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ALSUntangled 51: RCH4

The ALSUntangled Group

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RESEARCH ARTICLE

ALSUntangled 51: RCH4

THE ALSUNTANGLED GROUP*

ALSUntangled reviews alternative and off-label therapies (AOTs) for people with ALS (PALS). Here we provide our opinion on RCH4, for which we have had more than 1700 requests (1). We were first asked to review this product 3 years ago by the family member of a person with ALS. Since then, in spite of our best efforts, we have not been able to obtain much useful disclosable information on RCH4. We define "useful" as information that helps us describe exactly what a product is and helps us complete our Table of Evidence (2). "Disclosable" means information that is in the public domain or that we have been given permission to discuss in a public forum. Since it does not appear to us that any new useful disclosable information is forthcoming, we elected to move forward with the information we have. This is the first and only ALSUntangled review on RCH4. A previous unfavorable review of this product by a person with ALS on their blog (3) has been inaccurately attributed to ALSUntangled (4,5). While this person has done valuable work with our team before, he has clearly stated that his RCH4 review is separate from any work he has done with us and was not formulated using ALSUntangled standard operating procedures (SOPs) which includes review by our international team of clinicians and scientists.

Overview

RCH4 is described as "an investigative new drug" (6) that "does not have Regulatory Authority marketing approval in any country" (6). A United Kingdom-based website states that it will "probably slow the progression of your ALS" (6). In the words of patients who believe in RCH4, this website "is not the easiest or most organized" (7). Information about the product is interspersed between cartoons (8), stories of famous scientists whose breakthroughs were initially met with skepticism (8), controversial medical advice for PALS ("do not go to the gym" (6), "we do not recommend winter flu jabs" (6), attacks on respected clinicians, scientists and institutions in the ALS community (9–11), and cynicism about academia itself (12). Neither the molecular structure nor the chemical class of RCH4 is described. The RCH4 website authors identify themselves as "an informal charity group of retired scientists with lifetimes of experience in membrane osmosis and immunity research" (8). Our Pubmed search identified no published papers on RCH4, and we recall no scientific presentations about it at ALS meetings we have attended. The RCH4 website claims its submissions for publication and presentations have always been rejected (12). In fact, as recently as 2018, a "Michael Curan" had an abstract on RCH4 accepted for poster presentation at the Motor Neurone Disease Association's International Symposium (13,14). No authors appeared to present this abstract (14).

Mechanistic plausibility

RCH4 is claimed to cross link a "B-cell lipid raft target receptor" (6) which then suppresses a "previously unrecognized agent exclusively found in MND, FTD, Alzheimer's, and Huntington's" (13). This agent reportedly "evidences numerous effects including upregulating glutamate expression" (13). There are existing drugs that target B-cells and decrease the levels of proteins involved in other neuromuscular diseases (15). However, we did not find any publications implicating B-cells in ALS pathophysiology, and the

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Table 1. TOE Grades for RCH4 in ALS.

	Grade	Explanation
Mechanistic Plausibility	U	Purported to target B cells and a downtream agent. We have seen no convincing evidence that RCH4 does this.
Pre-Clinical	U	The RCH4 website describes a study in an ALS animal model but there are not enough details provided for us to scientifically review it
Cases	C	We were able to independently confirm an ALS diagnosis and slowing in ALSFRS-R progression in 1 person on RCH4
Trials	U	We found no trials of RCH4 in PALS
Risks	U	It is not clear to us that adverse events are being carefully and systematically monitored in RCH4-exposed patients

exact agent ultimately being targeted here is said to be "previously unrecognized" (13). We found no convincing data in the above-referenced website or abstract to support this proposed mechanism. Therefore, we assign a "Mechanistic Plausibility" grade of U (Table 1).

Pre-clinical data

The RCH4 website claims RCH4 was given to "transgenic mice with very aggressive ALS" (6) and increased lifespan by 18% (6). The specific mouse model is not disclosed, nor are important methodological details that might allow us to scientifically review this study (16). Given this lack of information, ALSUntangled assigns a TOE "Pre-Clinical" grade of U (Table 1).

