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NeuroAiD™ (MLC601, MLC901): A New Bench-to-Bedside Approach to the Treatment of Ischemic Brain Injury

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Authors' contributions

This work was carried out in collaboration between all authors. All authors reviewed the published articles on NeuroAiD™ and contributed equally in summarizing the important findings included in this in this review. All authors have read and approved the final manuscript.

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Review Article

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ABSTRACT

Background and Aim: Faced with the public health burden of stroke and brain damage, various synthetic drugs with different pharmacological targets have been investigated in an attempt to improve clinical outcome, but many failed in clinical trials. In this article, we aimed to outline the current knowledge on the main clinical and pharmacological data of NeuroAiD™ (MLC601, MLC901), a novel product combining extracts from natural sources, in improving neurological and functional recovery after a stroke.
Methods: We reviewed and summarized important findings reported in pre-clinical and clinical publications that investigated the role of NeuroAiD™ in stroke.
Summary of Review: NeuroAiD™ has shown significant pharmacological properties for neuroprotection and neurorestoration in preclinical studies involving animal and cellular models of focal and global ischemia. Clinical studies have shown safety and efficacy data for enhancing neurorecovery beyond acute neuroprotection by reducing long-term neurological deficits and improving functional outcome in post-stroke patients.
Conclusion: NeuroAiD™ offers a safe therapeutic solution likely through a multi-modal mode of action in reducing the burden of ischemic brain injury.

Keywords: NeuroAiD; MLC601; MLC901; stroke; stroke recovery; neuroprotection; neuroplasticity.

1. INTRODUCTION

Stroke is a major cause of death and disability worldwide. In Western countries, stroke is a leading cause of acquired disability in adults, the second cause of dementia after Alzheimer's disease and the third leading cause of death. With the rapid growth of the aging population, stroke and its prevention has become an urgent public health problem [1].

Despite many researches carried out for decades in various therapeutic targets (e.g. antioxidants, calcium channel blockers, antagonists of glutamate receptors and neurotropic factors), over 1000 candidate agents and more than 200 clinical trials, there is unfortunately still no synthetic compound able to provide a clinically effective protection for the brain [2]. The drugs tested so far were targeting a single stage of the ischemic cascade, whereas the biological consequences of ischemia are multiple at the tissue level. It becomes necessary to search for new therapeutic approaches and, based on the complex pathophysiological cascade associated with acute ischemic stroke, a multimodal approach targeting an array of key mechanisms appears to be a key future approach to enhance therapy [3]. Natural medicines seem to be a promising track. Traditional Chinese Medicine (TCM) used combinations of herbs successfully for centuries, acting on several biological targets in order to maximize therapeutic efficacy in fostering synergistic actions, and preventing potential adverse effects [4].

NeuroAiD™, a compound of TCM origin developed using international standards, has been the subject of numerous scientific and clinical studies reviewed in this article.

2. NEUROAID™

There are two proprietary formulations of the product for stroke patients: MLC601 and MLC901. NeuroAiD™, Nu-rAiD™ and NurAiD™ II are trademarks of Moleac. In Europe and some other countries, MLC901 (NeuroAiD™ II/NurAiD™ II) is available as supplement, consisting of nine herbal ingredients (i.e. *radix astragali, radix salvia mitorrhizae, radix paeoniae rubrae, rhizome chuan xiong, radix angelicae sinensis, Carthamus, Prunus persica, radix Polygalae*, and *rhizome acori tatarinowii*) with pharmacological effects equivalent to those of MLC601 (NeuroAiD™, Nu-rAiD™) which is available mainly in Asia [5].

Each capsule contains 400mg of extracts. The recommended dosage is 2 capsules of MLC901 (or 4 capsules of MLC601) three times daily for 3 months. The capsules are swallowed as such

with water. If needed, the capsules may be opened and drunk or administered via gastric tube after powder is diluted in water. The product should be used as an add-on on top of standard secondary prevention management, such as anti-thrombotic therapies and treatments for cardiovascular risk factors (e.g. statin, anti-hypertensive, anti-diabetic).

