thrombosis (CVST) who received MLC901 in addition to standard of care. The prescribed dose of MLC901 is 400 mg/cap two capsules, three times a day. Data from these patients were prospectively collected at baseline and at monthly visits, for a duration of 3 mo. Outcome measures included adherence to therapy, side effects, National Institutes of Health Stroke Scale, Glasgow Coma Scale, modified Rankin Scale, and the Short Orientation-Memory-Concentration Test. MLC901 was well tolerated and no side effects were reported. All patients were stable with improved condition.

CONCLUSION

This case series highlights the potential therapeutic effects of MLC901 on CVST and provides support for further studies.

Key Words: MLC901; Cerebral venous sinus thrombosis; Anticoagulation therapy; Safety; Case report

Core Tip: The purpose of this study was to assess the potential role of NeuroAiD II™ (MLC901; Moleac Pte, Ltd, Singapore) in post-stroke recovery in a series of patients diagnosed with cerebral venous sinus thrombosis and treated with anticoagulation therapy.

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INTRODUCTION

About 0.5%–2% of all stroke cases are caused by cerebral venous sinus thrombosis (CVST), an uncommon form of cerebrovascular disease. Female sex is a predisposing factor for CVST, with studies showing that 75% of CVST patients are women between 20 years and 35 years of age [1]. Indeed, CVST accounts for up to 50% of strokes during pregnancy and puerperium. The clinical picture consists of various symptoms and signs that are not always recognized at the beginning of the disease. Headache is the most common presenting symptom, occurring in 90% of cases. Other symptoms include motor deficit, focal seizures, and consciousness impairment. According to the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), the most common affected is the sagittal superior sinus ,second is the transverse sinuses at (41.2%-44.7%), whereas and less commonly affected are the straight and cavernous sinus (18% and 1.3%, respectively)[2].

CVST is a potentially life-threatening condition and may result in long-term neurologic sequalae. NeuroAiD II™ (MLC901; Moleac Pte, Ltd, Singapore), a product containing nine herbal extracts, shown its neuroprotection and neurorestoration properties in animal models of stroke and traumatic brain injury, leading to a reduction in neurological deficits and improvement in functional outcomes[3].

Patients were enrolled in the NeuroAid Safe Treatment Registry (NeST Registry). This is an observational and propective registry to assess use and safety of NeuroAiD in real world setting[4]. Physicians access the online registry with a protected password. Patients who agreed to be included in the registry, were prospectively entered in the database using online forms for baseline and subsequent visits.

We assessed the potential role of MLC901 in post-stroke recovery in a series of patients diagnosed with CVST in the NeST Registry.

CASE PRESENTATION

Chief complaints

Case 1: A 33-year-old female presented to our hospital with headache and right arm weakness.

Case 2: A 35-year-old female was referred with complaints of headache and right-sided weakness.

Case 3: A 25-year-old presented to our hospital with residual weakness and spasticity of the right-sided extremities.

History of present illness

Case 1: For 4 mo prior to consultation, the patient experienced an intense, diffuse headache and sudden weakness of the right arm.

Case 2: The patient spontaneously delivered a full-term live baby 19 d prior to consultation. She was referred due to the sudden onset of headache and right-sided weakness that occurred 7 d prior to the examination.

Case 3: The patient had been diagnosed with CVST 5 years prior with residual weakness and spasticity of the right-sided extremities. She had also been diagnosed with ulcerative colitis for which she was prescribed sulfasalazine and azathioprine, had a history of symptomatic epilepsy for which she was given levetiracetam, and had spasticity of the right-sided extremities for which she was given baclofen. She had been followed up regularly for the past 5 years.

History of past illness

Case 1: Unremarkable.

Case 2: The patient's significant obstetrics and gynecologic history was an *in vitro* pregnancy, without any recurrent abortion.

Case 3: The patient was diagnosed with CVST, ulcerative colitis, and symptomatic epilepsy 5 years prior.

