Publication

Early biomarker response and patient preferences to oral and intramuscular vitamin B12 substitution in primary care: a randomised parallel-group trial

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Vitamin B12 (VB12) deficiency can be treated with oral high-dose substitution or intramuscular (i.m.) injection of VB12. Whenever alternative routes of administration exist, patient preferences should be considered when choosing the treatment. We aimed to assess outpatient preferences towards oral or IM VB12 substitution and confirm noninferiority of early biomarker response with oral treatment, in a typical primary care population.; Prospective randomised nonblinded parallel-group trial. Patients were recruited by their general practitioner and randomly assigned to oral or IM treatment. Group O-oral was given 28 tablets of 1000 ţg cyanocobalamin in a monthly punch card fitted with an electronic monitoring system. Group I-IM received four, weekly injections of 1000 ţg hydroxocobalamin. Blood samples were drawn before the first administration and after 1, 2 and 4 weeks of treatment, and analysed for VB12, holotranscobalamin (HoloTc), homocysteine (Hcy) and methylmalonic acid (MMA). For group O-oral, treatment adher-ence and percentage of days with ş2 dosing events were calcu-lated. Before and after 28 days of treatment, patients were asked to fill in a questionnaire about their preference for the ther-apy options and associated factors.; Between November 2013 and December 2015, 37 patients (age: 49.5 ś 18.5 years; women: 60.5%) were recruited for oral (19) or IM (18) treatment. Baseline values with 95% confidence intervals for serum VB12, HoloTc, Hcy and MMA were 158 pmol/l [145-172], 49.0 pmol/l [40.4-57.5], 14.8/ţmol/l [12.0-17.7] and 304 nmol/l [219-390], respective-ly, in group O-oral and 164 pmol/l [154-174], 50.1/pmol/l [38.7-61.6], 13.0 ţmol/l [11.0-15.1] and 321/nmol/l [215-427], respec-tively, in group I-IM (not significant). After 1 month of treatment, levels of VB12 and HoloTc showed a significant increase compared with baseline (group O-oral: VB12 354 pmol/l [298-410] and HoloTc 156 pmol/l [116-196]; group I-IM: VB12 2796 pmol/l [1277-4314] and HoloTc 1269 pmol/l [103-2435]). Hcy and MMA levels showed a significant decrease compared with baseline (group O-oral: Hcy 13.8/ţmol/l [10.7-16.8] and MMA 168/nmol/l [134-202]; group I-IM: Hcy 8.5/ţmol/l [7.1-9.8] and MMA 156/nmol/l [121-190]). HoloTc and MMA levels were normalised in all patients after 4 weeks of treatment, where-as normalisation of VB12 and Hcy was reached by all patients in group I-IM only. Response of VB12, HoloTc and Hcy was more pronounced in group I-IM ($p < 0.01$) and the primary hypothesis that oral VB12 treatment would be noninfe-rior to IM treatment was rejected. Average adherence to thera-py was 99.6 ś 1.1% and days with ş2 dosing events reached 5.6%. Before randomisation, preference was in favour of oral treatment (45.9%, n = 17) over IM administration (21.6%, n = 8). Twelve patients (32.4%) had no preference. Nine (24.3%) patients changed their preference after treatment. Patients who obtained their

preferred route of administration main-tained their preference in the case of oral treatment and changed their preference after IM treatment.; Differences in VB12 levels between groups were higher than expected. Therefore, noninferiority of oral treat-ment had to be rejected. However, normalisation of HoloTc and MMA was reached by all patients after a 1-month treatment period. The clinical benefit of the exaggerated biomarker re-sponse after IM treatment within a typical primary care popula-tion is questionable. Midterm biomarker effects and patient preferences should be considered when a therapeutic scheme is chosen. Initial rating in favour of either IM or oral therapy can change over time and justifies repeated re-evaluation of patient preferences. (ClinicalTrials.gov ID NCT01832129).
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