3. PHARMACOLOGICAL PROPERTIES

Neuroprotection refers to mechanisms that defend the brain tissue against injury due to an acute neuronal insult (e.g. stroke, cardiac arrest), or chronic neurodegenerative process (e.g. Alzheimer's and Parkinson's). On the other hand, brain plasticity is another important phenomenon wherein new synaptic connections are formed. Cell proliferation, migration and differentiation are three key mechanisms that allow neuroplasticity. Furthermore, neurogenesis and angiogenesis are the main coupled mechanisms in post-stroke recovery. The processes implicated in neurorepair, i.e. angiogenesis, neurogenesis and synaptic plasticity, would naturally occur in adult brains, but could also be stimulated through endogen neurorepair phenomena after injury [6].

Ideally, a therapeutic agent for stroke should be able to:

- prevent the spread of the ischemic cascade acutely, thereby limiting neuronal damage and clinical deficits,
- stimulate the proliferation and differentiation of new nerve cells to repair damaged areas, thereby improving functional recovery, and
- safely reducing the risk of suffering a recurrent cardiovascular event

The nature of NeuroAiD^{TM} as a combination of extracts makes it difficult to conduct pharmacokinetic studies. It is recognised that often the active constituents of herbal preparation are not easily identified nor their biological activities well characterised. Moreover, in the practice of TCM, often no single active constituent is responsible for the overall efficacy. Hence, it is acknowledged that bioavailability (pharmacokinetic) studies may not always be feasible.

Lazdunski and his team studied the pharmacological effects of NeuroAiD^{TM} by in vivo and in vitro experiments using mouse model of stroke (focal ischemia), rat model of global ischemia and cortical neuronal culture model of oxygen-glucose deprivation.

These experiments provide evidence of the neuroprotective and neuroregenerative properties of NeuroAiD^{TM} [5,7,8], showing how it:

- improves survival, attenuates infarct size, improves functional recovery in the model of focal ischemia.
- protects neurons against glutamate-induced injury.
- enhances cognitive recovery by reducing hippocampal CA1 cell degeneration, DNA fragmentation, Bax expression and malondialdehyde release in the model of global ischemia.
- activates the opening of K-ATP channels that may contribute to neuroprotection and ischemic preconditioning.
- increases Brain-Derived Neurotrophic Factor (BDNF) expression and induces proliferation of cells which differentiate and mature into neurons (neurogenesis).
- enhances rosette formation of human embryonic stem cells.
- induces longer neurites, denser outgrowths and networks, and more synaptic release sites in embryonic cortical neurons.

These properties of NeuroAiD^{TM}fulfill the criteria for an ideal stroke therapy and are important as treatment strategies in reducing the long-term disability of stroke, cardiac arrest and other brain injuries. These findings opened new encouraging perspectives for the protection and repair of the brain from ischemic injury, justifying prospective randomized double blind controlled trials of NeuroAiD in humans.

4. POST-STROKE TREATMENT

4.1 Effectiveness in the Chronic Phase of Stroke

Initially, various studies have been conducted with NeuroAiD^{TM} in patients within 1 week to 6 months of ischemic stroke onset. Results are presented here according to the nature of the main objectives of these studies.

4.1.1 Functional independence

Two randomized double-blind trials [9] have included 605 patients between 2 weeks and 6 months after a stroke of mostly intermediate to

high severity (Study 1: 200 patients; Study 2: 405 patients). They were treated with either NeuroAiD™ or Buchang Naoxintong Jiaonang, another TCM product largely prescribed for post-stroke recovery in China. For the functional independence subcategory of the Diagnostic Therapeutic Effects of Apoplexy Score (DTER), transposable to the modified Rankin Score (mRS), NeuroAiD™ treatment was associated with a higher improvement in functional recovery at 1 month. The pooled results showed that patients on NeuroAiD™ were 2.4 times more likely to achieve an independence functional outcome at one month than the control group (RR 2.4, 95% CI 1.28 to 4.51, *P*=.007).

A randomized, placebo-controlled, double-blind trial in 80 stroke patients treated with NeuroAiD™ or placebo for 3 months evaluated functional outcome as measured on the Barthel Index (BI) [10]. While the average BI score improved significantly in both groups at 3 months, patients who received NeuroAiD™ had a greater improvement in BI score than those who received placebo (36 vs. 29, *P*<.001). The mRS improved in both groups (*P*<.001), but significantly better for patients in the NeuroAiD™ group (mean rank 28.4 vs. 41.3). Setting a BI cut-off score of 65 as threshold for "assisted independence", 69.4% of patients treated with NeuroAiD™ achieved this level compared to 18.7% in the placebo group (*P*<.001).