Personal and family history
Cases 1 and 2: Unremarkable.

Case 3: The patient's personal and family history was unremarkable.

Physical examination
Case 1: On physical examination, the patient's vital signs were stable. She had mild right arm drift.

Case 2: She had a right-sided hemiparesis (motor weakness 3/5) and sensory loss, with a National Institutes of Health Stroke Scale (NIHSS) score of 3.

Case 3: Current neurological status revealed a right residual hemiparesis motor score of 3/5, hemihypoesthesia of the right-sided extremities, and motor dysphasia. Spasticity of both the upper and lower extremities was also observed [NIHSS score of 6, modified Rankin Scale (mRS) of 3].

Laboratory examination
Case 1: Initial blood tests and tests for vasculitis were normal. D-dimer level was elevated (1092 ng/mL; normal: < 500 ng/mL). Follow-up blood tests at 1 mo and 2 mo showed D-dimer levels of 585 ng/mL and 342 ng/mL, respectively.

Case 2: Initial laboratory tests showed elevated D-dimer level (1950 ng/mL; normal: < 500 ng/mL). Other laboratory tests such as complete blood count, erythrocyte sedimentation rate, and liver and kidney function tests were all normal. Follow-up laboratory tests showed normal D-dimer levels of 670 ng/mL and 495 mg/mL, respectively.

Case 3: The initial D-dimer level was elevated (1200 ng/mL; normal: < 500 ng/mL). Repeat D-dimer tests showed values of 492 ng/mL, 490 ng/mL, and 480 ng/mL.

Imaging examination
Case 1: Initial magnetic resonance imaging of the brain showed thrombosis of the superior sagittal sinus. Follow-up magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) at 3 mo showed recanalization of the superior sagittal sinus.

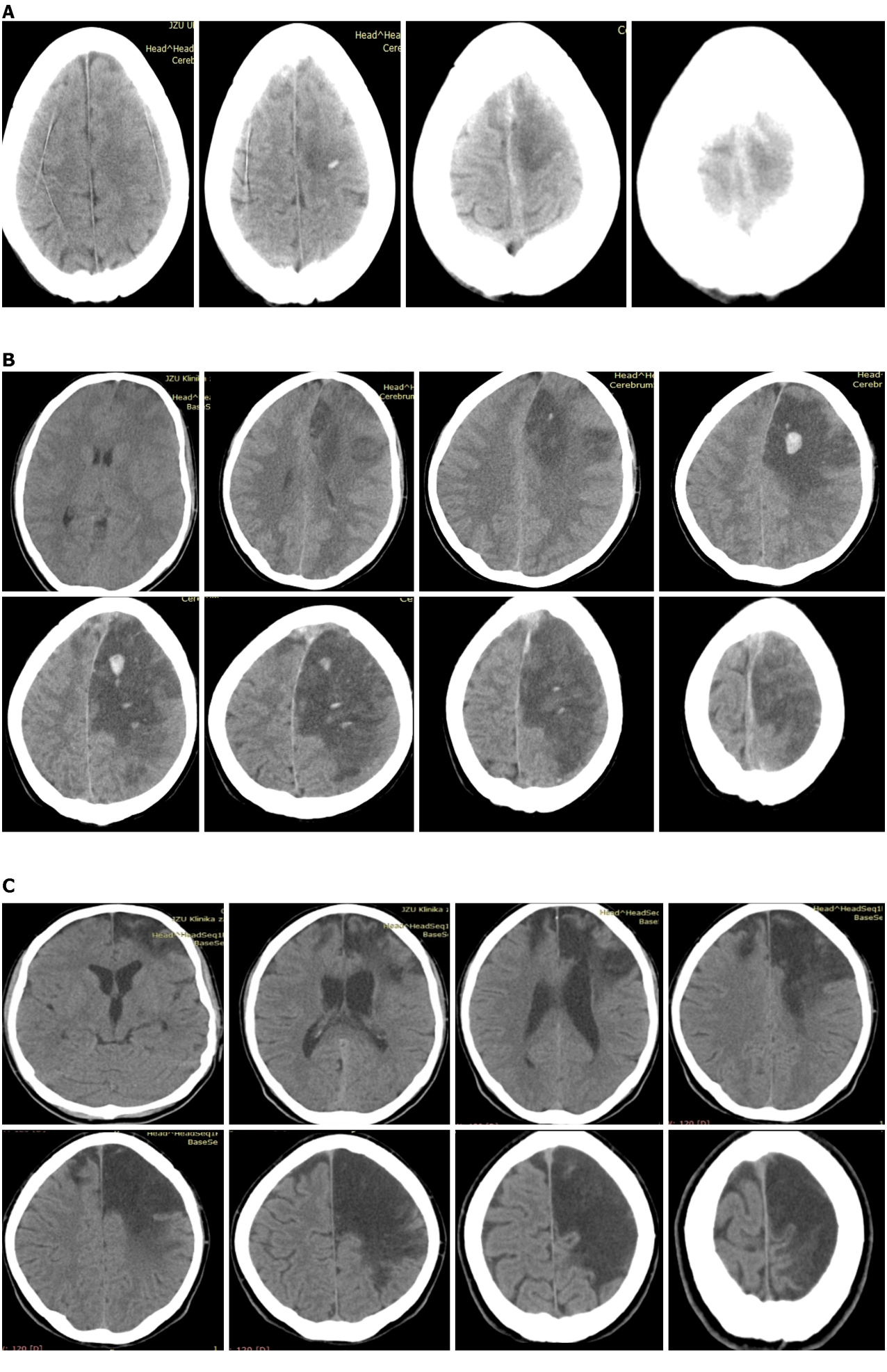
Case 2: Initial MRI/MRA revealed thrombosis of the superior sagittal sinus. Follow-up MRI/MRA at 3 mo showed recanalization of the superior sagittal sinus.

