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ALSUntangled No. 34: GM604

The ALSUntangled Group

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ALSUntangled Update 34

ALSUntangled reviews potential therapies on behalf of patients with ALS (PALS). Here we provide our opinion on GM604 (sometimes called GM6), a compound owned by Genervon Biopharmaceuticals, for which we have had more than 950 requests (1).

Overview

GM604 is a synthetic six-amino acid peptide fragment of a larger protein growth factor called motoneurotrophic factor (2).

Mechanism(s)

Genervon makes several claims on its website (3) regarding possible mechanisms of GM604 without any supporting data or references. Multiple members of ALSUntangled contacted Genervon by phone and emails in the hope of establishing a dialogue that would allow us to eventually better understand this and several other issues described below; unfortunately, our requests were either never answered (4) or were answered along with the following statement, which prevents us from sharing: 'This email is sent on behalf of Genervon Biopharmaceuticals, LLC. It may be privileged and contains confidential information intended only for the use of the recipient(s) named above. Use by anyone else is strictly prohibited' (5).

PubMed searches of GM6 and GM604 identified only a single possibly relevant publication (2). In this study, GM604 or vehicle were administered to mice following an experimentally induced stroke and reperfusion. Treatment with GM604 was associated with lower markers of inflammation and apoptosis, reduced stroke size, and improved behavioral outcomes relative to treatment with vehicle. It is not clear that recovery from stroke bears any similarity to neuroprotection in ALS, so this paper cannot be relied upon to provide foundation for a relevant ALS mechanism. This study was funded by Genervon, and one of the authors of this paper is a member of the Genervon leadership team (6), which creates a potential conflict of interest.

There may be other unpublished mechanistic data on GM604. The paper on GM604 (2) states 'Studies with the synthesized GM6 also demonstrated similar trophic effects in a transected femoral nerve rat model. In a zebrafish bioassay, GM6 protected the organism from L-2-hydroxyglutaric acid (LGA), induced oxidative stress and apoptosis in the CNS, and reduced apoptosis by 85% in the midbrain'. However, the only references we can find to support this work are patent applications. Based on all this, ALSUntangled assigns a TOE 'Mechanism' grade of D.

It should be noted here that various other neurotrophic factors have been tested in ALS, including IGF1 (7), CNTF (8) and BDNF (9)

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Note: this paper represents a consensus of those weighing in. Every investigator in this group does not necessarily share the opinions expressed in this paper.

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and were largely ineffective. Trophic factors have also been tested for a variety of other neurodegenerative diseases, including Parkinson's and Alzheimer's, without clear benefit to date. A challenge for many of these prior studies has been demonstrating that the neurotrophic factor has hit its target within the CNS.

Pre-clinical data

Genervon claims to have positive pre-clinical data on GM604 in ALS models. Its website (3) says 'GM604 also proved to be quite effective in the disease modification of ALS in ALS animals with mutant SOD1. It led to an improved clinical score in SOD1 mice ($p < 0.001$ for all groups compared to control). Moreover, GM604 delayed the onset of ALS symptoms by 27%, extended life by 30% and delayed the median clinical score deterioration time in ALS mice by 41%'. It further states 'GM604 dramatically increased the survival life span by 500% (six-fold from 7–14 weeks to 55–65 weeks) and increased preservation of motor neurons by 160% (2.6-fold) in a wobbler mouse model for motor neuron diseases such as ALS'. Important design issues necessary to interpret ALS animal studies are not provided in these website statements (10). No references are provided. PubMed search identifies no published peer-reviewed papers that support these claims. Based on all this, ALSUntangled assigns a TOE 'Pre-clinical' grade of D. Even if these data are eventually published and determined to be scientifically sound, there is no guarantee that they will translate into humans (11).