A meta-analysis of these 3 studies showed an overall relative risk (RR) of 2.35 (95% CI 1.31 to 4.23) in favour of NeuroAiD™ [11].

In a retrospective cohort study of 30 patients within 6 months of stroke and treated with NeuroAiD™ for 3 months and another 30 matching patients who did not receive the treatment, more patients in the treated group achieved functional independence (OR 1.79, 95% CI 0.62 to 5.2, *P*=.29) and twice as many patients attained their pre-stroke mRS than the non-treated group (OR 3.14, 95% CI 1.1–9.27, *P*=.038) [12].

4.1.2 Motor recovery

In a study of 150 patients, the Fugl-Meyer Assessment (FMA) score was significantly higher at each post-baseline evaluation in the group receiving a 3-month regimen of NeuroAiD™ post-stroke compared to placebo (*P*<.001) [13]. These patients had a better motor recovery as early as 4 weeks and remained durable up to 12 weeks after start of treatment (Fig. 1).

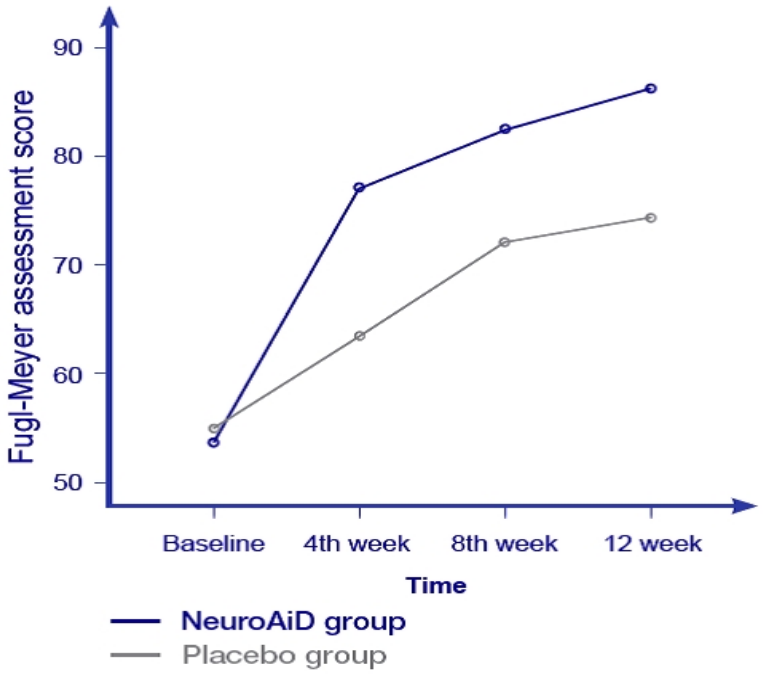

Fig. 1. Fugl-meyer assessment scores in two groups at baseline, 4, 8, and 12th week [13]
Additional 22% recovery of motor function in NeuroAiD™ group P<.001 at each assessment time from 4th to 12th week, From http://www.hindawi.com/journals/srt/2011/721613/ - publication covered by Creative Commons Attribution License

Among the four trials evaluating motor recovery included in the meta-analysis, two studies [9] used the motor score of DTER scale, while the other two [13,14] used the FMA. A meta-analysis of these studies shows a trend towards better improvement in motor function at the end of each study in patients treated with NeuroAiDTM (standard mean difference 0.27, 95% CI -0.02 to 0.55, P=.06) (Fig. 2) [11].

4.1.3 Recovery of visual field deficits

A study on recovery of post-stroke visual field deficit [15] randomized 40 patients with homonymous hemianopia from posterior cerebral artery infarction treated for 3 months with either NeuroAiD™ (n=20) or piracetam (n=20). A significant reduction in the measured area of deficits in both eyes was observed for each treatment group (*P*<.001). After treatment with NeuroAiD™, the relative improvement in the deficits of the visual fields was about 45% compared to only about 30% with piracetam.

