EFFECTS OF A NOVEL MULTIVITAMIN ANTIOXIDANT NUTRACEUTICAL IN CHRONIC KIDNEY DISEASE PATIENTS ON HEMODIALYSIS: A PROSPECTIVE TRIAL.

Amit Sharma, John Larkin, Padma Gadepally, Liza Bea; Boise Kidney and Hypertension Institute, Meridian, ID 83642, USA.

E-Mail: asharma@boisekidney.com Phone: 208-846-8335

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Abstract

The severity and extent of cardiovascular complications in patients with CKD is disproportionate to the number and severity of traditional risk factors necessitating attention on nontraditional risk factors that are particularly relevant to patients with CKD. These include decreased erythropoietin levels, increased inflammation, oxidative stress, and abnormalities in bone and mineral metabolism. We hypothesized that daily nutraceutical (MV-ONE®) with Alpha-Lipoic Acid (600mg), Cholecalciferol (1500IU) and Gamma-Tocopherol (300mg) will improve vitamin D levels, reduce the exogenous erythropoietin (EPO) dose and attenuate overall inflammation, thus, improving outcomes in dialysis patients. The purpose of this 12-week open label, non-randomized, single center study was to evaluate the effects of a novel multivitamin antioxidant nutraceutical on vitamin D levels, EPO dose, inflammatory factors and other biomarkers in a CKD population on hemodialysis. Twenty-five subjects participated in this study and took the experiential multivitamin antioxidant MV-ONE® orally once daily with food for 12 weeks. Baseline and monthly blood analyses for vitamin D dose, 25 OH vitamin D levels and EPO dose were used as primary endpoints with comparison between baseline and week 12 values. Analyses show a 12-week treatment of MV-ONE® caused: 1) the iv vitamin D dose to decrease (mean baseline dose 2.25mcg to week 12 dose 0.5mcg; $p < 0.05$), 2) marginal increases in 25 OH vitamin D levels (mean baseline levels 25ng/mL to week 12 levels 30ng/mL), 3) the EPO dose decreases (mean baseline dose 3500IU to week 12 dose 2200IU), and 4) a significant marked improvement in cholesterol levels (mean baseline levels 50mg/dL to week 12 levels 160mg/dL; $p < 0.001$). These results identify the efficacy of this novel multivitamin antioxidant nutraceutical therapy in this subset of the population, but indicate a potential need for an increased dose of Cholecalciferol. Although continuing studies are needed, it is evident that this MV-ONE® therapy does improve the anemic and abnormal bone metabolism observed in CKD patients on hemodialysis.

Introduction And Overview

As of October 2010, the National Institutes of Health had estimated that 23 million American's have been diagnosed with chronic kidney disease (CKD), and it is evident that this population continues to segue from special to a significant one in the world. The major physiological disturbances that characterize the effects of worsening states of CKD are the onset of cardiovascular diseases (5, 7, 8), bone/mineral metabolism disturbances, such as secondary hyperparathyroidism (4, 6, 8), and hematological disorders (3, 4, 8). It has been firmly identified in the literature that the leading cause of death in patients with CKD stages 4 and 5 is of cardiovascular origin (5, 7, 8). Recent studies have indicated that the chronic inflammation induced by end stage renal disease (ESRD) exacerbates not only cardiovascular risks (1, 2, 5), but also bone physiology disturbances (4, 7, 8) and anemic states (1, 2, 3). It is predicted that these negative health consequences could be onset due to prolonged hyperphysiological stress hormone and oxidative stress factor synthesis and secretion (2, 5, 10). The influences of physiological and oxidative stressor transduction signals induced by hyper- secretion and/or production of cortisol, cytokines, tumor necrosis factors, reactive oxidative species and other stress and inflammatory responses have been suggested to alter the homeostasis of normal bone physiology and erythrocyte production at both genetic and non-genetic levels (1, 3, 5, 10), and this could possibly be a major influence aiding in the generation of the progressive negative health states observed in ESRD patients requiring dialysis.

