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ALSUntangled No. 30: Methylcobalamin

The ALSUntangled Group

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ALSUntangled reviews alternative therapies on behalf of patients with ALS (PALS). Here we review the use of methylcobalamin (MeCbl) for ALS, for which we have had more than 250 requests (1).

Overview

Cobalamin, also known as vitamin B12, is a water-soluble vitamin that plays key roles in DNA synthesis and regulation, fatty acid and amino acid metabolism, blood formation and normal functioning of the nervous system (2). Humans are incapable of synthesizing cobalamin and thus must acquire it via diet or oral or injected supplements (2). Absorption of oral cobalamin requires functioning of the stomach, pancreas and small bowel (2,3). Cobalamin deficiency from insufficient intake or, more commonly, impaired absorption, can lead to fatigue, anemia, impaired memory, confusion, psychosis, peripheral neuropathy and spinal cord degeneration (2,3). There are many forms of cobalamin. Cyanocobalamin is the most commonly manufactured form, and must be converted by the body into an 'active form' before it can be utilized (2). MeCbl is an active form, which does not require further conversion (2,3).

Mechanism(s)

There are several ways that MeCbl could be useful in slowing ALS progression. In cell culture studies, MeCbl has been shown to ameliorate oxidative stress (4), glutamate toxicity (5,6) and apoptosis (5,7). Oxidative stress (8), glutamate toxicity (9) and apoptosis (10) are believed to play important roles in ALS progression and have been targeted in previous clinical trials; riluzole, the only medication reproducibly shown to prolong survival in PALS, is believed to act at least in part through ameliorating glutamate toxicity (11). High doses of MeCbl can inhibit DNA methylation (12), which is known to be increased in the spinal cords of PALS and is potentially responsible for harmful transcriptional dysregulation (13). Finally, MeCbl lowers plasma homocysteine levels (14). Plasma homocysteine levels are elevated in PALS with a shorter time to diagnosis (15) and homocysteine can be toxic to motor neurons in culture (7). ALSUntangled assigns a TOE 'Mechanism' grade of A based on this information (Table I).

Pre-clinical data

There are two studies of MeCbl in pre-clinical ALS models. First, in a motor neuron-like cell line, MeCbl was shown to reduce homocysteine-induced apoptotic cell death (7). There is at least one methodological problem with this study in that it does not appear that raters were blinded. Secondly, in the wobbler mouse model of ALS, post symptomatic treatment with high dose MeCbl (30 mg/kg) was associated with better preserved grip strength compared to lower dose MeCbl (3 mg/kg) or vehicle (16). There are methodological problems with this study according to published guidelines (17), including small animal numbers, and failure to randomize. These findings have not been independently confirmed. ALSUntangled assigns a TOE 'Pre-clinical' grade of C based on this information (Table I).

Data in PALS

Within the online community PatientsLikeME, 40 PALS reported taking MeCbl and nine completed evaluations on doses ranging from 2500 mcg to 25 mg daily (18). The route of administration (oral or injected) was not specified. Of these nine, only two reported any effectiveness (18). Both rated this as 'moderately effective' but did not give specifics (18). Google search identified one additional PALS who reported using MeCbl injections at 25 mg daily, along with other supplements (19). He credited MeCbl as helping to preserve his muscle strength but it is not clear to us how that was determined. ALSUntangled assigns a TOE 'Cases' grade of D based on this information (Table I).

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Table I. TOE grades for methylcobalamin as an ALS treatment.

	Grade	Explanation
Mechanism	A	MeCbl can lower homocysteine levels in humans
Pre-clinical	C	Multiple flawed peer-reviewed publications report benefits of MeCbl in ALS models
Cases	D	Subjective report(s) of MeCbl benefit without validated diagnoses and/or benefits
Trials	D	Multiple flawed human trials reporting benefits
Risks	B	More than 0% but less than 10% of exposed patients in human trials experienced adverse events related to IM injections (but no serious adverse events)

