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The ALSUntangled Group

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REVIEW ARTICLE

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Off-label use of sodium chlorite by patients with ALS (PALS) has received much recent attention in the lay press (1–3). Here, on behalf of PALS who requested it we review the evidence for sodium chlorite in ALS.

Rationale

Over-activation of immune cells called macrophages and microglia occurs prior to symptom onset in animal models of ALS (4,5). PET imaging has similarly suggested widespread microglial activation in some PALS (6) and both patient blood samples and autopsy studies suggest that the degree of immune activation may correlate with disease progression (7,8). The intravenous agent NP001 modulates the activation of macrophages and is currently being studied in human ALS trials (9). Preliminary results are discussed further below (10,11). At the present time NP001 is not available outside of research trials. Sodium chlorite is the active ingredient in NP001 (12), and is available for off-label use, both orally (13) and intravenously as WF10 (14,15).

Relevant animal data

NP001 has been studied in the C57B1/6 G93A congenic SOD mouse model of ALS (16). Nineteen mice given NP001 every three weeks (five days on, 16 days off) starting at 65 days survived 13 days longer and had slower decline in blinded neuroscore evaluations compared to saline injected animals.

ALSUntangled finds no ALS animal studies of oral sodium chlorite or WF10.

Relevant human data

A randomized, double-blind, placebo-controlled phase IIa trial of intravenous NP001 in 136 PALS was recently completed (10,11). Although the predefined study endpoints of efficacy did not meet statistical significance, subjects taking NP001 showed a trend toward slowed disease progression as measured by the ALSFRS-R. Post hoc analysis also suggested that a greater percentage of subjects on NP001 (27%) experienced a halt in disease progression over the six-month trial compared to a combination of placebo-treated and historical controls (10%). Additional trials are being planned (11).

ALSUntangled is not aware of any clinical trials of oral sodium chlorite or WF10 in PALS. However, there are online anecdotal reports from PALS taking these formulations. The most widely publicized case is that of Eric Valor (1–3). He experienced the following while taking oral sodium chlorite: "My speech did get a little clearer and projection was louder. My left thigh muscle also awoke and you can see it in my video data. To this day I retain most of that regained movement." (17). Heywood et al. analyzed a group of anecdotal reports from patients taking oral sodium chlorite (18). They compared the change in ALSFRS-R scores reported by 17 PALS on PatientsLikeMe taking oral sodium chlorite over 2.5 months to 85 matched historical controls. Patients on oral sodium chlorite appeared to progress faster than matched controls; the authors reported an 80% confidence that oral sodium chlorite was worsening ALS progression rate. One criticism of this study is that 2.5 months is a short duration over which to look for an effect on ALS disease progression.

No similar analysis is available for WF10 due to the very small numbers of PALS on PatientsLikeMe that reported taking it ($n = 9$, of which only three are publicly reviewable). Of these, only the user named 'Persevering' reported "major" effectiveness and described it as follows: "Hands uncurled mostly and have become more 'flexible' and dexterous, beginning day 1. Walking has improved significantly. Balance, gait speed and foot lift improved and were noticed by several others on the third day, without me commenting. Continued improvement on day 3 thru 6. Was highly dependent on cane, now again am confident without. Speech has improved, to where some words and phrases are understandable again. Swallowing better. Cough far more productive from day 2. Elimination of minor day drooling, and even

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while sleeping" (19). Two other users reported minor transient improvements such as decreased mouth/lip numbness and improved tongue strength (20).

Dosing, potential side-effects and costs

In the above-described phase IIa trial, NP001 was used at 1 mg/kg and 2 mg/kg given intravenously as an induction cycle of five consecutive daily doses followed by five monthly cycles of three consecutive daily doses (10,11). These dosages appeared to be safe and well tolerated (10,11). NP001 is not currently available for purchase by PALS.

A popular dose of WF10 among PALS is 0.5 ml/kg per day, given intravenously in cycles for 3–5 days, followed by 14–21 day rest periods (21). Like NP001, these doses can alter human macrophage function (14). However, WF10 is not the same as NP001 (12); it contains other anions including chlorate, and has a much higher pH of 12 (14). These may create more side-effects compared to NP001. In one study of 102 patients with radiation cystitis treated for six weeks with either WF10 or placebo, roughly twice as many patients on WF10 experienced grade 1–4 anemia (22). Side-effects reported (23) in the PatientsLikeMe group taking WF10 ($n = 9$) were fasciculations ($n = 4$), fatigue, drowsiness or tiredness ($n = 5$), burning at injection site ($n = 2$), weakness, constipation or dizziness ($n = 1$ each). The cost of one-year supply of WF10 is reported by PALS to be between $17,000 and $60,000 (24).

While a wide range of oral sodium chlorite regimens have been used, the most popular are between 0.75 and 1.5 mg/kg given over 2–7 days in a row, followed by a rest period of 7–16 days, then repeating (17,25,26). Importantly, it has never been shown that oral sodium chlorite can be absorbed at levels that affect human macrophage function. In rats given radiolabeled chlorite, 34% of the initial dose can be found excreted in the urine over the next 72 h (27). However, in monkeys, chlorite is neutralized in saliva within 1 min and by gastric fluid in vivo in 5 min (28). Keuhne, one of the world's experts on WF10, states that he studied oral WF10 and found that it "can act on these mechanisms only intravenously, not orally" (29). Furthermore, there are data that raise concerns about the safety of oral sodium chlorite. According to McGrath and Keuhne, sodium chlorite is converted under acidic conditions (such as those in the stomach) to chlorine dioxide, which can be poisonous (12,29). While a small, short-duration study failed to show evidence of oral chlorite toxicity in humans (30), Keuhne stopped his research on oral WF10 "after two patients collapsed and one nearly died" while taking it (29). The most common side-effects in the PatientsLikeMe group taking oral sodium chlorite (31) were fatigue ($n = 10$), diarrhea ($n = 5$), headaches ($n = 5$), hospitalizations ($n = 4$), excess saliva ($n = 3$) and insomnia ($n = 2$). The cost of a one-month supply of oral sodium chlorite is reported to be between less than $25 and $99 (32).

Conclusions

The NP001 formulation of sodium chlorite acts through a plausible mechanism and preliminary data suggest that it is safe and may slow ALS progression in some PALS. The WF10 formulation of SC appears to act through this same mechanism. Although WF10 is available for off-label use, it is very expensive, may have more side-effects than NP001, and at this time has only scant anecdotal evidence for efficacy in PALS. ALSUntangled supports further carefully monitored studies of NP001 and WF10 in PALS. In contrast, oral sodium chlorite has potentially dangerous and toxic side-effects, may hasten disease progression, and is not clearly absorbed from the gut. We do not recommend further use of oral sodium chlorite unless it can at least be shown to be safe and to act on mechanisms in humans that are relevant to ALS.

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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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