The studies presented here hypothesized that providing dialysis patients with an additive active vitamin D xenobiotic in combination with a mixture of antioxidant nutraceutical therapies could assist in treatment of secondary hyperparathyroidism, and also, target inflammation to improve dialysis patient's anemic parameters. The study paradigm consisted of 25 male and female hemodialysis patients that gave informed consent and met all criteria outlined in the materials and methods section. This study was designed to be an open label, non-blinded, non-randomized single site protocol with a treatment period that consisted of 12 weeks. The oral antioxidant nutraceutical (MV-ONE®) therapy consisted of Cholecalciferol 1500 IU, Gamma-Tocopherol 300mg and Alpha Lipoic Acid 600mg and was administered once daily. Control laboratory values were obtained from both baseline and retrospective values using an average of 4 months prior to treatment, unless laboratory test were not consistently attained routinely by the dialysis center. The laboratory values for 25-hydroxyvitamin D, vitamin D dose and Epogen dose were utilized for primary endpoints for analysis of the efficacy of the MV-ONE® antioxidant nutraceutical. Secondary endpoints consisted of routine monthly laboratory values for complete blood counts, transaminases, general chemistry, lipid panel, uric acid, and c-reactive protein (CRP).

Interim results are documented in the published abstract. Final results identified that 12 weeks of treatment with MV-ONE® caused 25-OH vitamin D levels to significantly increase by a mean 33% (P=0.0058), but despite this there was a slight non-significant increase in mean intravenous (iv) vitamin D dosing of 8% (P = 0.3203). Importantly, there was an inter-study facility change in vitamin D therapies (Hectorol to Rocaltrol) and this could play a role in the iv vitamin D dosing results observed. No clinically significant alterations were seen in parathyroid hormone or calcium levels. It was observed that the erythropoietin stimulating agent (Epogen) dosing was significantly decreased by a mean value of 34% (P= 0.0475), while transferrin saturation, hemoglobin and platelet values remained clinically stable. Unlike the interim results, cholesterol levels remained unchanged through the study. It was identified that MV-ONE® caused no clinically significant changes to the inflammation markers of uric acid or CRP. It is noteworthy to mention that CRP is a highly variable biomarker for inflammation, and is not well accepted as a definitive endpoint without exceedingly large subject numbers. This brings up rationale to possibly measure cortisol, thymus-cells, and cytokines, such as, interleukins, tumor necrosis factors and other exploratory markers like hepcidin in further studies to better understand any possible alterations in inflammation from the MV-ONE® therapy.

Due to studies that suggest that vitamin D itself is a potent anti-inflammatory agent (11), it is possible that the anti-inflammatory effects of MV-ONE® require a longer monitored treatment period to revel a philological steady state effect for the parameters of increased vitamin D levels to initiate treatment of secondary hyperparathyroidism, which might only be produced after a decreased inflammatory state is reached by this antioxidant nutraceutical. Especially since 12 to 16 weeks is common for a steady state to be reached by nuclear drug actions according to common pharmacology practice (9). Overall, these studies present a strong case that the MV-ONE® antioxidant nutraceutical is physiologically beneficial and also, a cost effective and adjuvant for dialysis patients that require consistent treatment for secondary hyperparathyroidism and anemia. However, further multicenter studies with larger subject numbers and longer treatment periods are needed to fully determine the therapeutic potential of MV-ONE® as an additive therapy.

Materials And Methods

Sponsor:
The protocol MV-1-201 conducted at Boise Kidney and Hypertension Institute was sponsored by Nephrian Inc. and was conducted under the supervision of the principle investigator Amit Sharma, M.D.