There have been three trials of MeCbl in ALS, all by the same Japanese group. In the first, 12 PALS were randomized to receive 25 mg IM daily and 12 to receive 0.5 mg IM daily (20). This was a double-blind trial in which compound muscle action potential amplitudes (CMAPs) were obtained in six muscles and averaged at day 0, day 14 and day 28; the ratio of the day 28 CMAP averages to the starting CMAP averages was the sole outcome measure. This ratio was statistically greater in the high dose group. Eight patients in the high dose group had an increase in their CMAP average (and were called 'responders') while all patients in the low dose group had a decrease ('non-responders'). It was noted that 'responders' had a significantly longer mean disease duration (23.1 months) compared to non-responders (18.1 months), and fewer upper motor signs. Problems with this study include small sample size, short duration of follow-up, incomplete sample characterization (some enrolled participants had purely lower motor neuron signs, and the tests used to exclude ALS/PMA mimics were not specified), and use of CMAP amplitude, which is fraught with potential errors and inaccuracies (21).

The second trial was published in Japanese (22), but the author provided a summary in English for us (23). This was a non-randomized, non-blinded trial of 41 PALS by Airlie House criteria (24). Every other patient who came to the clinic was assigned to MeCbl and compared to untreated patients. In this study, MeCbl was dosed at 50 mg IM twice a week because this dose appeared similar to 25 mg IM daily with regard to CSF levels (23). Of the original 41, seven dropped out, leaving 18 treated and 16 untreated. There were no obvious differences in Airlie House level, age or gender between these two groups. The group assigned to MeCbl survived an average of 27.7 months, while the untreated group survived 17.7 months, a difference that was statistically significant (23). This trial suffers from major design flaws, including small sample size, lack of randomization or blinding, and lack of adequate sample characterization to determine if there were other baseline prognostic variables that differed between the two treatment groups and might have contributed to the difference in survival (25).

The third trial was randomized and double-blinded, and enrolled 370 PALS by Airlie House criteria (24), who were within the first three years of their illness and had their ALSFRS-R score drop by 1–3 points during a 12-week lead-in period (26). Participants received either MeCbl 50 mg IM twice a week, or MeCbl 25 mg IM twice a week, or placebo and were followed for 3.5 years. Primary outcome measures included ventilator-free survival and change in ALSFRS-R score. Treatment groups appeared similar in terms of baseline demographic factors and ALSFRS-R changes during the lead-in period. No differences were found across these treatment groups in the primary outcome measures. In a sub-group analysis consisting only of patients within the first 12 months of their illness, treatment with 50 mg MeCbl was associated with significantly longer survival versus 25 mg or placebo. In this same sub-group analysis, treatment with 50 mg was associated with a significantly smaller change in ALSFRS-R score over the course of the study compared to 25 mg or placebo. This sub-group analysis was reportedly pre-planned and there were no other sub-group analyses, so no adjustments had to be made for multiple comparisons (23). The number of drop-outs was similar across all treatments, and results were the same whether drop-outs were included or not (23). This is generally a well-designed study but we question the choice of sub-group. This is not a typical pre-planned sub-group in ALS trials, at least in part because it is impractical; many PALS do not receive an ALS diagnosis until their symptoms have been continuing for more than 12 months (27). It is also odd because, as described above, an earlier trial by this group suggested that patients with longer disease duration were more likely to 'respond' to MeCbl (20). We question why more traditional sub-group analyses (28) were not performed, at least in addition to this one. Also, since one proposed mechanism of MeCbl is the lowering of homocysteine, it is surprising that homocysteine levels were not measured with a plan for a subgroup analysis in PALS with elevated homocysteine. Of note, none of these three trials report measuring B12 levels in PALS; it is not clear whether PALS with B12 deficiency might have been included in these or not. ALSUntangled assigns a TOE 'Trials' grade of D based on this information (Table I).

Dosing, risks and costs

The optimal dose and route of administration of MeCbl for ALS has yet to be determined. The trials above suggest that higher injected doses (25 mg daily or 50 mg twice a week) may be more effective in some patients on some measurements than lower

injected doses. The use of higher doses makes sense mechanistically, as pre-clinical studies suggest these are necessary to provide neuroprotection and promote regeneration (29). ALSUntangled is unaware of any MeCbl trials in PALS using oral administration. Higher doses of MeCbl, even injected IM, do appear reasonably safe. No MeCbl related adverse events were encountered in any of the above ALS trials, nor in a trial of ultra-high dose MeCbl for peripheral neuropathy (30). IM injections themselves can produce minor adverse events such as pain and bruising. ALSUntangled assigns a TOE 'Risks' grade of B based on this information (Table I).

