



Short report

Goat serum product “Aimspro” restores conduction in demyelinated human optic nerve fibres [☆]B.D. Youl ^{a,*}, S.D.T. White ^b, M. Cadogan ^c, D.W. Maizels ^d, I.C. Brooman ^e,
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Abstract

Acute optic neuritis is a common manifestation of multiple sclerosis. It presents as an episode of monocular blurring of central vision, with a pronounced effect on colour discrimination. While spontaneous resolution usually follows, successive attacks may result in irreversible and often, slowly progressive, visual loss. No medication has yet been available to improve visual function in these chronically affected patients. Here we present evidence of a promising approach to therapy along with electrophysiological indications of a remarkable rapidity of onset.

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Six multiple sclerosis patients with stable visual dysfunction due to chronic optic neuropathy (2 male, 4 female, aged 32–42 years, disease duration 8–16 years) were treated with Aimspro, an unlicensed polyclonal antibody product derived from purified goat serum. The drug was being made available free of charge, on an informed consent basis, by Daval International Limited. One of the authors (BY) was engaged by the company to monitor the response to administration of the drug (1 mL by sub-cutaneous injection, generally self-administered after the first or second dose). The frequency of administration, adjusted according to response by DM and IB, varied from once,

to three times weekly. No patient had received the product previously, but one (Case 2) had been taking interferon beta-1a for nearly a year. This treatment was ceased the day prior to treatment with Aimspro. Distance and colour vision acuity recordings and visual evoked potential (VEP) studies were carried out immediately prior to the first injection, and at approximately one hour, one week and 4–7 weeks thereafter. Prior to treatment, all subjects described that their vision had slowly and progressively deteriorated over periods of 3–14 years and none could recall intervening periods of what may have represented acute optic neuritis.

Corrected distance acuity (Snellen chart) and colour vision (square root of total error score from the Farnsworth-Munsell 100-Hue test¹) data, acquired under standardized lighting conditions, are presented (Table 1). Monocular VEP studies were carried out on each occasion. Perimetry was not performed. Sub-lingual temperature was monitored and showed no significant variability, within

[☆] Sources of funding: The medication was provided free of charge by Daval International Limited, for which BY was a paid consultant. SW, DM and IB were directors of the company, which also funded research carried out by MC and AD.

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Table 1
Demographic, psychophysical and neurophysiological data

MS Type	Dx Years	VsDtn Years	Eye	P100		VA 1		CV	CV	CV 7	CV FU
				ms	VA pre-	Hour	VAFU	Pre-	Post	Days	
SP	16	14	R	146	6 6-3	6 6-2	6 6	11.83	10.77	10.77	10.2
			L	158	6 9-2	6 9 -2	6 6-2	15.23	11.66	9.8	9.8
SP	9	3	R	152	6 6-1	6 6-1	6 6	7.75	8.72	6.93	6.32
			L	161	3 24-1	3 12-1	3 12-1	21.82	19.8	19.08	12.33
SP	8	6	R	173	6 18	6 12	6 18	21.26	17.2	16.37	13.42
			L	207	6 18-1	6 18 + 1	6 18	19.6	18.97	19.18	12.96
SP	12	5	R	NR	1 18-1	1 9-1	1 18 + 1	30.59	27.86	33.29	29.33
			L	161	3 18-1	3 18	3 18 + 1	27.42	25.69	28.21	27.78
SP	16	14	R	112	3 36	3 24	3 18-1	14.97	13.56	11.66	12.96
			L	115	6 18	6 18	6 18 + 1	14.28	13.11	11.83	10.95
RR	14	4	R	114	6 6	6 6	6 6	7.21	6.63	7.75	5.29
			L	114	6 6	6 6	6 6	7.75	7.75	7.21	6.02

MS type = multiple sclerosis type, SP = secondary progressive, RR = relapsing remitting, Dx years = years since probable onset of multiple sclerosis, VsDtn years = years of progressive visual deterioration, Eye = right and left eyes are treated independently, P100 ms = P100 VEP positivity latency in milliseconds ($n < 117$), VA pre = Snellen chart derived visual acuity pre-treatment, VA 1 hour = as previously, ≈ 1 hour post-treatment, VA FU = as previously, at follow-up (4–7 weeks), CV pre = square root of the Farnsworth-Munsell 100-Hue score, CV 1 hour = as previously, at ≈ 1 hour post-treatment, CV 7 days = as previously, at 7 days, CV FU = as previously, at follow-up (4–7 weeks).

subjects, over time. Data from left and right eyes were considered to be independent for analysis and colour vision scores were treated as non-parametric.