Study Population:
Inclusion Criteria - End stage renal disease and on hemodialysis for 90 days prior to screening.
Exclusion Criteria - Study subjects on an active clinical trial that uses an investigational medication, age < 18years old, thrombocytopenia (platelet count < 60,000), abnormal liver function tests (3 times upper limit of normal transaminases), have a known sensitivity to any of the active ingredients, patients currently taking vitamin C > 500 mg per day, vitamin E supplements > 60 mg (90 IU) per day, vitamin D supplements > 300 IU (7.5μg) per day, ferritin < 100, Tsat < 10%, pregnant subjects, sexually active female subjects who are of childbearing potential and not willing to use an acceptable form of contraceptive.

Demographics:
A total of 25 hemodialysis subjects signed informed consent and were enrolled into the study after meeting all inclusion and no exclusion criteria. This population consisted of one African American male, one Hispanic male, 13 Caucasian females, and 10 Caucasian males. The average age of the study subjects was 65 years old with an average BMI of 36.69. The hemodialysis accesses of enrolled subjects consisted of 16 arteriovenous fistulas, 3 arteriovenous grafts, and 6 central venous catheters.

General Study Design:
Open label, non-blinded, non-randomized single site study lasting 12 weeks (excluding screening and baseline laboratory periods). Multiple laboratory parameters were monitored on a routine basis to determine the efficacy of the multivitamin.

Description of Drug:
The ingredients of the nutraceutical MV-ONE® are formulated in capsules, which include Cholecalciferol 1500 IU, Gamma-Tocopherol at 300mg and Alpha Lipoic Acid 600mg given once in the morning with food (two capsules were self administered to provide the total daily amount).

Ethical Considerations:
All study procedures were performed using good clinical research practices that abided by the regulations of the FDA and ICH guidelines.

Adverse Events:
Adverse events were recorded, assessed for severity and reported to the proper authorities if applicable. Study data points were removed from analyses if adverse event was related to physiological abnormality and observed to be a significant outlier.

Compliance:
Self drug administration compliance was expected to be ≥ 85%. Non-compliant subject laboratory values were excluded from the analyses.

Dialysis Facility Xenobiotic Parameters:
The study subject xenobiotic requirements for iv erythropoietin stimulating agents (Epogen) and iv active vitamin D2/D3 (Hectorol and Rocaltrol) were recorded and analyzed. In the cases of inter-study dialysis center changes in vitamin D, equivalent doses were determined and used.

Laboratory Parameters:
Analytes of interest included routine monthly laboratory values (i.e. CBC, AST/ALT, general chemistry) and a baseline and end of study period (Week 12) laboratory lipid panel, uric acid, 25-OH vitamin D, c-reactive protein.

Statistical Analyses:
Statistical analyses of data were performed using unpaired one tailed Student's t-tests of column comparisons versus control. A minimum alpha value (p) of 0.05 was used for all analyses. Mean laboratory values were used for determining total and percent differences between control and week 12 when relevant.