4.1.4 Effect on cerebral blood flow velocity

The effect of NeuroAiD™ on cerebral blood flow (CBF) as measured by transcranial Doppler was assessed in a double-blind placebo trial on 80 patients with stroke in the territory of the middle cerebral artery occurring within one week of initiation of treatment with either NeuroAiD™ or placebo for 3 months [10]. The CBF velocity at 3 months significantly normalized in both groups, but more so in the NeuroAiD™ group than the placebo group (15.9 vs. 9.6 cm/sec, *P* =.009).

4.2 Effectiveness in the Acute Phase of Stroke

4.2.1 Chinese medicine NeuroAiD efficacy on stroke recovery (CHIMES study)

CHIMES, a multicentre, double-blind, placebo-controlled trial, randomized 1100 patients within 72 hours after the onset of an acute ischemic stroke of intermediate severity with National Institutes of Health Stroke Scale (NIHSS) score of 6 to 14 treated for 3 months [16]. The results of the primary and secondary endpoints were in favour of NeuroAiD™ although they did not reach statistical significance:

- mRS score shift (primary endpoint): odds ratio (OR) = 1.09 (95% CI 0.86 to 1.32)
- mRS score 0-1 at 3 months (secondary endpoint): OR = 1.11 (95% CI 0.86 to 1.42).

However, the odds of recovery obtained with NeuroAiD™ are the highest observed among recently reported studies on post-stroke neuroprotection [17-20]. The absolute benefit of achieving functional independence (i.e. mRS 0-1) with NeuroAiD™ corresponds to 26 additional patients for every 1000 treated. With a larger population, such a moderate but clinically relevant treatment effect may have become statistically significant.

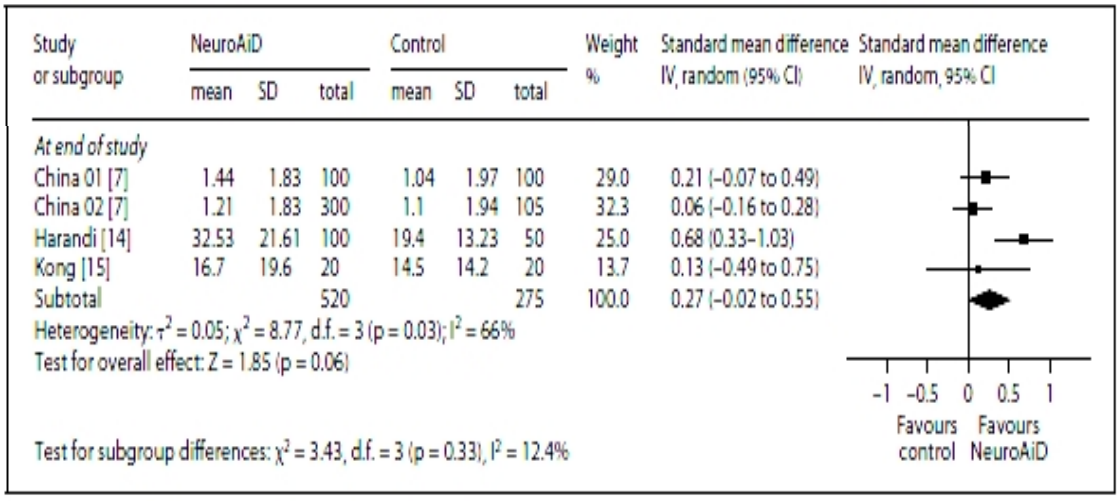

Fig. 2. Motor recovery as measured by fugl-meyer assessment score or DTER subscales among patients with stroke [11]

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Among patients whose study treatment was initiated beyond 48 hours after stroke onset (n=520), NeuroAiD™ improved the month 3mRS (mRS shift OR = 1.29 and mRS dichotomy 0 to 1 OR = 1.39). This corresponds to 78 additional patients reaching functional independence per 1000 patients treated [16].

In a pre-planned analysis of patients from the Philippines included in the CHIMES Study [21], the authors found a statistically significant treatment effect in favour of NeuroAiD™in the primary outcome of mRS and other secondary outcomes (NIHSS and Barthel Index) (Fig. 3). This was likely attributable to the inclusion of patients with more severe stroke and longer delay from stroke onset to treatment initiation.