Comparison of pre-treatment and follow-up distance acuities showed no significant change and in only two of the 12 eyes (case 2 left eye and case 5 right eye) was there an improvement of one line or more on the Snellen chart. A repeated measures analysis of variance (ANOVA) test on the colour vision scores, however, yielded $F(2.16, 23.73) = 8.52$, $p = 0.001$. Within approximately one hour of injection, there was significant improvement in colour vision in 10 of 12 eyes ($p = 0.008$, $Z = -2.667$, Wilcoxon signed ranks test). Comparison of pre-treatment and “one week” values showed no significant difference ($p = 0.055$, $Z = -1.923$) but comparison of pre-treatment and follow up data (at 4–7 weeks) showed a significant group benefit ($p = 0.003$, $Z = -2.981$). No significant side effects other than local pain and swelling at injection sites over the first 2–3 weeks, in three patients, were encountered.

For cases 5 and 6, VEP response latencies lay towards the upper limits of normal. Pre-treatment VEP studies from all but one of the remaining eyes showed delay in the P100 response, consistent with demyelination within visual pathways. In only one instance (case 4 right eye) was no response obtainable prior to treatment and this was the only eye from the entire series to show a significant change in averaged cortical responses at any time during the observation period. This 42-year-old woman with secondary progressive multiple sclerosis of spinal onset in 1992, had complained of gradually deteriorating vision since 1998. There had been four periods of 3–7 days’ duration of resolving blurring of vision between 1993 and 1997, but there had been no more recent episodic visual features in the history. Examination showed bilateral optic atrophy and marked impairment of distance and colour vision. Pre-treatment full field pattern reversal VEP studies at 15:02 h

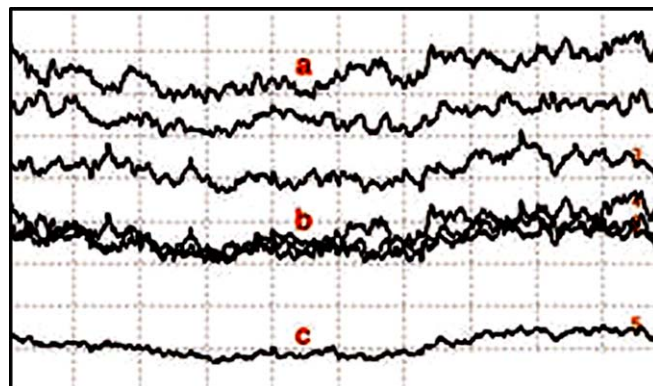


Fig. 1. Visual evoked potentials pre-treatment. Visual evoked potentials, recorded from the occipital cortex in response to standard checkerboard stimuli (OZ-FZ). (a) three individual runs; (b) the same runs, superimposed; (c) mean response.

yielded no reproducible tracings from the right eye (Fig. 1). A test dose of Aimspro (0.1 mL) was administered subcutaneously at 15:13 h, followed by an additional 0.9 mL at 15:25 h. A markedly delayed but reproducible P100 response could now be obtained at 15:43 h, at 165 ms (Fig. 2). The scalp leads had remained attached throughout the study and test conditions, including body temperature, were monitored. While this neurophysiological finding was consistent with reversal of conduction block in severely demyelinated fibres,² it was not accompanied by a clinically significant improvement in acuity data either immediately or on follow-up. The fact that no improvement in P100 latency could be detected from any eye over the study period argues against there having been significant remyelination during this time. Longer term observations would be needed to assess this adequately.