Results

1 MV-ONE® Therapy Significantly Increases Vitamin D Levels In Hemodialysis Subjects

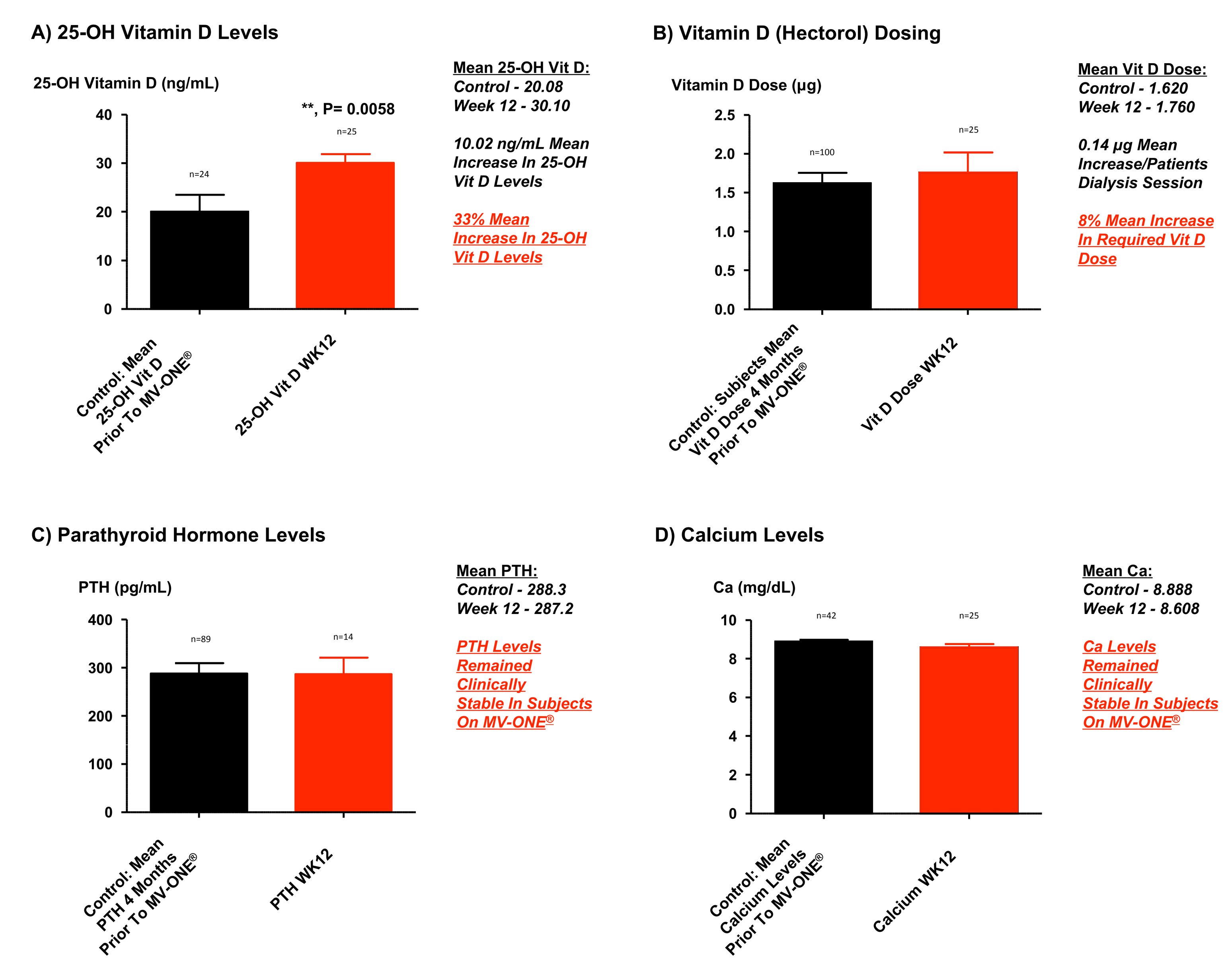

Figure 1. A) The 12 week administration of the novel renal multivitamin antioxidant nutraceutical MV-ONE® caused a 33% increase in 25-hydroxyvitamin D levels in hemodialysis study subjects (red) compared to the controls (black). B) The administration of MV-ONE® was correlated with an 8% mean increase in the required vitamin D (Hectorol) dose for hemodialysis study subjects (red) compared to the mean controls (black). C) The administration of MV-ONE® did not significantly alter parathyroid hormone levels observed in hemodialysis study subjects (red) compared to controls (black). C) The administration of MV-ONE® did not clinically alter calcium levels observed in hemodialysis study subjects (red) compared to controls (black). Bar height represents the mean ± SEM. Control 25-OH Vit D versus week 12 (P = 0.0058), control Vit D dose versus week 12 (P = 0.3203), control PTH versus week 12 (P = 0.4923), control Ca versus week 12 (P = 0.0440).