4.2.2 Updated meta-analysis including CHIMES

The CHIMES authors updated the previous meta-analysis [11] by including all CHIMES patients. Functional improvement was significantly greater with NeuroAiD™ compared to control (OR = 1.25, 95% CI 1.00 to 1.56, *P* =.05) (Fig. 4-A) [16].

Because previous studies included in the earlier meta-analysis focused on non-acute stroke between 1 week and 6 months after stroke [9,10], an additional meta-analysis that included CHIMES patients having started treatment beyond 48 hours after onset of symptoms showed a statistically significant increased effect on recovery with NeuroAiD™ (OR = 1.63 95% CI 1.20 to 2.22, *P* =.002) with lower heterogeneity between studies (Fig. 4-B).

4.2.3 Effects on early vascular events in stroke patients

Given the positive effects of NeuroAiD™on cerebral blood flow velocity and its potential role in ischemic preconditioning, the CHIMES authors hypothesized that NeuroAiD™ could have preventive effect on the occurrence of early vascular events after stroke onset. Hence, they performed a post-hoc intention-to-treat analysis on the patients who were recruited and randomised in the CHIMES study. The number of patients who experienced any vascular event or vascular death was counted for each treatment. Each event was prospectively reported while blinding was still maintained during the 3 months of treatment. NeuroAiD™ or placebo was given in addition to standard treatment of cardiovascular risk factors (i.e. antiplatelet agents, statins, antihypertensives and antidiabetics) [22].

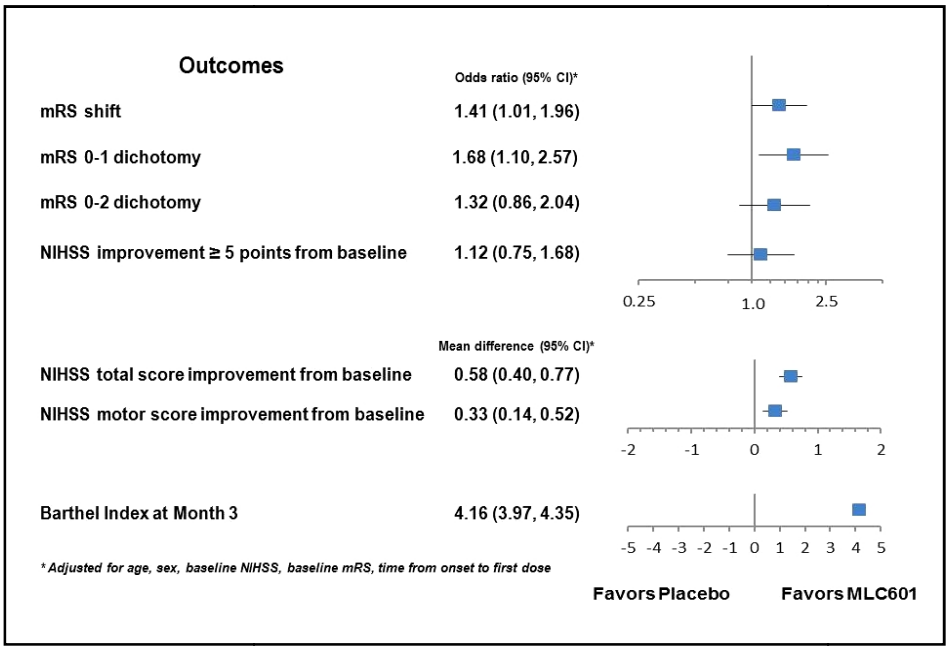

Fig. 3. Primary and secondary analyses in the Philippine cohort in the CHIMES Study showing effects favoring NeuroAiD [21]

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Overall the composite vascular outcome of recurrent stroke, acute coronary event and vascular death occurred in 47 (4.3%) patients over the 3-month follow-up period, with 16 (2.9%) patients in the NeuroAiD™ group and 31 (5.6%) in the placebo group. This difference was statistically significant between the two groups (*P* =.025). The number of each individual event/death was consistently lower in the NeuroAiD™ group, although they did not reach statistical significance, except for fatal stroke (*P*=.045), mainly due to the relatively small numbers of event in each subgroup. In absolute terms, about 27 fewer patients suffered a recurrent vascular event or death over 3 months per 1000 patients treated (Fig. 5).