The cost for a one-month supply of MeCbl at 25 mg IM daily is around $300 (31).

Conclusions

MeCbl has promising mechanisms and positive pre-clinical data from two different ALS models. Unfortunately, the anecdotal data we found did not identify any clear specific benefit, and the best of three clinical trials was unable to show an overall difference in ALSFRS-R progression or survival between PALS treated with MeCbl and those treated with placebo (26). A sub-group of patients with very specific pre-treatment progression rates of 1–3 ALSFRS-R points over 12 weeks, and very early disease (less than 12 months from symptom onset) may have had benefit (26). This finding needs to be replicated, especially since an earlier study suggested patients with longer disease duration were more likely to benefit (20). We would like to see a full traditional sub-group analysis (28) carried out on the data from the third trial (26). This sub-group analysis could then be used to design inclusion criteria for a new phase III trial comparing MeCbl 50 mg twice a week IM to placebo. The new trial could measure serum B12 and homocysteine, and have pre-planned sub-group analyses that are both logical and practical. While we wait for this, PALS who wish to try MeCbl are reminded that the above studies used very high, injected doses, which appear to be available only by prescription. Lower over-the-counter doses administered orally have not been studied. It is well established that over-the-counter oral supplements may be of poor and inconsistent quality (32). Some over-the-counter oral vitamin B supplements contain not only B12 but also B6, which in large quantities can be harmful to the nervous system (33).

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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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References

1. http://www.alsuntangled.com/open.php. Accessed June 1, 2015.
2. http://en.wikipedia.org/wiki/Vitamin_B12. Accessed June 2, 2015.
3. O'Leary F, Samman S. Vitamin B12 in health and disease. Nutrients. 2010;2:299–316.
4. Birch C, Brasch N, McCaddon A, Williams J. A novel role for vitamin B12: cobalamins are intracellular antioxidants in vitro. Free Radical Biology and Medicine. 2009;15:184–8.
5. Kikuchi M, Kashii S, Honda Y, Tamura Y, Kaneda K, Akaike A. Protective effects of methylcobalamin, a vitamin B12 analog, against glutamate-induced neurotoxicity in retinal cell culture. Invest Ophthalmol Vis Sci. 1997;38:848–54.
6. Akaike A, Tamura Y, Sato Y, Yokata T. Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate toxicity in cultured cortical neurons. Eur J Pharmacol. 1993;241:1–6.
7. Hemendinger R, Armstrong E, Brooks B. Methyl vitamin B12 but not methylfolate rescues a motor neuron-like cell line from homocysteine-mediated cell death. Toxicology and Applied Pharmacology. 2011;251:217–25.
8. Carri M, Valle C, Bozzo F, Cozzolino M. Oxidative stress and mitochondrial damage: importance in non-SOD1 ALS. Front Cell Neurosci. 2015;9:41.
9. Foran E, Trotti D. Glutamate transporters and the excitotoxic path to motor neuron degeneration in amyotrophic lateral sclerosis. Antioxid Redox Signal. 2009;7:1587–602.
10. Ghavami S, Shojaei S, Yeganeh B, Ade S, Jangamreddy R, Mehrpour M, et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders. Prog Neurobiol. 2014;112:24–49.