Data in PALS

Cases

Genervon's website describes six patients who were treated with GM604 via compassionate use programs (12,13). These patients received different numbers of GM604 treatments. It is not clear how many patients have been treated via these programs, exactly how these patients were selected, or whether any objective validated ALS outcomes are being systematically gathered during treatment. Genervon describes improvements in subjective, non-validated measures such as swallow volume (12), energy and mood (13). Improvements in fasciculation frequency are described in two patients (13); fasciculation frequency is not a useful ALS outcome measure, as it does not correlate with strength or progression rate (14). ALSFRS-R scores during treatment are described for only one of the patients (13); these improved by 1 point over two months, a change that is not uncommon in the natural history of ALS (15). ALSUntangled attempted to independently validate the reported diagnoses and benefits in these patients, as we have done for every treatment we review; unfortunately, we were told they had signed confidentiality agreements and thus could not share any information with us (16). Searches on PatientsLikeMe and Google identified no other reports. Based on all this, ALSUntangled assigns a TOE 'Cases' grade of D.

Trial

Genervon sponsored one small, brief, randomized, double-blind, placebo-controlled pilot trial of GM604 in PALS (17). Eight patients received GM604 for two weeks, four patients received placebo for two weeks, and these patients were followed for a total of 12 weeks. Outcomes included clinical measures (ALSFRS-R, FVC, timed get up and go (TUG), muscle strength, mortality), candidate biomarkers, and safety and tolerability (17). This study started in August 2013, and was completed in April 2014 (17,18). To date, the only publicly available source of results from this trial that we are aware of is the Genervon website. There is a potential for bias and conflict of interest when the company that owns a drug reviews, interprets and reports on its efficacy and safety data.

With regard to ALSFRS-R, the website states (19) 'seven out of the eight treated patients had their ALS disease progression slowed or stopped by week 12'. The website does not appear to describe what happened in the eighth treated patient nor in the placebo treated patients in this same analysis. Since ALSFRS-R plateaus (periods where this measure of disease seems to slow or stop) are not uncommon, especially over short intervals (15), it is not clear to us that this is evidence of treatment benefit. In an assay comparing imputed ALSFRS-R changes before and after treatment, the website states that there was no statistically significant difference between their two treatment groups (20). The website does report a statistically significant difference in ALSFRS-R slope between GM604 treated patients and the placebo group of the ceftriaxone trial (21). However, when using historical controls, it is critical to match according to demographic and disease-related variables that predict progression (22). The GM604 and ceftriaxone trials had different entry criteria (17,23) including some that are known to influence the rate of disease progression such as body mass index (24). Since it is not clear whether these groups were appropriately matched, these data are presently uninterpretable in our opinion.

With regard to FVC, the Genervon website states (20) 'The mean change in FVC from screening to week 12 for the placebo group was -17.5, while the change in the treated group was -5.6, $p = 0.0476$. The mean percentage change in FVC from screening to week 12 for the placebo group was -22.61% while for the GM604 treated group it was -5.6%, $p = 0.0359$'. As highlighted previously (25),

one problem here is the odd FVC change seen in the placebo group. In previous ALS trials, the percentage change in FVC has typically been 2–3% per month. The GM604 placebo group progressed much faster than this. There are different possible interpretations of this finding. Genervon claims to have enrolled rapidly progressing patients into both their treatment groups, and that GM604 slowed FVC progression in the PALS who received it (26). In our opinion, the inclusion criteria for this study do not appear likely to have selected a rapidly progressive population (27,28); the ALSFRS-R slope in the placebo (−0.034 units/day) group does not suggest rapid progression on this measure (27). On the other hand, it is also possible that some or all of the four PALS randomized to placebo may have been rapid FVC progressors by random chance. If so, they would not have been a fair comparison group (25). This is one of the problems with such a small sample size, and one of the reasons that small trials have a high false-positive rate (29,30); examples of small 'false-positive' ALS trials include lithium (31) and dexpramipexole (32). Larger sample sizes are more likely to be representative of the true population, more likely to produce fair comparison groups and more likely to produce 'true-positive' results (29,30).

With regard to other clinical measures, we have been unable to find the results from TUG, strength and mortality analyses. Genervon has multiple website entries devoted to its biomarker data. We asked ALSUntangled team member Robert Bowser, Genervon's own biomarker consultant (33), to comment on these data.