2 MV-ONE® Therapy Significantly Decreases The Epogen Dosing Required In Hemodialysis Subjects

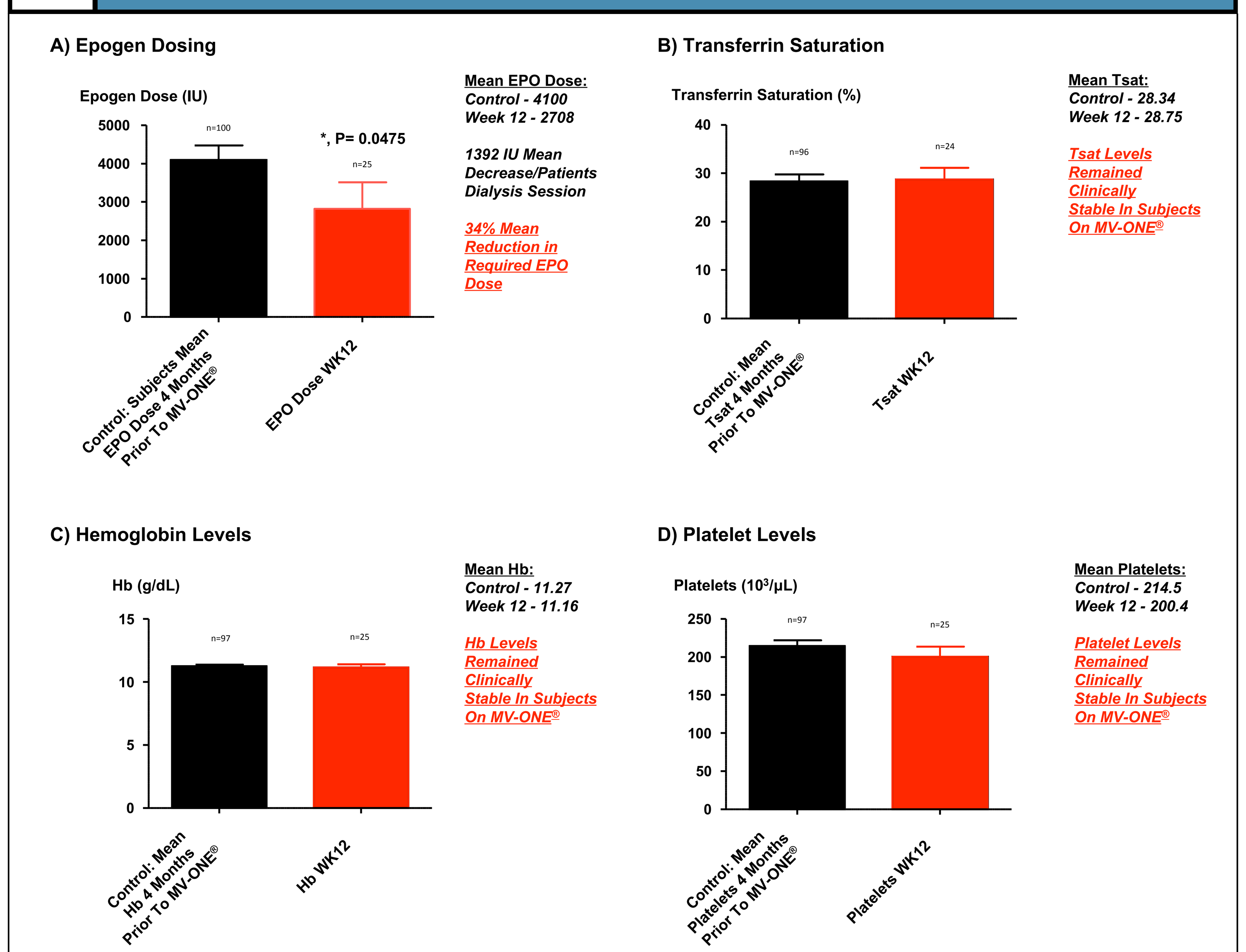

Figure 1. A) The 12 week administration of the novel renal multivitamin antioxidant nutraceutical MV-ONE® caused a significant 34% mean decrease in the required Epogen dose for hemodialysis study subjects (red) compared to the mean controls (black). B) The administration of MV-ONE® did not significantly alter transferrin saturation levels observed in hemodialysis study subjects (red) compared to controls (black). C) The administration of MV-ONE® did not significantly alter hemoglobin levels observed in hemodialysis study subjects (red) compared to controls (black). D) The administration of MV-ONE® did not significantly alter platelet levels observed in hemodialysis study subjects (red) compared to controls (black). Bar height represents the mean ± SEM. Control EPO dose versus week 12 (P = 0.0475), control transferrin saturation versus week 12 (P = 0.4485), control hemoglobin versus week 12 (P = 0.3271), control platelets versus week 12 (P = 0.1917).

