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SHARING EXPERTISE

Safety and Tolerability of Targeted Medical Nutrition for Cachexia in Non-Small-Cell Lung Cancer: A Randomized, Double-Blind, Controlled Pilot Trial

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ABSTRACT

Backround

This pilot, double-blind, comparator-controlled trial evaluated the safety and tolerability of an oral targeted medical nutrition (TMN) supplement for the management of cachexia in patients with non-small-cell lung cancer (NSCLC).

Methods

Patients receiving first-line chemotherapy for NSCLC with weight loss or low BMI were randomized 1:1 to receive juice-based TMN (~200 kcal; 10 g whey protein; ≥ 2.0 g eicosapentaenoic acid / docosahexaenoic acid in fish oil; and 10 µg 25-hydroxy-vitamin D3) or a milk-based isocaloric comparator twice daily for 12 weeks (ClinicalTrials.gov: NCT02515032). Primary endpoints included number / type of adverse events and changes in vital signs / laboratory parameters. Secondary endpoints included measures of clinical relevance. Survival was an exploratory endpoint.

Results

The TMN group (n=26; mean 64.4 years) experienced fewer adverse events (64 vs. 87) than the comparator group (n=29; mean 66.0 years), including fewer cases of neutropenia (0 vs. 4). Compliance was slightly lower in the TMN (58.5 %) vs. comparator group (73.6 %). There were no statistically significant between-group differences in efficacy endpoints. Fewer (4 vs. 10) patients who received TMN than comparator had died by 1-year post baseline.

Conclusion

TMN was well tolerated. Trends for improved clinical outcomes with TMN identified in this study warrant further investigation.

OBJECTIVE

This pilot, randomized, double-blind, comparator-controlled trial is the first to evaluate the safety and tolerability of a ready to drink oral nutritional supplement (ONS, Remune™) [1] containing a combination of n-3 PUFAs, 25-hydroxy-vitamin D3 and high-quality whey protein, compared with an isocaloric comparator matched for energy content, in pre-cachectic and cachectic patients with NSCLC.

INTRODUCTION

Cachexia is a complex wasting syndrome, known to have a negative impact on clinical outcomes in patients with cancer and several other chronic diseases. Nutritional supplementation with omega-3 fatty acids from fish oil may have beneficial effects in cachectic cancer patients. Deficiency of vitamin D has also been associated with poor outcome and protein supplementation is crucial for maintenance of sceletal muscle mass in cancer.

Literature: 1. Trade name of investigated product: „Nutrifriend Cachexia", Smartfish, Norway. Sold by B. Braun Melsungen AG under the trade name „Remune™"

Study design	12-week, randomized, double-blind, parallelgroup, comparator-controlled, multicenter trial
Patients	Initiating first-line standard chemotherapy as treatment for NSCLC; patients required to initiate their first cycle of platinum-based chemotherapy at the baseline visit.
Study groups	TMN group: Juice-based drink Remune™[1] (~200 kcal; 10 g whey protein; 11 g fat incl. ≥ 2.0 g docosahexaenoic acid + eicosapentaenoic acid [~1,200 mg DHA + ~800 mg EPA] in fish oil; 20 g carbohydrate and 10 µg 25-hydroxy-vitamin D3 per 200 ml) Comparator group: Milk-based isocaloric comparator drink (~200 kcal; 6 g milk protein; 11 g fat incl. sunflower oil in place of DHA- and EPA-containing fish oil; 20 g carbohydrate, no 25-hydroxy-vitamin D3)
Primary outcome	Safety and tolerability endpoints (number and type of adverse events (AEs), changes in vital signs)
Secondary and exploratory outcomes	Clinical measures of efficay (e.g. changes in body weight, body composition, triglycerides, inflammatory biomarkers, hand grip strength, walking distance, 1 year survival)

Main Results for the Remune™ Group (vs. Comparator Group)

Safety and tolerability endpoints

- Smaller number of AEs (64 vs. 87, respectively), AEs occurred in fewer patients (18 vs. 26, respectively)
- Decreased heart rate (n.s. in full analysis set; p=0.04 in per protocol set (PPS))
- No significant between-group changes in laboratory parameters