Case 3: Previous neuroimaging (computed tomography and MRI; Figure 1) showed large post-apoplectic sequela due to thrombosis of the superior sagittal sinus.

TREATMENT
Case 1
The patient was administered a low-molecular-weight heparin (LMWH) (Clexane; Sanofi, Berkshire, United Kingdom) at 40 mg twice daily subcutaneously for 3 mo. The patient was also prescribed MLC901 at two capsules, three times a day for 3 mo.

Case 2
The patient was administered Clexane at 40 mg once a day subcutaneously for 3 mo. MLC901 was also prescribed at two capsules, three times a day for 3 mo.

Case 3
Initially, the patient was treated with an LMWH (Clexane) 40 mg subcutaneously for 3 mo, and then switched to a vitamin K antagonist. Due to side effects and interactions with food and other medications, the vitamin K antagonist was discontinued and switched to rivaroxaban 15 mg per day. The patient was prescribed MLC901 for 3 mo, at a dose of two capsules, taken three times a day, which was continued during her rehabilitation. The patient also continued her regular treatment of rivaroxaban 15 mg once a day, levetiracetam 250 mg once a day, sulphasalazine 500 mg once a day, and azathioprine 50 mg per day.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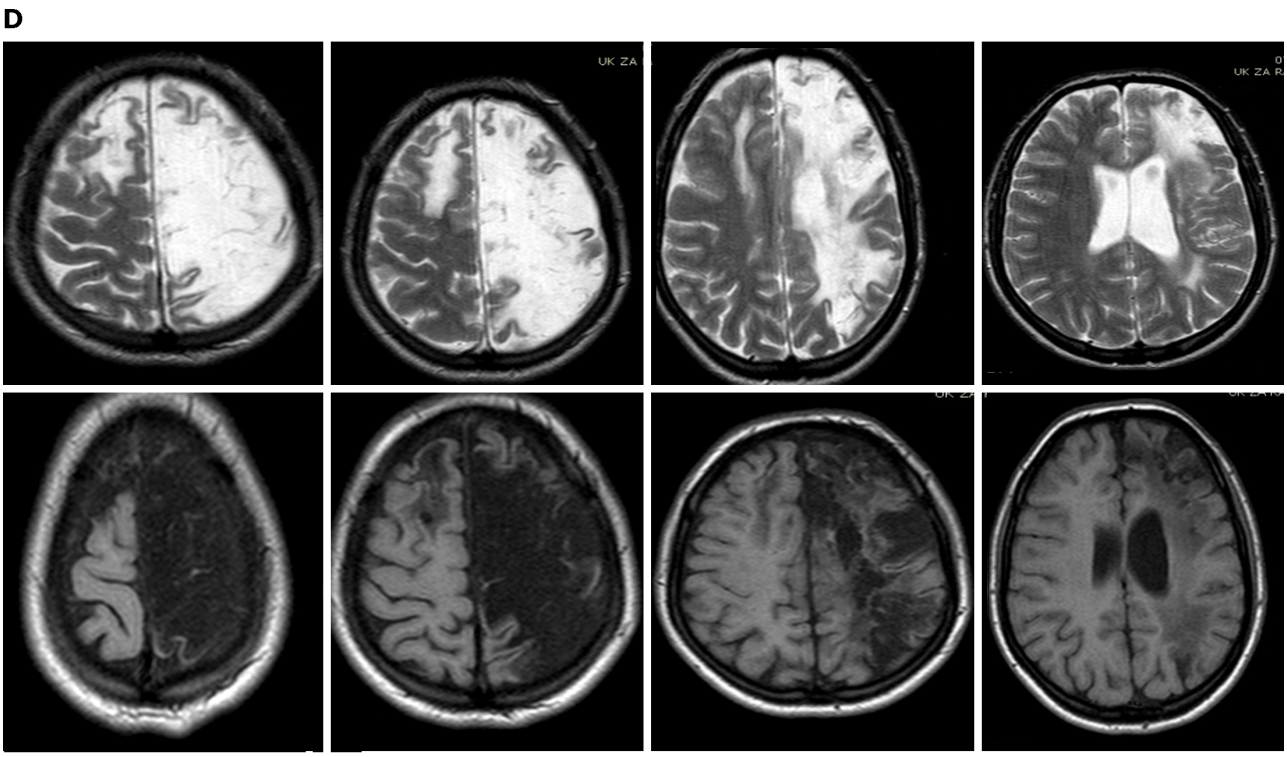

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Figure 1 Brain imaging of case number 3. A: First computed tomography (CT) of the brain (at first admission in the hospital): Hypodense are in the left parietal cortical and subcortical region with hyperdensities in the affected area, due to venous infarction with haemorrhagic transformation due to sagittal superior sinus thrombosis; B: Brain CT 2 d after- venous infarction in the left parietal cortical and subcortical region, with dimensions 98 mm × 56 mm and strong compressive behaviour towards cerebral falx and left lateral ventricule, with haemorrhagic transformation and fewer small haemorrhagic changes; C: Brain CT 6 mo after: Large post-apoplectic sequelae; D: Brain CT 6 mo after: Large post-apoplectic sequelae.

FINAL DIAGNOSIS

Cerebral venous thrombosis.

OUTCOME AND FOLLOW-UP

Case 1

The patient remained neurologically stable with mild drift of the right arm. No side effects were reported NIHSS score of 1, mRS score of 1).

Case 2

The patient remained stable with noted improvement in neurological status (NIHSS score of 2) at month 2 and no symptoms at month 3 (NIHSS score of 0, mRS score of 0).

Case 3

The patient remained neurologically stable with mild drift of the right arm. No side effects were reported (NIHSS score of 1, mRS score of 1).

