

## REPORT

# ALSUntangled Update 1: Investigating a bug (Lyme Disease) and a drug (Iplex) on behalf of people with ALS

## THE ALSUNTANGLED GROUP

### Overview

ALSUntangled, a global scientific effort to help people with ALS (PALS) investigate alternative and off-label therapies (AOTs) for ALS (1), has now been active for 3 months. To date, we have received 10 unique queries from PALS, with these coming in via face-to-face meetings in our clinics, via email and via twitter. Within our NING, we have 38 ALS clinician-scientists from 4 countries participating in the investigations, with 13 active discussions underway. Specific ALS AOTs currently being investigated include:

1. Lyme Disease Testing and Treatment
2. Iplex
3. Dr. Zannos Grekos' Stem Cell Clinic
4. Equilibrium Therapy
5. Pulsed Electromagnetic Fields
6. The Bronx Project's Therapy
7. The Hickey Wellness Center
8. The X-Cell Center
9. The Eric is Winning Regimen
10. Diaphragmatic Pacing

To date, the discussions with the most activity have been the one on Lyme Disease Testing and Treatment, and the one on Iplex. We will now present a summary of these two discussions.

### Lyme Disease Testing and Treatment

**Background:** A number of websites claim a causal link between ALS and Lyme disease. The websites are often sponsored by "Lyme literate clinics" specializing in the treatment of chronic Lyme, or by the sellers of products for Lyme, which they state can cause hundreds of misdiagnosed illnesses (2,3). The evidence for their proposed link between Lyme and ALS comes from poorly documented case reports or small series in which there is either insufficient evidence provided to establish a diagnosis of ALS in the first place, or inadequate

follow-up to establish a true improvement in the ALS coincident with Lyme treatment (4–6). These Lyme literate clinics often state that the current standard of testing for Lyme (ELISA followed, if positive, by Western Blot) is inadequate, and they offer Lyme testing which they claim is better. We have seen no data to support the claim of superior testing.

**Investigation:** Ten ALS clinician-scientists from across the United States and Ireland have thus far shared their experiences with Lyme disease testing and treatment. All those weighing in use standard testing for Lyme, as is recommended by the American Academy of Neurology, the Center for Disease Control and the Association of State and Territorial Public Health Laboratory Directors (7, 8). Only 3 clinician-scientists have routinely tested most or all newly diagnosed patients with ALS for Lyme, the other 7 test it only when there are other symptoms or signs of possible Lyme, or when a patient asks for it. In all, more than 4,000 newly diagnosed PALS have been tested for Lyme by our group, with only 30 having had positive Elisa and Western Blot tests. Thus, in our experience, the incidence of positive Lyme disease testing in PALS is less than 1%, which is similar to the background incidence positive testing in people without ALS across the United States (9). Of the 30 PALS with positive Lyme tests, most were treated with intravenous antibiotics effective against Lyme for recommended durations (10), and none was ever seen to improve.

**Recommendation:** There is no convincing evidence that ALS can be caused by Lyme disease. PALS who exhibit symptoms of co-morbid Lyme disease can request standard, CDC-approved testing for Lyme from their neurologist, with the understanding that treatment of a positive Lyme test will not reverse their ALS. Until Lyme literate clinics can provide reasonable data supporting their claims, we do not recommend that PALS pursue evaluation or treatment in such clinics.

## Iplex

**Background:** Iplex, also called mecasermin rinfabate, is Inmed Incorporated's (11) complex of recombinant human insulin-like growth factor-1 (rhIGF-1) and its predominant binding protein IGFBP-3 (rhIGFBP-3). IGF-1 has been tested in 3 large double blind, placebo-controlled ALS trials (12–14). One trial demonstrated a statistical benefit in slowing ALS progression relative to placebo, though the clinical significance of this small effect is debatable. The other two trials showed no benefit. The addition of the binding protein in Iplex may increase IGF-1 bioavailability, and thus its potency (15). In 2007, Iplex was made available to PALS in Italy under an expanded access program. In February, 2009, Inmed released its data related to this Italian cohort (16). A small number of PALS in the United States were recently granted a similar “compassionate use” access to Iplex by the FDA. A clinical trial was being planned, but Inmed has decided not to move forward with the trial at this time (11).

**Investigation:** None of us have had PALS under our care try Iplex so we are unable to offer that kind of collective experience. We have, however, critically reviewed the data from the Italian Iplex cohort (11). Details on how the ALS diagnosis was confirmed in this cohort have unfortunately not been provided. Patients in this cohort differ from those in most prior ALS studies in that they had a longer time from symptom onset to start of treatment (38 months) and lower ALSFRS-R scores at the start of treatment (28 points). The dosing of Iplex in this cohort may not have been uniform, as evidenced by the statement “a majority of the patients initiated treatment at a dose of 1 vial per day . . . over time most patients have been escalated (11).”

With regard to safety and tolerability, 110 patients were exposed to Iplex, 57 discontinued treatment and 34 of these died. Five of the patients who stopped Iplex reportedly did so because of adverse events possibly related to treatment; these included muscle twitching, fatal cholelithiasis and infection following gallstone surgery, and three fatal cardio-circulatory arrests. The other 30 patients who died reportedly did so either from disease progression ( $n = 29$ ) or suicide ( $n = 1$ ). The discontinuation and death rates here appear much higher than those reported in prior ALS treatment trials. This has been attributed to the advanced stage of disease these patients were in at the time of enrollment, but there is no way to prove this theory with the data provided.

With regard to efficacy, we point out that without a concurrent control group there is no scientific way to determine efficacy. Inmed has shown data from 54 patients in the cohort who were treated for at least 6 months, and 24 patients in the cohort who were treated for at least 12 months. In the former group, they note a decline in ALSFRS of 0.68 points per month, with 20% of the group showing either no

change or a slight increase in this score. In the latter group, they note a decline in ALSFRS of 0.38 points per month, with 25% of the group showing either no change or a slight increase. The implication is that these patients progressed more slowly than patients in prior ALS trials. However, an obvious selection bias ensues when only patients who “do well” on a therapy are considered in an analysis. ALS is known to be a heterogeneous disease in terms of progression, making it especially important to consider all patients who start a study in the final intention-to-treat-analysis. Furthermore, the ALSFRS is known to be non-linear, with the rate of decline naturally flattening out in advanced stages of ALS (where the patients in this cohort were said to be).

**Recommendation:** There remains no convincing evidence that any form of IGF-1, including Iplex can significantly slow progression in human ALS. We do not recommend that PALS pursue off-label IGF-1 in any form at this time outside of a well-designed trial. We hope the planned trial of Iplex will carefully define the ALS diagnosis, use a standard dosing regimen, have a careful data safety monitoring plan (given the high number of drop-outs and deaths seen in the Italian cohort), and be placebo-controlled.

## Conclusion/Discussion

The ALSUntangled program is off to a good start, with a number of specific requests from PALS being investigated by a multi-national group of ALS clinician-scientists. PALS and other clinician-scientists who want to become involved in ALSUntangled can find instructions on line (16).

The ALSUntangled Group currently consists of the following members: Richard Bedlack, Orla Hardiman, 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, Merit Cudkowicz, Jonathan Goldstein, Jeffrey Rothstein, Bryan Traynor, Dan Pastula. Note: this paper represents a consensus. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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