Secondary Efficacy Outcomes

- No significant between-group changes in body weight, BMI and body composition
- Lower triglyceride level (p<0.01 in PPS)
- Numerical improvements in walking distance
- Significantly increased omega-3:omega-6 (O3:O6) ratio, EPA, DHA and vitamin D3 content in plasma (Figure 1)

Exploratory Outcomes

- Numerically higher 12 month survival (Fig. 2(a))
- Statistically significant better survival in the subset of patients with pre-cachexia (*post hoc* analysis) (Fig 2(b))
- No between-group difference in chemotherapy tolerability and development of dose-limiting toxicity

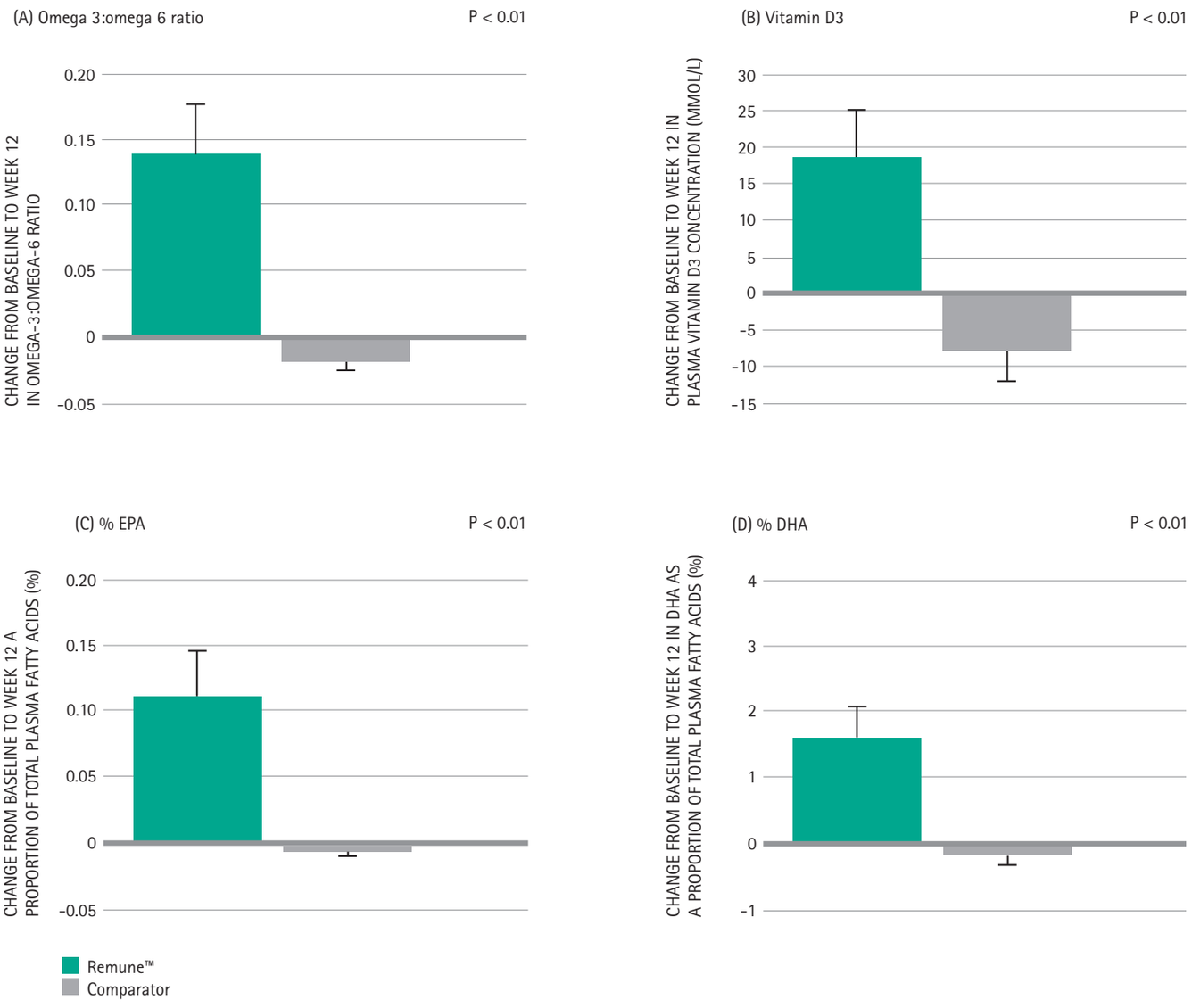

Figure 1 | Change from baseline to week 12 in the Remune™ group and the isocaloric comparator group in (a) plasma omega-3 to omega-6 ratio, (b) plasma vitamin D3 level, (c) EPA as a proportion of total plasma fatty acids, and (d) DHA as a proportion of total plasma fatty acids. Data are mean ± SEM for the full analysis set; P values were estimated by analysis of covariance adjusted for baseline value. Mean change from baseline to week 12 was calculated as: week 12 value minus baseline value for each patient, divided by the n number. Remune™ group, n = 16–17; comparator group, n = 22. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SEM, standard error of the mean; TMN, targeted medical nutrition.