3 MV-ONE® Did Not Alter Uric Acid, C-Reactive Protein Or Cholesterol Levels In Hemodialysis Subjects

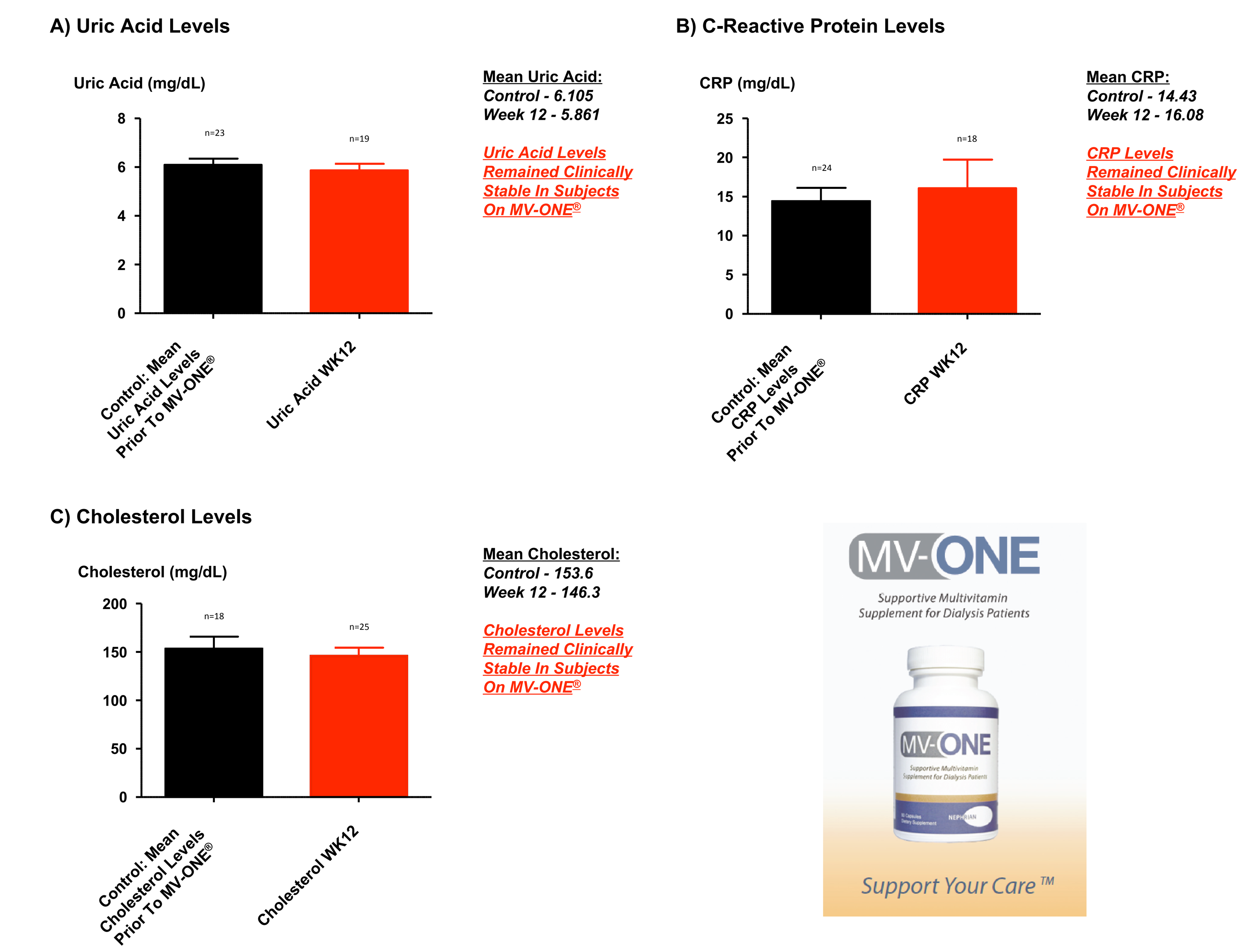

Figure 3. A) The 12 week administration of the novel renal multivitamin antioxidant nutraceutical MV-ONE® caused a non-significant 4% mean decrease in the uric acid levels of hemodialysis study subjects (red) compared to the mean controls (black). B) The administration of MV-ONE® did not significantly alter c-reactive protein levels observed in hemodialysis study subjects (red) compared to controls (black), although there was a 10% increase in mean values. Importantly, CRP is still an exploratory indicator of inflammation and longer studies with a larger study population are required to validate results. C) The administration of MV-ONE® did not significantly alter cholesterol levels observed in hemodialysis study subjects (red) compared to controls (black). Bar height represents the mean ± SEM. Control uric acid versus week 12 (P = 0.2588), control CRP versus week 12 (P = 0.3290), control cholesterol versus week 12 (P = 0.3077).

4 MV-ONE® Pharmacoeconomic Advantages (HYPOTHETICAL)

Hypothetical ESA Cost Comparison For Patients On MV-ONE Therapy

	Epogen Cost / 1000 IU	Sales Tax	Adjusted Cost	EPO Dose (IU) / Patient	Weekly Costs / Patient	Annual Cost / Patient
Standard Costs	$9.35	6%	$9.91	4100 TIW-HD	$121.89	$6338.44
34% Reduction In EPO Dose Due To MV-ONE	$9.35	6%	$9.91	2708 TIW-HD	$80.51	$4186.46

Costs of MV-ONE Therapy And Hypothetical Total Annual Patient Reduction In ESA Costs