In summary, non-blinded, uncontrolled observations in six patients with slowly progressive visual dysfunction due to optic neuritis, show a significant improvement in colour

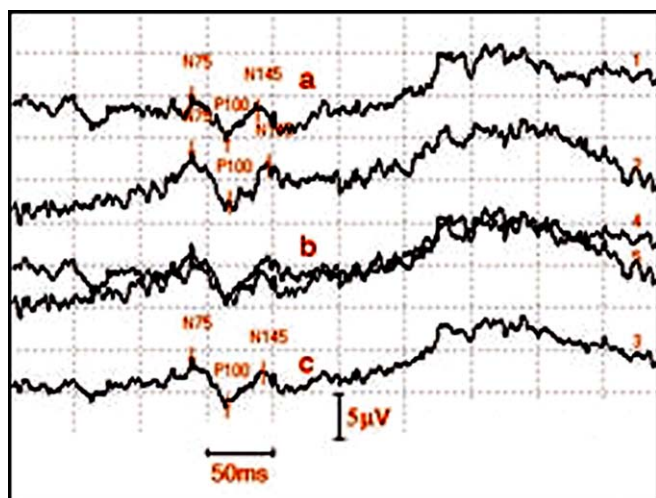


Fig. 2. Visual evoked potentials post-treatment. Using the same recording paradigm as Fig. 1, 30 min after sub-cutaneous injection of Aimspro. (a) two individual runs; (b) the same runs, superimposed; (c) mean response. A reproducible P100 response is now evident, with a markedly delayed latency of 165 ms.

vision over the course of 4–7 weeks of treatment with a novel medication, Aimspro. Other interpretations may be placed on this small study as well. First, learning effects have been described in colour vision testing of this kind,³ highlighting the need for confirmation of these findings under controlled, double-blinded conditions. Secondly, while neurophysiological data from one affected eye in a patient with a 5-year history of marked visual deficit are consistent with an interpretation that the drug's administration caused a reversal of axonal conduction block, one must have reservations about the significance of a single observation of this kind. The phenomenon was shown to have occurred within 30 min of treatment but a clinical observation by one of the authors (Youl, unpublished observation) on a 38-year-old female patient with a 'spinal' relapse of relapsing remitting MS, suggests that restoration of conduction may arise within as little as 10 min. Further clinical and neurophysiological observations on two patients with chronic inflammatory demyelinating polyneuropathy and four with Charcot-Marie-Tooth disease Type1A suggest that this rapid effect may pertain to the peripheral nervous system as well.

Visual deficit in acute optic neuritis is thought to reflect axonal conduction block related to local inflammatory demyelinating activity,^{4–6} but inflammation seems unlikely to be a persisting factor in chronically affected patients such as those described above. Aimspro is a polyclonal serum initially intended to provide high titre neutralizing antibodies for use in HIV patients. Characterization of the

serum has revealed a high titre of anti-HLA class 2 antibodies which are able to inhibit a variety of mixed lymphocyte reactions (Cadogan and Dalglish, unpublished observations). As increased HLA class 2 expression on brain cells and lymphocytes is recognized to be a major factor in the inflammatory process in multiple sclerosis, it was postulated that the polyclonal serum may be beneficial in multiple sclerosis and similar conditions.⁷ Indeed, monoclonal antibodies against HLA class 2 are under development by several companies. However, the rapidity of the clinical responses seen here suggests that other mechanisms may be operating *in vivo*. A delay in the inactivation of sodium channels, and the blockade of potassium channels have both been shown to improve conduction in experimentally demyelinated axons.⁸ Alternatively, a removal of the blockade of axonal sodium channels by endogenous substances such as nitric oxide⁹ may explain the rapidity of the drug effect. It is therefore hypothesised that in addition to any effects that the medication may have in influencing immunological events, it may also affect the security of axonal conduction directly, possibly via an alteration of the triggering levels of voltage gated sodium channels (Hugh Bostock, personal communication).

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