MULTIPLE SCLEROSIS JOURNAL | MSJ

Controversies in Multiple Sclerosis

4-aminopyridine is not just a symptomatic therapy, it has a neuroprotective effect – Yes

Eva MM Strijbis, Jenny A Nij Bijvank and Joep Killestein

Multiple Sclerosis Journal

2020, Vol. 26(11) 1309–1310

DOI: 10.1177/1352458520923951

Correspondence to:
EMM Strijbis
Department of Neurology, MS Center Amsterdam, Amsterdam UMC, Location VUmc, de Boelelaan 1117, Amsterdam 1081 HV, The Netherlands.
e.strijbis@amsterdamumc.nl

Eva MM Strijbis
Joep Killestein
Department of Neurology, MS Center Amsterdam, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands

Jenny A Nij Bijvank
Department of Neurology, MS Center Amsterdam, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands/Department of Ophthalmology, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands

With the improved control of focal inflammation in multiple sclerosis (MS), the focus of treatment is increasingly shifting toward neuroprotective strategies and symptomatic treatment in early and later disease stages. New and well-known compounds are under renewed interest for the possibility of long-term neuroprotective effects.

An intriguing group of compounds that has been around for quite some time now are the aminopyridines. Prolonged release 4-aminopyridine (Fampridine®, 4-AP) has reached the market in 2010 after approval by the Food and Drug Administration (FDA) for the treatment of walking disturbances in MS. Enhanced axonal conduction by non-specific blockage of the voltage-gated potassium (Kv) channels of demyelinated fibers leads to increased axonal action potential propagation and improvement of the probability of synaptic vesicle release.[1] This basic mode of action suggests a potential to enhance virtually every neurological system that is affected by focal, demyelinating pathology but the clinical effect has been mainly proved for walking abilities. Phase 3 trials showed an improvement on walking tests in a subset of patients (fampridine responders) after short-term treatment, with consistent effects compared to controls over the longer term.[2,3] Since then, subsequent studies found small, but beneficial effects on a broad range of other clinical and self-reported outcome measures assessing mobility, visual disturbances in internuclear ophthalmoplegia, cognition, fatigue, and quality of life. These effects remain over longer treatment periods and after discontinuation of therapy.[4]

These long-term effects suggest additional, more long-lasting changes other than electrophysiological properties. Besides enhancing axonal conduction, experimental blockage of Kv-channels reversibly inhibits T-cell activation in vitro.[5] Subsequently, suppression of inflammation, demyelination, and axonal degeneration was confirmed in a Kv3.1 knock-out (KO) mouse model: the animals had significantly reduced clinical signs after induction of chronic experimental autoimmune encephalomyelitis (EAE), and there was a decreased underlying lesion load. Interestingly, activated immune cells from these Kv3.1 KO mice were as effective as those from wild-type mice in adoptive transfer of EAE suggesting that the anti-inflammatory properties were not through change of the immune cells.[6] Further analyses then showed increased astrocyte markers and brain-derived neurotrophic factor (BDNF) expression suggesting that the anti-inflammatory effect of Kv3 blockage was indeed not exerted through suppression of immune cells but rather through protection of axons for inflammatory damage. These results were confirmed in a different study. Treatment with 4-AP ameliorated the clinical course in a relapsing-remitting EAE model. In addition, also in this work, 4-AP did not inhibit the proliferative response of antigen-specific T-cells but the treated mice had less severe demyelination and less cellular infiltrates than control mice.[7]

Very recently, Dietrich et al.[8] confirmed these findings in a large multi-center effort that studied the neuroprotective effects of 4-AP in a myelin oligodendrocyte glycoprotein (MOG)-induced EAE–optic neuritis (ON) model, an optic nerve crush model and retrospectively in MS patients. In line with the other EAE studies, treatment with 4-AP gave better clinical scores in mice with EAE-ON compared to sham-treated mice. The effect was comparable to treatment with fingolimod, which was used as a control situation. Improvement of clinical scores remained present still 21 days after 4-AP withdrawal. A reduced degeneration of the inner retinal layers was present in the 4-AP-treated EAE-ON mice, suggestive of less axonal damage. This was also seen in the fingolimod-treated control EAE-ON mice. A combination of treatment with fingolimod and 4-AP showed an additive beneficial effect. Here, clinical disability was even less and retinal degeneration almost completely prevented. These effects did not seem to be driven by inflammation, since microglial and T-cell activation were comparable between EAE-ON mice treated with and without 4-AP, while it was significantly reduced in fingolimod-treated mice. Interestingly, there was an increased myelin density in the optic nerves of 4-AP-treated mice, and oligodendrocytes of the

4-AP-treated animals were less sensitive to glutamate toxicity. In the same study, the authors sought to confirm the findings from the animal studies in an in vivo setting in MS patients. A large retrospective multicenter cohort of MS patients was investigated with optical coherence tomography (OCT) and showed that indeed similar effects on retinal nerve fiber layer (RNFL) thickness exist in MS patients. There was a decreased loss of the macular retinal nerve fiber layer (mRNFL) in 52 MS patients after 12 and 24 months of treatment with 4-AP, compared to 51 age, disease duration, subtype, and disease modifying therapy-matched MS controls.

Now, how does this translates to neuroprotection in MS patients? The RNFL is quite a robust and accurate measure for neurodegeneration in MS.[9] MS patients with and without optic neuritis have a decreased RNFL thickness compared to controls. Thinning of the RNFL increases over the course of the disease and is most prominent in secondary progressive MS. RNFL thickness is correlated with increased disability, progressive disease, and accelerated atrophy on brain magnetic resonance imaging (MRI).[10] In the study by Dietrich et al., a similar pattern was present. Median Expanded Disability Status Scale (EDSS) scores did not change over time and did not show significant differences between the two groups. But, a thinner mRNFL was significantly associated with a higher EDSS in the control group. High EDSS scores are a prerequisite for the prescription of 4-AP but are also often quite insensitive to capture any relevant change in underlying pathology. Perhaps, RNFL changes are more sensitive to capture long-term treatment effects. The significant differences in both groups are given the small sample size quite remarkable. Of course, claims of neuroprotection must be made with the greatest care and yet we do not have all answers to make definitive claims. These promising effects first need to be researched longitudinally in a cohort that is well controlled and monitored for the presence of inflammation to rule out any additional anti-inflammatory effects. Then, assessment of the long-term clinical benefit of treatment with 4-AP is needed, preferably with more sensitive outcome measures than EDSS scores. But a crucial question is if we are not too late when the effects of treatment are studied in the progressive patients with walking disturbances for which 4-AP is currently prescribed, or if it is worth the investment to also study the long-term protective effects in patients that are earlier in their disease course.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Jenny A Nij Bijvank https://orcid.org/0000-0001-6956-6369

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