MV-ONE Cost / Day / Patient	MV-ONE Cost / Week / Patient	MV-ONE Cost / Year / Patient	Sales Tax	Adjusted Annual Cost MV-ONE	Total Annual Reduction In ESA Costs / Patient On MV-ONE
$1.00	$7.00	$364.00	6%	$385.84	$1766.14

System Wide Hypothetical Pharmacoeconomic Impact Of MV-ONE Therapy

Hypothetical Dialysis System Population	Estimated Percent On ESA Therapy	Annual Reduction In ESA Costs / Patient	Annual System Wide ESA Cost Reduction Using MV-ONE	Estimated Compliance	Adjusted Annual System Wide ESA Cost Reduction Using MV-ONE
3000	75%	$1766.14	$3,973,815.00	80%	$3,179,052.00

Figure 4. The costs of Epogen were attained from Liberty Dialysis for January 2011. Adjusted sales tax was set as 6%. Mean values of Epogen were used for determining the hypothetical pharmacoeconomic impact of MV-ONE therapy. The system wide hemodialysis population was estimated as 3000 with 75% on ESA therapy. Patient compliance was estimated to be 80%.

Conclusions

- MV-ONE® increases active vitamin D blood levels in hemodialysis patients identifying it's efficacious ability to potentiate treatment for secondary hyperparathyroidism.
- MV-ONE® decreases the ESA therapy required in hemodialysis patients identifying it's benefits aiding in the treatment of CKD- and hemodialysis- induced anemia.
- Approximately 85% patients reported overall improved well-being after taking MV-ONE®. Quality of life questionnaires should be used in future studies.
- The antioxidative properties of MV-ONE® therapy may be a useful cost-effective adjuvant in an increasingly challenging clinical environment.

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