DISCUSSION

The aim of the study was to present a case series of CVST patients administered MLC901 in addition to standard treatment. CVST is usually treated with anticoagulation therapy, regardless of the presence of hemorrhage. The suggested regimen includes a LMWH in the acute phase of the disease followed by oral anticoagulation therapy[5]. The American Heart Association/American Stroke Association suggest treatment with vitamin K antagonists for 3-6 mo in patients with provoked CVST and for 6-12 mo in patients with unprovoked CVST, with a target international normalized ratio (INR) of 2.0-3.0[6]. In Pregnant women diagnosed with CVST, it is recommended that a full anticoagulant dosage of LMWH is given for the duration of the pregnancy, and to continue taking an LMWH or vitamin K antagonist for at least

six weeks after giving birth, with a target INR of 2.0–3.0 and for or a total minimum duration of 6 mo. Other treatment options are fibrinolytic therapy, endovascular, surgical thrombectomy, aspirin, steroids, and antibiotics.

Several studies have suggested that use of direct oral anticoagulants (dabigatran, rivaroxaban, and apixaban) can also be safe and effective for the treatment of CVST[7-9]. Comparing the treatment between patients with endovascular treatment and standard medical care and those who received standard medical care alone did not differ in the degree of disability at 12 mo[10].

Over the last few years, the use of complementary and alternative medicine has gained popularity and acceptance as an add-on therapy to standard care for stroke recovery[11]. MLC901 is a traditional Chinese medicine that contains nine herbal components. The previous formulation, MLC601, was a traditional Chinese medicine that combined extracts of nine herbal and five animal components in capsule form. Both formulations have similar neuroprotective and neurorestorative properties demonstrated in both animal and cellular models of cerebral ischemia and brain injuries. Biologically active substances that are plant components of MLC901 act synergistically, with a multimodal mechanism of action involving neuroregeneration, neuroprotection, and prevention of neuronal death in ischemic conditions of the central nervous system. MLC901 treatment stimulates neurogenesis and neuroplasticity, increases the number of neurons, and promotes the potentiation of endogenous mechanisms of long-term vascular reconstruction and stimulation of angiogenesis[12,13].

Increased local venous pressure brought on by thrombosis reduces cerebral perfusion, resulting in cytotoxic edema and ischemic damage; vasogenic edema is caused by disruption of the blood-brain barrier; and parenchymal hemorrhage is the end result of venous and capillary rupture[14]. MLC601/MLC901 has shown both neuroprotective and neuroregenerative properties in preclinical and animal investigations using cortical cell cultures and rodent models of focal and global ischemia. Treatment with MLC601/MLC901 showed benefit in cerebral infarct survival rate, decreases the extent of the cerebral infarct, reduces the blood-brain barrier leakage and neurologic impairment after ischemia and reperfusion [15]. These may be the potential mechanism of action of MLC901 in preventing the ischemic injury and cytotoxic edema brought about by the increase venous and capillary pressure from the CVST.

The neuroprotective qualities of NeuroAiD may be attributed to the opening of KATP channels and activation of the Akt survival pathway[16]. NeuroAiD increases brain-derived neurotrophic factor expression and induces the proliferation of cells, which differentiate and mature into neurons.

MLC601/MLC901 aids in the brain's natural recovery and healing process. This is seen in individuals who showed improvement in their neurologic function after stroke or other acute brain injuries in the post-acute period and beyond. Its benefits have been demonstrated in several randomized clinical trials while given in patients with stroke as an add-on to secondary prevention treatment and to rehabilitation. Several studies and case reports have shown the benefits of MLC601 and MLC901 in patients with stroke (ischemic and hemorrhagic) and brain injury. Both products were well tolerated, without serious side effects[17]. The safety of MLC601 was confirmed, as there was no significant difference in the adverse events reported between MLC601 and placebo[18]. For post stroke patients, there was a significant increase in the probabilities of obtaining functional independence, (mRS < 1). This increase remained for up to 18 mo[19].