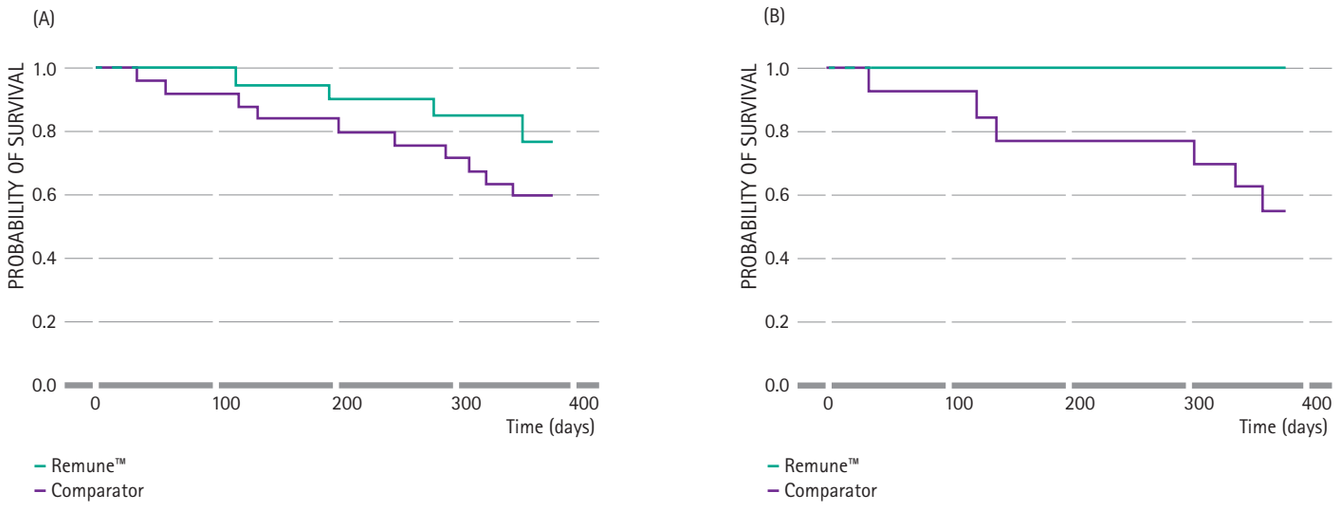

Figure 2 | Kaplan–Meier curves showing survival from baseline to 1 year (a) overall and (b) in the subset of patients with pre-cachexia, in the TMN group and the isocaloric comparator group. a) TMN group, n=25; comparator group, n=28; *P*=0.18. b) TMN group, n=14; comparator group, n=14; *P*=0.02. TMN, targeted medical nutrition.

STUDY LIMITATIONS

- Small sample size
- Study was not powered to detect between-group differences in the secondary and exploratory outcomes studied, several of which might have been expected to improve with Remune™ vs. comparator

SUMMARY

This pilot study, has demonstrated for the first time the safety and tolerability of a targeted nutritional supplement (Remune™) containing n-3 PUFAs, vitamin D3, and whey protein in pre-cachectic and cachectic patients with NSCLC receiving patinum-based chemotherapy. Remune™ was well tolerated with a favorable safety profile compared with a comparator that was matched for energy content. Signs of potential clinical benefits warrant exploration in further trials.

FOR HEALTH CARE PROFESSIONALS

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