There was no increase in bleeding or non-vascular death, confirming the excellent safety profile of the product in combination with standard antiplatelet agents.

Stroke from small artery disease may be of particular interest. Lacunes are mostly due to lipohyalinosis and microatheromatosis of perforating cerebral arteries [23] and the use of NeuroAiD™ in this important and common condition may be considered in future clinical trials.

4.2.4 Extension study

CHIMES-E ("Extension"), an extended follow-up of patients who participated in the main CHIMES trial, is underway [24]. The purpose is to test the hypothesis that at 2 years an initial regimen of NeuroAiD™ for 3 months in addition to standard treatment is superior to placebo in reducing neurological deficit and improving functional outcome after a cerebral infarction of intermediate severity.

4.2.5 Imaging study

CHIMES-I ("Imaging") is a post-hoc analysis of the effects NeuroAiD™ in stroke according to baseline brain imaging characteristics in patients randomized in the CHIMES trial [25]. It plans to test the hypothesis that certain initial imaging features may predict treatment effect with NeuroAiD™.

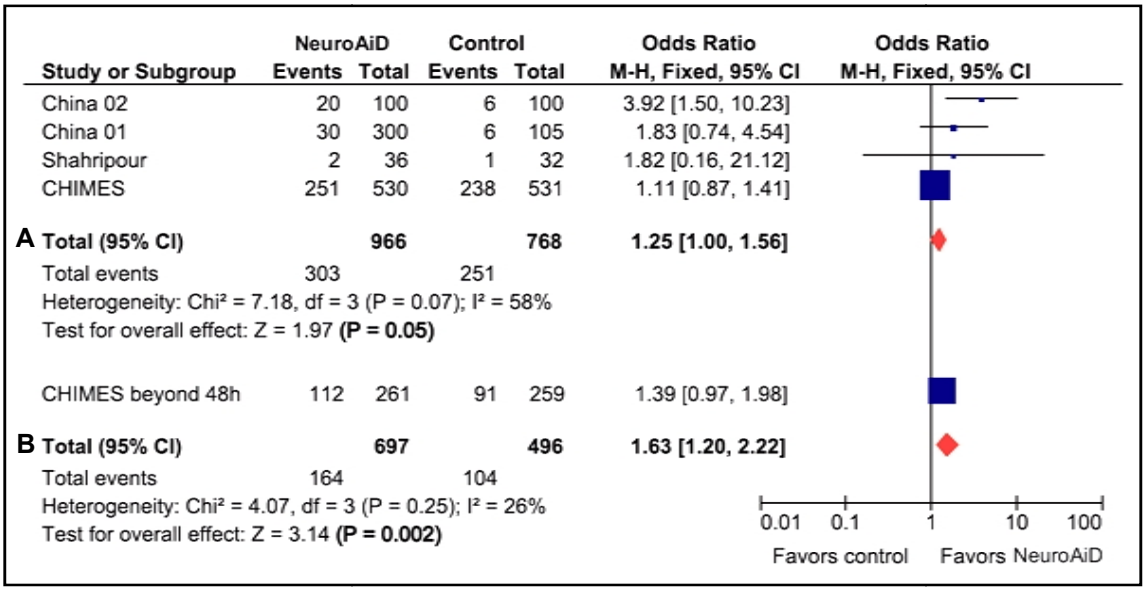

Fig. 4. Forest plots for updated meta-analysis on NeuroAiD [16]. A. Functional outcome at end of study, including all patients in the CHInese Medicine NeuroAiD Efficacy on Stroke recovery (CHIMES) Study. B. Functional outcome at end of study, including patients treated >48 hours from stroke onset in the CHIMES Study