Robert Bowser writes: 'Genervon has created numerous press releases regarding biomarker results from their 12-week study of GM604 in ALS patients, suggesting that changes in biomarker levels indicated positive drug effects in patients. For example, "Genervon is particularly excited about the biomarker data, given that biomarkers are highly sensitive to changes in the underlying disease processes and are useful in predicting drug efficacy. In addition, biomarker measures are usually immune to the placebo effect" (34). The biomarkers examined in the blood and CSF samples collected during their small trial were selected based upon Genervon's prior unpublished in vitro cell culture data on gene expression changes that occurred in the presence of GM604. The goal was to determine if proteins predicted to be altered due to GM604 (based on the prior gene expression studies) could be detected in patients during the small clinical trial. The selected biomarker proteins were linked to ALS and included TDP-43, tau and SOD1. All of the biomarker assessments used research grade immunoassays (not fully validated assays) for measurements within the Genervon study. The exploratory goal for these biomarkers in the small trial should be to demonstrate the ability to detect and measure the candidate biomarker in each biofluid, with results supporting further use of the candidate biomarker in subsequent and larger clinical trials. The results indicate the ability to detect the candidate biomarkers in patient biofluid samples and support continued drug development in larger clinical trials. The biomarker data from this small trial do not indicate drug effectiveness in the patients, as the time-course of drug treatment is short, with no long-term outcome measures or long-term biomarker measurements. Any small changes in biomarker levels in the CSF or blood between groups may reflect the small sample size of the treatment and placebo groups as well as the short duration of this study. Larger clinical trials with longer drug treatment should be performed to test the efficacy of GM604, using biomarkers to assist in determining the ability of the drug to target particular pathways. Without these larger clinical trials, it remains unclear if GM604 alters biomarker levels during disease course, or what these alterations might mean with regard to clinical efficacy.'

In addition to all the above issues and problems, Genervon's pilot trial of GM604 fails to comply with consensus guidelines for the design and implementation of clinical trials in ALS due to its very short duration and lack of information release for peer review (35). Based on all this, ALSUntangled assigns a TOE 'Trials' grade of U.

Risks and costs

Genervon's website reports that GM604 'is very safe and tolerable as shown in phase I (32 subjects), ALS phase IIA (12 subjects), PD phase IIA (six subjects) and Stroke (28 of 36 subjects, as yet unblinded) trials. The number of adverse events (AEs) and serious adverse events (SAEs) are comparable to placebo, with no reported drug-related clinically (SEs)' (20). However, as mentioned above, we have been unable to review any of these data independently or even question patients who took GM604 in the trial or in the compassionate use program. This level of secrecy is unusual in our experience. Based on this, ALSUntangled assigns a TOE 'Safety' grade of U.

GM604 has been offered to patients in compassionate use programs outside the United States at a cost of $94,500 per six-dose treatment (16).

Conclusions

At this time ALSUntangled finds no independently verifiable data supporting the efficacy or even the safety of GM604 in patients with ALS. We believe that independent peer review and replication are fundamentals of good science (36,37). Accordingly, we share the FDA's April 2015 opinion that the data on GM604 in ALS should be released now for

Table I. TOE Grades for GM604 as an ALS treatment.

	Grade	Explanation
Mechanism	D	Acts on a biological mechanism (in an animal model of stroke) but it is not clear that this mechanism is relevant in ALS
Pre-clinical	D	Non-peer reviewed studies reporting benefit in ALS models (on the Genervon website)
Cases	D	Subjective reports of benefit without independently validated diagnoses or benefits
Trials	U	Data from one small, short duration study but this has not been published in a peer reviewed journal
Risks	U	Not enough independently verifiable information for us to make any conclusion here

independent peer review (38). If these preliminary data are confirmed to be positive, statistics on the false-positive rate of small trials (29,30) and consensus ALS trial guidelines (35) dictate that they be replicated in a larger, longer duration study before GM604 is deemed effective or even safe for patients with ALS.

ALSUntangled generally supports the use of expanded access programs during ALS drug development. We believe that these should be reserved for treatments that have at least some independently verifiable safety data. In our opinion, that is not the case with GM604, so we feel that expanded access is premature at this time. When we can independently verify safety data, we hope to see a GM604 group expanded access program that has transparent entry criteria, systematic objective outcome measures, full disclosure of results, and, as suggested by the FDA, allows for a sponsor's cost recovery but not for profit (39).

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