Data in PALS

Cases

The reported ability of RCH4 to slow ALS progression is based upon a collection of cases described in a website (6) and abstract (13). Some of these same cases are also described on PatientsLikeMe (17) and a chat room (18). There are several problems with these descriptions that limit our ability to interpret them. First, the exact number of PALS that have received RCH4 is not consistently stated; one part of the website says "$n = 249$ (ALS & another indication)" (6), while the abstract refers to "51 subjects" (13). When analyzing results, it is important to know the total number of people who were exposed to the drug to avoid any possible ascertainment bias in which only those who do well on the drug are analyzed in detail rather than everyone who was exposed (19). For some, ALS diagnoses were reportedly confirmed by their treating neurologist (6), but the website also states, "if we are not satisfied with the diagnosis, the patient would need to be willing to travel to Europe for a physical examination" (6). It is not clear how many treated PALS had to travel to Europe to get their diagnoses confirmed, nor who actually did the confirming there. The main outcome measure was monthly ALSFRS-R measured by patients themselves and sent in electronically (6). It is not clear to us that treated patients had any training in completing this, nor that their measurements were ever validated via comparison to those with experience in performing this outcome measure. It is also not clear whether effects of symptomatic medications on ALSFRS-R were considered. Medications for drooling, for example, can transiently increase the ALSFRS-R (20, and personal observation by RB). If such medications were started during RCH4 exposure, they might have been confused as an RCH4 treatment effect. Finally, there are problems with the control groups selected. PALS on RCH4 were said to have a significantly slower ALSFRS-R progression compared to same PALS before they started RCH4 (incorrectly referred to as a "placebo comparison" (6)). This comparison assumes that, without treatment, ALSFRS-R progression is linear. It is actually curvilinear (it is faster in the beginning and very end of the disease, and often slows down in the middle stages of the disease where RCH4 treatment likely occurred (21)). Natural ALS progression can also have spontaneous plateaus and rarely even reversals (22). PALS on RCH4 were said to have significantly slower ALSFRS-R progression compared to those in the PRO-ACT database (6), or the pivotal Radicava trial (6). It is not clear how similar the demographics and baseline disease characteristics of RCH4 treated patients were to patients in PRO-ACT or the Radicava trial. Demographics and baseline disease characteristics have a strong effect on ALS progression (23,24), so imbalances in these alone may be a reason that two groups progress at different rates, independent of treatment. PALS with genetic ALS on RCH4 were said to have slower progression compared to family members with the same mutations (25). It is well reported that different family members with the exact same ALS-causing mutation can progress at different rates (26). Even genetically identical family members with ALS-causing mutations can be discordant for ALS progression (27,28).

One RCH4-treated patient gave us permission to talk to his neurologist and review his medical records. We were thus able to independently

confirm his ALS diagnosis and slower ALSFRS-R score progression rate on RCH4 (-0.2 points per month) compared to before they started RCH4 (-0.7 points per month). As mentioned above, these kinds of changes in ALSFRS-R progression can occur spontaneously (21,22). Two months into their RCH4 treatment, this patient began receiving botulinum toxin for drooling. Coincident with this, his ALSFRS-R "drooling" sub score improved from a 1 to a 4 (29), which confounds attempts to determine RCH4 treatment effects. Nonetheless, based upon this one case with validated diagnosis and validated slight slowing in ALSFRS-R progression, ALSUntangled assigns a TOE "Cases" grade of C (Table 1).

Trials

We found no clinical trials of RCH4 in PALS. Therefore, ALSUntangled assigns a TOE "Trials" grade of U (Table 1).

Risks, dosing and costs

The RCH4 website states that this product is safe (6) and the RCH4 abstract states that there are no reported side effects from its use (13). However, it is unknown to us whether there has been any kind of systematic monitoring for adverse events in patients on this product. Some countries require specific, rigorous, governmental and/or institutional safety oversight when investigational products are being sent to their citizens. In the United States, for example, the FDA and Institutional Review Boards oversee protocols for both "compassionate use" (30), and drug research studies (31). This kind of oversight has clearly prevented patient harm from other investigational products in the past (32). To our knowledge, RCH4 has not been approved or vetted through these established pathways. The website does mention some side effects in patients on RCH4 that were later determined to be due to "counterfeit edaravone" (6). Exactly what these side effects were, or how this determination of causality was made are not specified. Of concern, one website mentions 2 cases of anaphylaxis on RCH4, one of whom died (33). We attempted to obtain more information on these cases without success (34). Also, the one patient on whom we had records experienced a much faster decline in respiratory function (percent predicted FVC) while on RCH4 (5.7% per month) than they had before they started this product (1.2% per month (29)). Of course, just as with the slowing in ALSFRS-R, this association between RCH4 and increased FVC progression may not be causal. Considering all this uncertainty, ALSUntangled assigns a TOE "Risks" grade of "U" (Table 1).

RCH4 is dosed via "muscle injection" at a frequency of "twice weekly typical" (35). Treatment reports on PatientsLikeMe suggest a regimen ranging from 0.18 ml to 4.41 ml weekly (17). It is reportedly supplied to PALS for no cost through a "charity" (35). No more details on the "charity" are given. We found no record of any charity with the term RCH4 in its name registered in the United Kingdom (36).

Conclusion

RCH4 is an unlicensed, unapproved product reported to "probably slow the progression of your ALS" (6) on a website. The only peer reviewed publication we found on this product is a single abstract which was never presented at a meeting. We have been unable to determine RCH4's structure or chemical class, and its purported mechanism is one that has never been shown to be useful in treating PALS before. We have been unable to independently verify RCH4's reported efficacy or even safety. Thus, at this time, we cannot advise PALS to use this product. We hope the proponents of RCH4 will someday present more useful information about their product at a scientific meeting or in a peer reviewed publication.

We believe that regulatory oversight is important for optimizing patient safety on experimental drugs, and that independent peer review and replication are fundamentals of good science. Caution should be exercised around any product being developed and in clinical use without these safeguards and fundamentals in place.

Declaration of interest

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