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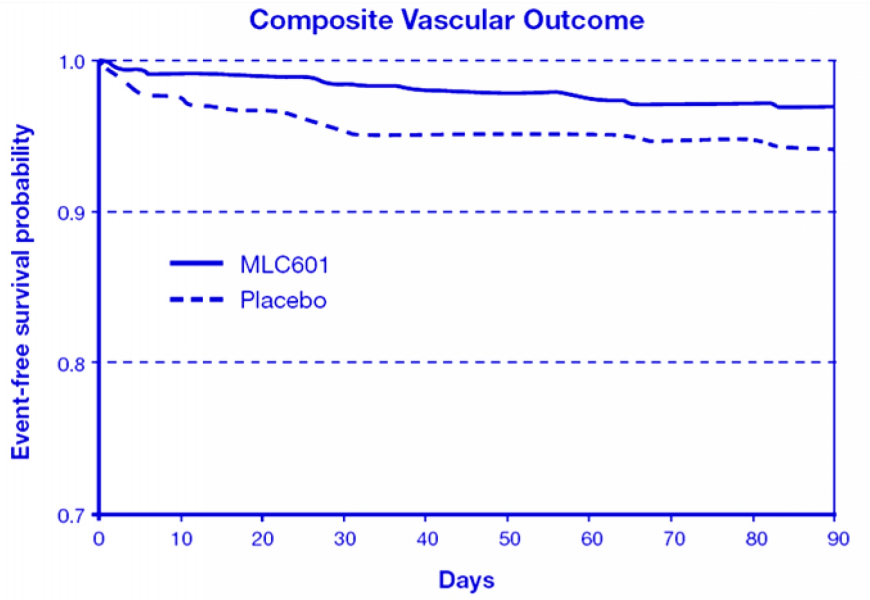

Fig. 5. Kaplan–Meier curve of composite outcome of recurrent stroke, acute coronary event, or vascular death in the CHIMES study [22]

Log-rank test: P=.024, hazard ratio, 0.51; 95% confidence interval, 0.28–0.93; Copyright permission obtained

5. SAFETY AND TOLERABILITY

5.1 Drug Interactions

The safety profile of NeuroAiD™ is well established in patients with ischemic stroke in the acute and chronic phase. In all clinical trials, NeuroAiD™ was investigated as an add-on treatment in conjunction with standard therapies for stroke and control of cardiovascular risk factors, like antiplatelets, anti-hypertensives, anti-diabetic medications, and lipid-lowering agents [11,16]. There were no report of major interaction between NeuroAiD™and these usual standard treatments used in ischemic stroke.

5.2 Patients at Risk

NeuroAiD™ has been prescribed in patients who suffered a hemorrhagic stroke and traumatic brain injury in the chronic phase [26]. In patients receiving anticoagulants, INR should be monitored carefully as with any modification of treatment. There are currently no systematic clinical trial data of use in children.

5.3 Clinical and Biological Safety

No serious side effects associated with NeuroAiD™ have been reported and the recent CHIMES study confirmed the excellent clinical tolerance of the product as being comparable to placebo [16]. Although rare transient and mild side effects (nausea, headache or vomiting) were reported [9,11], they are usually well controlled by reducing the dose by half during the first week of treatment. No changes in cardiac, hematological, hemostatic and biochemical parameters were observed, even with co-administration of aspirin [27,28].

6. CONCLUSION

Studies suggest that NeuroAiD™ treatment after a stroke may allow for a better recovery of motor and functional state when administered after stroke onset. The potential effectiveness and safety of NeuroAiD™ in a therapeutic stage where there is no proven efficient drug is worthy of research. A meta-analysis of clinical trials provides data on improved recovery at the chronic stage after an ischemic stroke, and it is of significant interest that treatment early after stroke onset may provide additional protection from further vascular events. These findings are supported by animal and cellular models clearly showing the neuroregenerative and neuroprotective properties of NeuroAiD™. The use of NeuroAiD™ in other specific stroke situations, for example, in different stroke subtypes, in the setting of transient ischemic attack, growth of atheroma, hemorrhagic stroke, etc., may be of particular interest in future studies. Hence, further data from new and

ongoing clinical studies will further strengthen the evidence for the role of NeuroAiD™ in neurological diseases and brain injuries.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

The authors declare that there is no major conflict of interests regarding the publication of this paper. IKA, SC, AM, HM, IM, HP, DT have received partial or full support to attend meetings, discussions, or presentations of NeuroAiD study results and publications.

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