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The Use of MLC901 in Combination with Anticoagulant among an Eastern European Cohort - Real World Data from NeuroAiD Safe Treatment Registry (NeST Registry)

Anita Arsovska[1]*, Brola Waldemar[2], Frasineanu Armand Daniel[3], Marceanu Manuela[4] Reisz Daniela[5], Sarzyńska-Długosz Iwona[6], Serdahely Vlastimil[7], Simu Mihaela Adriana[8], Valkovič Peter[9] and Narayanaswamy Venketasubramanian[10]

[1]*Department of Neurology, University Clinic of Neurology, University "Ss. Cyril and Methodius", Skopje, North Macedonia*
[2]*Department of Neurology, Collegium Medicum, Jan Kochanowski University,Kielce, Poland*
[3]*Department of Neurology, Colentina Clinical Hospital 19-21 Stefan cel Mare st, Bucharest, Romania*
[4]*Department of Neurology ,Clinical Hospital of Psychiatry and Neurology, Prundului street 7-9, Brasov, Romania*
[5]*Department of Medicine, Victor Babes university of Medicine and Pharmacy Timisoara Piata Eftimie Murgu Nr2 300041 Timisoata Romania*
[6]*Department of Neurology, Institute of Psychiatry and Neurology,Sobieskiego 9 Str, 02-957 Warsaw, Poland*
[7]*Department of Neurology, Faculty Hospital AGEL Skalica, Slovakia*
[8]*Department of Medicine, University of Medicine and Pharmacy "Victor Babes" Timisoara, Clinic of Neurology II Clinical County Emergency Hospital "Pius Brinzeu" TRimisoara Romania*
[9]*Department of Neurology, University Hospital Bratislava Slovakia (Slovak Republic)*
[10]*Department of Neurology, Raffles Neuroscience Centre, Raffles Hospital, Singapore*

Abstract

Objectives: The efficacy and safety of NeuroAiD™ is well-established in patients with ischemic stroke in the acute and chronic phase. It is an add-on treatment to standard therapies and there were no reports of major interactions. However, there is currently no data on the use of NeuroAiD™ in combination with anticoagulants. We aimed to determine the safety of using MLC901 (NeuroAiD II) with anticoagulants among patients in the Eastern European Cohort.

Methods: We performed a subgroup analysis of patients enrolled in the NeuroAiD Safe Treatment Registry (NeST). Patient who were given anticoagulants were included. Data collected were baseline demographics, diagnosis, concomitant medications and adverse events.

Results: A total of 98 patients were included. There were 48 female (49%), median age 64 years IQR (50,71), baseline median NIHSS 16, IQR (11,20), median mRS 4, IQR (3.25,5). Diagnoses included: Ischemic Stroke -80%, Traumatic Brain Injury - 7%, Cerebral Venous Thrombosis - 3%, Global hypoxic encephalopathy - (2%), Venous infarct - 1 %, AV Malformation - 1%, Meningoencephalitis - 1%. Risk factors were: hypertension - 72%, diabetes mellitus - 21% and hyperlipidaemia - 31%. The presence of cardiac disease was seen in 38% of which 24% had non-valvular atrial fibrillation. The concomitant anticoagulants were used in 98% of patients and included: low-molecular-weight heparin (LMWH), direct acting oral anticoagulants (DOACs), and Vitamin K antagonist (VKA). Neither adverse events nor side effects were reported.

Conclusions: The study provides new evidence for the safe use of MLC901 when combined with anticoagulants in a real-world setting.

Keywords: NeuroAiD II • MLC901 • Real-world registry • Anticoagulant • Neuroprotection • Safety

Introduction

MLC901 (NeuroAiD II), is a Traditional Chinese Medicine (TCM) that contains 9 herbal components. It is a simplified formulation of MLC601 (NeuroAiD) which contains 9 herbal and 5 non-herbal components [1]. MLC601/MLC901 has neuroprotective, anti-inflammatory and neurorestorative properties. Both have been used mainly used for post-stroke recovery, traumatic brain injury and other neurological conditions. Its efficacy has been established in clinical studies in stroke [2-4]. *In vitro* and *in vivo* studies have demonstrated its neuroprotective and neurorestorative properties using animal and cellular models of ischemia [5-7]. NeuroAiD does not significantly modify haematological, haemostatic, and biochemical parameters in normal subjects and stroke patients [8]. After 3 months of NeuroAiD treatment in stroke patients, there is no significant change across biochemical parameters and it is comparable to placebo [9].

Long-term safety up to 6 months also showed no evidence of NeuroAiD effect on liver enzymes; levels were comparable to placebo at 1, 3, and 6 months [10]. In the CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) Study, the effectiveness of NeuroaAID in acute Stroke did not reach statistical significance in both primary and secondary outcomes, however a trend toward benefit in the subgroup receiving treatment beyond 48 hours from stroke onset was noted. The safety of NeuroAiD was demonstrated showing serious and non-serious adverse event were similar between group [11]. The post-hoc analysis of severe adverse events (SAEs) from the CHIMES study database showed that subjects receiving a 3-month course of NeuroAiD experienced fewer SAEs, with lower rates of harmful clinical impacts, especially in terms of hospitalisation duration [12].

***Address for Correspondence:** Anita Arsovska, Department of Neurology, University Clinic of Neurology, University "Ss. Cyril and Methodius", Skopje, North Macedonia, E-mail:anita70mk@yahoo.com*

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The extension study CHIMES-E showed the benefit of long-term functional outcome persisting up to 18 months with an excellent safety profile [13]. However, in the CHIMES study, patients on anticoagulation were excluded because of safety concerns due to the lack of published data on the interaction of MLC601 with anticoagulants, particularly in the acute phase of stroke. Similarly, in a double-blind placebo controlled randomised Phase II Pilot Study investigating the efficacy of MLC601 in post-stroke recovery, patients on full-dose or long-term anticoagulation therapy were excluded [14]. Hence, we aimed in this study to investigate safety and the frequency of adverse events or side effects among patients on anticoagulation and using NeuroAiD II in a real-world setting.