Bavarsad Shahripour *et al*[20] evaluated the long term 6 mo safety profile in patients with acute ischemic stroke and given a 3-mo regimen of NeuroAiD. The study demonstrated that there were no significant side effects that necessitated stopping the trial medication. During 3-mo treatment, the mean arterial blood pressure, hemoglobin, and laboratory markers related to the liver or kidney did not significantly change. Individuals with a comparatively worse prognosis for stroke recovery are probably going to benefit more from MLC601 treatment[21]. Subjects having received persistent rehabilitation up to M3 shows that MLC601 supplementation to rehabilitation increases the likelihood of improving functional recovery and independence at 3 mo and beyond compared to placebo[22]. This showed a beneficial and sustained effect of MLC601 on brain neuro-repair processes after an acute ischemic stroke.

MLC601/MLC901 amplifies multimodal mechanism which act synergistically to boost neurorepair which translate to a persistent functional recovery. Key mechanism of neuro- vascular repair includes increase neuronal network plasticity by upregulating the expression of Brain Derived Neurotrophic Factor involve in neural strengthening plasticity. MLC601/MLC901 enhances neurogenesis by increasing neurite outgrowth and synaptogenesis. It also promotes neurogenesis by increasing the number of glial cells. MLC601/MLC90 stimulates angiogenesis by upregulates the natural expression of Vascular Endothelia Growth Factor which amplifies the development of micro vessels in the damaged areas. It also modulates neuroinflammation by reducing the leakage of blood brain barrier and optimise its repair and modulates the mediators of inflammation.

Kumar *et al*[23] evaluated the use and safety of MLC901 in patients with intracerebral hemorrhage (ICH). The study showed that NeuroAiD was safe and had the potential to have a long-lasting beneficial impact on neurological rehabilitation following ICH in the real-world context. Early recognition and treatment of CVST are essential to minimize morbidity and improve survival. There are currently no published reports on the use of MLC901 in CVST patients. This report is the first case series to show the use of MLC901 in patients with CVST. In the CHIMES trial, patients who were on anticoagulants were excluded due to safety concerns.

In the current case series, the use of MLC901 in combination with an anticoagulant, heparin, or Direct Oral Anticoagulant was demonstrated with no report of side effects. All 3 patients were young females who presented with mild to moderate severity at baseline, had elevated D-dimer levels, and MRI-detected thrombosis of the superior sagittal sinus. The third case showed a follow-up MRI result 5 years after the initial event. Magnetic resonance venography was not performed in the cases as the initial MRI confirmed the presence of the thrombosis. Case #2 improved neurologically, and Case #1 and Case #3 were stable over the 3-mo observation period. In Case #3, MLC901 was started 5 years after the diagnosis; she also had persistent neurological disability. In addition to her current medications and rehabilitation, the addition of MLC901 may have provided potential benefit in combination with her neurorehabilitation

Two of our cases showed recanalization in neuroimaging findings. This is consistent with findings from another study, which showed that partial or complete recanalization occurred in 47%-100% of patients treated with anticoagulant alone [24]. Small studies have reported that recanalization occurs at 3 mo to 6 mo[25]. The neuroprotective and neuroproliferative effects of MLC901 have been demonstrated in various preclinical and animal studies and clinical observations have shown improvement of neurological deficits, indicating the potential usefulness of MLC901 in cases of CVST. The study has several limitations. In this case series, the degree of each patient's motor recovery is variable which make it challenging to determine MLC901's effectiveness. More research including a larger patient cohort is required to fully investigate the role of MLC901 in CVST patients.

CONCLUSION

This case series highlights the potential role of MLC901 in post-stroke recovery in CVST patients and provides support for future studies.

FOOTNOTES

Author contributions: Arsovska A contributed to the conceptualization, supervision, manuscript writing, editing, and data collection; Venketasubramanian N contributed to the conceptualization, manuscript writing, and editing; All authors have read and approved the final manuscript.

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