11. Cheah B, Vucic S, Krishnan A, Kiernan M. Riluzole, neuroprotection and amyotrophic lateral sclerosis. Curr Med Chem. 2010;17:1942–99.
12. Pfohl-Leszkowicz A, Keith G, Dirheimer G. Effect of cobalamin derivatives on in vitro enzymatic DNA methylation: methylcobalamin can act as a methyl donor. Biochemistry. 1991;30:8045–51.
13. Figueroa-Romero C, Hur J, Bender D, Delaney C, Cataldo M, Smith A, et al. Identification of epigenetically altered genes in sporadic amyotrophic lateral sclerosis. PLoS One 2012;7:e52672.
14. Koyama K, Usami T, Takeuchi O, Morozumi K, Kimura G. Efficacy of methylcobalamin on lowering total homocysteine plasma concentrations in haemodialysis patients receiving high-dose folic acid supplementation. Nephrol Dial Transplant. 2002;17:916–22.
15. Zoccolella S, Simone I, Lamberti P, Samarelli V, Tortelli R, Serlenga L, et al. Elevated plasma homocysteine levels in patients with amyotrophic lateral sclerosis. Neurology. 2008;70:222–5.
16. Ikeda K, Iwasaki Y, Kaji R. Neuroprotective effect of ultrahigh dose methylcobalamin in wobbler mouse model of amyotrophic lateral sclerosis. J Neurol Sci. 2015;354: 70–4.
17. Ludolph A, Bendotti C, Blaugrund E, Chio A , Greensmith L, Loeffler J, et al . Guidelines for pre-clinical animal research in ALS/MND: a consensus meeting. Amyotroph Lateral Scler. 2010;11:38–45.
18. https://www.patientslikeme.com/treatments/show/487-vitamin-b12-methylcobalamin-side-effects-and-efficacy# overview. Accessed June 22, 2015.
19. http://www.winningthefight.org/Forum/default.aspx?g= posts&t=17. Accessed June 12, 2015.
20. Kaji R, Kodama M, Imamura A, Hashida T, Kohara N, Ishizu M, et al. Effect of ultra-high dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study. Muscle and Nerve. 1998;21:1775–8.
21. Dengler R. Quantitate compound muscle action potential: con. Amyotroph Lateral Scler Other Motor Neuron Disord. 2002;(Suppl 1):S105–7.
22. Izumi Y, Kaji R. Clinical trials of ultra-high-dose methylcobalamin in ALS. Brain Nerve. 2007;59:1141–7.
23. E-mails between R. Kaji and ALSUntangled. June 2015.
24. Belsh J. ALS diagnostic criteria of El Escorial revisited: do they meet the needs of clinicians as well as researchers? Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;(Suppl 1):S57–60.
25. Atassi N, Berry J, Shui A, Zach N, Sherman A, Sinani E, et al. The PRO-ACT database: design, initial analyses and predictive factors. Neurology. 2014;83:1719–25.
26. Kaji R, Kuzuhara S, Iwasaki Y, Okamoto K, Nakagawa M, Imai T, et al. Ultra-high dose methylcobalamin prolongs survival of ALS: report of seven years' randomized double-blind phase III clinical trial. Presented at American Academy of Neurology Meeting, April 23, 2015.
27. Pagonini S, Macklin E, Lee A, Murphy A, Chang J, Zipf A, et al. Diagnostic timelines and delays in amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:453–6.
28. Rudnicki S, Berry J, Ingersoll E, Archibald D, Cudkowicz M, Kerr D, et al. Dexpramipexole effects on functional decline and survival in subjects with amyotrophic lateral sclerosis in a phase II study: subgroup analysis of demographic and clinical characteristics. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:44–51.
29. Okada K, Tanaka H, Temporin K, Okamoto M, Kuroda Y, Morimoto H et al. Methylcobalamin increases Erk1/2 and AKT activities through the methylation cycle and promotes nerve regeneration in a rat sciatic nerve injury model. Exp Neurol. 2010;222:191–203.
30. Shibuya K, Misawa S, Nasu S, Sekiguchi Y, Beppu M, Iwai Y, et al. Safety and efficacy of intravenous ultra-high dose methylcobalamin treatment for peripheral neuropathy: a phase I/II open label clinical trial. Intern Med. 2014; 53:1927–31.
31. http://alsworldwide.org/care-and-support/article/methyl cobalamin-b12-informational-sheet. Accessed June 22, 2015.
32. Newmaster S, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. DNA barcoding detects contamination and substitution on North American herbal products. BMC Medicine. 2013;11:222.
33. Kulkantrakon K. Pyridoxine-induced sensory ataxic neuropathy and neuronopathy: revisited. Neurol Sci. 2014; 35:1827–30.