Methodology

The NeuroAiD Safe Treatment Registry (NeST Registry) Protocol (ClinicalTrials.gov NCT02536079.) was published in 2015 [15]. It is a prospectively-designed product registry to collect information in a real-world setting. Patients who were prescribed with MLC601/MLC901 by the attending physician were invited to participate in the registry. Anonymized data were collected which includes demographics, medical conditions, physical and neurological examinations, concomitant medications and adverse events. Ethical approval was based on the policies of the authors' institutions. For this study, we performed a subgroup analysis of patients who were entered in the NeST registry in Eastern European Cohort consisting of Macedonia, Poland, Slovakia and Romania, and who were prescribed with anticoagulants. All the demographics and baseline characteristics were collected in the summary table. The categorical variables were summarized by frequency and percent and continuous variables were summarized by descriptive statistics. Any adverse event that is considered by the treating physician as being possibly, probably, or definitely related to NeuroAiD II would be considered as a side effect. Any side effects reported will be summarized separately in the AE summary table.

Results

A total of 98 patients were included. There were 48 female (49%), median age was 64 IQR (50,71), baseline median NIHSS was 16 IQR (11,20), median mRS wass 4 IQR (3.55). Diagnosis included: Ischemic Stroke-80%, Traumatic Brain Injury-7%, Cerebral Venous Thrombosis - 3%, Global hypoxic encephalopathy-2%, Venous infarct-1%, Arterio-Venous Malformation–1% and Meningoencephalitis (1%). Among the major vascular risk factors were: hypertension-72%, diabetes-21% and hyperlipidaemia-31%. The presence of cardiac disease was seen in 38% of which 24% had atrial fibrillation (AF). The list of anticoagulants given at baseline and follow-up visits was summarised. Neither adverse events nor side effects were reported.

Discussion

Our study showed the safety of the combined use of NeuroAiD II with anticoagulants among real-world patients enrolled in the NeST Registry. There were no adverse events attributable to the combined use.

Anticoagulants are medications that interrupt the natural clotting mechanism. There are three main types of anticoagulant medications: Vitamin K antagonists (VKA – coumarin, acenocumarin, warfarin), Direct Oral Anticoagulants (DOACs – rivaroxaban, apixaban, dabigatran) and Heparin, consisting of Unfractionated heparin and Low Molecular Weight Heparins (LMWHs – nadroparin, enoxaparin, neoparin). VKA has been the anticoagulant approved for 60 years. Although they have been effective anticoagulants, their use is accompanied by several pitfalls, which has led to research and the discovery of new additional groups of anticoagulants. DOACs, comprising direct thrombin inhibitors, such as dabigatran, and direct factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban, are fast-acting, non-inferior and possibly superior to VKA (warfarin) or LMWHs in preventing stroke in patients with nonvalvular AF, reducing risk of thromboembolic complications with similar or reduced bleeding risk [16]. DOACs are recommended in patients with non-valvular AF for recurrent stroke prevention due to its favourable risk benefit profile, with significant reductions in stroke, intracranial haemorrhage and mortality.

Drug-to-drug interactions are a significant concern when patients are on anticoagulants. Concomitant medications that increase anticoagulant plasma concentrations can lead to bleeding events, and those decreasing anticoagulant concentration may increase risk for thrombus formation. When compared with VKA, DOACs have lower risk of drug-to-drug interactions, however it still has significant interactions involving renal, liver and haemostasis [17,18]. One case report of a 73-year-old man diagnosed with a stroke and atrial fibrillation. He was started on apixaban, beta-blockers, atorvastatin, pantoprazole and NeuroAiD-II. One month later presented with deranged liver enzymes [19]. However, in this case report, the causality of the NeuroAiD-II cannot be ascertained with the data presented.

At baseline, the anticoagulants given in our study were DOACS (32%), followed by LMWH at 25% from month 1 to 3. There were no adverse events attributable to the combined use with NeuroAiD.

A real-world registry is a valuable tool to assess treatment patterns to reflect the daily clinical decision-making among physician. Unlike clinical trials, registries have the advantage of enrolling larger and more diverse populations with a potential for longer follow-up. They provide data that are more reflective of real-world population and enable the study of longer-term outcomes including identification of infrequent safety outcomes [20]. In our cohort, the minimum and maximum age was 15 to 91 years, respectively, which represents a wide range of age distribution. The patients had a median NIHSS score of 16 and median mRS of 4 indicating severe stroke with severe disability. Our cohort is thus applicable to clinical practice and a realistic assessment of safety. The study addresses an important knowledge gap with lack of evidence in the combined use of NeuroAiD II and anticoagulants.

Limitations

Our study has the following limitations that make quality control of the data difficult with a potential for bias [21,22]. The sample size is small. We did not include compliance to the anticoagulant medications and information of laboratory parameters. There was no independent adjudication of adverse events, which may have been under-reported. Our study has the following strengths: it is a prospective registry; the individual data were pooled from multiple international sites. We were able to generate the hypothesis of safety of NeuroAiD II in combination with anticoagulants. Such data is not yet available from a randomised controlled trial (RCT).

Conclusion

The study provided new evidence indicating safety of combination of MLC901 and anticoagulants in a real-world setting. Larger prospective studies are needed to confirm our findings.

Conflict of Interest

All the authors declared no conflict of interest.

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