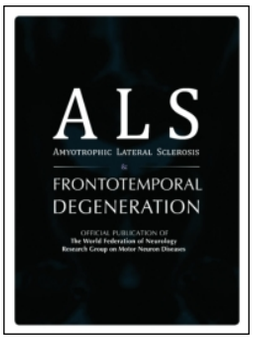
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The ALSUntangled Group

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REPORT

ALSUntangled No. 7: Investigating hyperimmune goat serum (Aimspro) for ALS

The ALSUntangled Group

Now in existence for 18 months, ALSUntangled has 263 twitter followers, and 69 ALS clinician scientists from across six countries participating in 32 active discussions in our NING. New discussions include Aimspro and 'Even Better Now'. We have published six investigations on seven different alternative and off-label treatment options, and have a new webpage up and running which should make it even easier for clinicians, scientists and patients with ALS (PALS) to find us and to interact (www.alsuntangled.org). At the request of PALS, we here investigate hyperimmune goat serum, also called Aimspro, as a treatment option for ALS.

Aimspro

Aimspro was initially created by inoculating goats with inactivated HIV virus, in an attempt to produce neutralizing antibodies for HIV infection. Daval International Limited, owners and distributors of Aimspro, report that their resulting goat serum-derived product is "composed of a set of peptides which act to stimulate the release and regulation of a molecular cascade that modulates the hypothalamo-pituitary-adrenal (HPA) axis. In addition, Aimspro has powerful anti-inflammatory properties as it contains cytokines that induce a predominantly TH-2 anti-inflammatory profile in the recipient. As well as a presumed general anti-inflammatory mechanism of action, a number of 'open-label' observations in patients with demyelinating diseases of the central and/or peripheral nervous system led to the hypothesis that Aimspro may improve the security of axonal conductance by a modification of voltage gated ion channels. Uncontrolled studies suggest a lowering of sodium channel triggering voltages" (1). Despite Pubmed searches of "Aimspro" and "hyperimmune goat serum" ALSUntangled has been unable to find any published evidence to support these proposed mechanisms. When these mechanisms are referred to in publications, "personal communications" and "unpublished observations" rather than peer reviewed publications are cited (2). A paper whose title suggested it might shed light on the mechanism of Aimspro was withdrawn (3).

Anecdotal reports suggest a possible therapeutic benefit of Aimspro for individual patients with a wide range of neurological diseases believed to have very different pathophysiologies; these include myasthenia gravis, CIDP, Charcot-Marie-Tooth Disease, FSH dystrophy, multiple sclerosis and Krabbe's disease (4). On the other hand, a placebo controlled trial of Aimspro for optic neuritis failed to show any benefits (5). If the above mechanisms are correct, it is not inconceivable that Aimspro could be useful for PALS. Inflammation may play a role in ALS pathophysiology (6). Numerous anti-inflammatory agents have been studied in ALS trials, although to date none has been effective. Riluzole, the only drug shown to prolong survival in ALS, may act in part through modification of sodium channels (7).

Beyond the theoretical, the only evidence that Aimspro might help patients with ALS comes from a single case published in two parts (2,8). The first author of the case is the actual patient, and received the Aimspro free (2), and the last author of the case is a director of Daval International Limited (2); thus, there is a potential for bias and conflict of interest. The case history reported is consistent with ALS, although details of neurological examinations, electromyography and testing to rule out mimics is lacking. From October 2003 through November 2008, the patient monitored his own disease progression mainly by performing monthly pulmonary functions on himself, including maximal expiratory pressure (MEP), maximal inspiratory pressure (MIP), sniff nasal inspiratory pressure (SNIP) and forced vital capacity (FVC). These measurements were combined into a "mean respiratory function (RFT)" whose rate of decline was calculated over various intervals. Less systematic measuring of strength was also performed. It is not clear that the patient's ability to make these measurements

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was validated in any way. Aimspro was injected subcutaneously at 4 mg twice weekly starting in October 2004, increased to 4 mg every second day in early December 2004, increased to 4 mg daily from late December 2004, increased to 4 mg twice daily from October 2005 and decreased back to 4 mg daily from September 2007. Serum sourcing changed from North America to Australia in September 2007. Multiple other therapies were also utilized including riluzole, minocycline, baclofen, dantrolene (all started well prior to Aimspro), bilevel positive airway pressure (started June 2004), and ambulation aids (started February 2004). In the pre-Aimspro period, mean RFT decreased by –2.3% per month (range –1.2 to –3.1%). During the first 13 months of Aimspro, mean RFT decreased by –1.3% per month (range –0.8 to –1.7%). During the period of twice daily injections, mean RFT decreased by –0.34% per month (range –1.01 to +0.34%). Finally, during the period of new serum sourcing, mean RFT actually improved by +0.72% per month (range –0.35 to +1.73%). There was no obvious change in the rate of decline of muscle strength over all these periods. No side-effects were reported.

The case report has been appropriately criticized in the literature (4,9). In addition to the problems noted in the preceding paragraph, Day has pointed out that the individual respiratory measurements reported in the case are noisy and inconsistent with each other in terms of change over time (9). Therefore, these should not have been pooled together into a single measurement. The SNIP data are especially noisy and show no clear change in rate of decline; MEP and FVC show progressive decline throughout, with some flattening over the final 12 months and MIP shows flattening over the final 12 months. Day goes on to suggest that rates of decline in the individual tests are comparable to rates seen in other ALS populations, and that changes in decline during Aimspro treatment could simply be the result of random variation, or bipap use (9). It is also odd that decline in respiratory functions might slow while decline in other motor functions would not.

As of 2007, Aimspro was available for purchase, at least in the United Kingdom, and reportedly cost £19,000 per year (10). It is unclear what the current availability and costs are. Our attempt to contact Daval International Limited has thus far met with no response. According to the company website, phase 2 trials of Aimspro are underway for patients with scleroderma and multiple sclerosis (1). Aimspro has recently received orphan drug status for ALS in the United States of America (1), suggesting that the company may be planning trials in PALS.

Conclusion

The mechanism of Aimspro remains unproven; if it is an immunomodulator and/or a modulator of sodium channels, it theoretically could be useful in ALS. A single, detailed but significantly flawed case report documents slowing in decline of certain respiratory functions in a patient claiming to have ALS, who started Aimspro shortly after bipap. Based upon this limited information, ALSUntangled supports further study of Aimspro, either in ALS animal models or in a small phase 2 trial with clear and objective endpoints carried out by skilled trialists familiar with the problems inherent with ALS clinical studies. Until a trial is undertaken, however, we do not support further use of this product by PALS.

The ALSUntangled Group currently consists of the following members: Richard Bedlack, Orla Hardiman, L.P. Rowland, Eric Pioro, Lisa Kinsley, Kathy Mitchell, Steven Novella, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Alex Sherman, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Marigakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Terry Heiman-Patterson, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Lisa Krivickas, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Tahseen Mozaffar, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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