Mesna for Treatment of Hyperhomocysteinemia in Hemodialysis Patients: A Placebo-Controlled, Double-Blind, Randomized Trial

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Background and objectives: Increased plasma total homocysteine is a graded, independent risk factor for the development of atherosclerosis and thrombosis. More than 90% of patients with end-stage renal disease have hyperhomocysteinemia despite vitamin supplementation. It was shown in previous studies that a single intravenous dose of mesna 5 mg/kg caused a drop in plasma total homocysteine that was significantly lower than predialysis levels 2 d after dosing. It was hypothesized 5 mg/kg intravenous mesna administered thrice weekly, before dialysis, for 8 wk would cause a significant decrease in plasma total homocysteine compared with placebo.

Design, setting, participants, & measurements: Patients with end-stage renal disease were randomly assigned to receive either intravenous mesna 5 mg/kg or placebo thrice weekly before dialysis. Predialysis plasma total homocysteine concentrations at weeks 4 and 8 were compared between groups by paired t test.

Results: Mean total homocysteine at 8 wk in the placebo group was 24.9 μmol/L compared with 24.3 μmol/L in the mesna group (n = 22 [11 pairs]; mean difference 0.63). Interim analysis at 4 wk also showed no significant difference between mesna and placebo (n = 32 [16 pairs]; placebo 26.3 μmol/L, mesna 24.5 μmol/L; mean difference 1.88). Multivariable adjustments for baseline characteristics did not alter the analysis. Plasma mesna seemed to reach steady-state concentrations by 4 wk.

Conclusions: It is concluded that 5 mg/kg mesna does not lower plasma total homocysteine in hemodialysis patients and that larger dosages may be required.


Homocysteine (Hcy) is a non–protein-forming, thiol amino acid derived from dietary methionine after its ATP-dependent activation and subsequent transmethylation of biologically important molecules. Hcy is found in the plasma of all mammals, and the term “total homocysteine” (tHcy) is used to describe a composite of free (sulfhydryl), protein-disulfide bound, and homocysteine-cysteine and other mixed disulfide species (1).

In the past two decades, retrospective and prospective studies have reported plasma tHcy as a graded, independent risk factor for cardiovascular and cerebrovascular disease (2–5). Meta-analysis of cohort studies suggested that a lowering of Hcy by 25% (approximately 3 μmol/L) may be associated with an 11% lower risk for coronary heart disease (odds ratio [OR] 0.89; 95% confidence interval [CI] 0.83 to 0.96) and a 19% lower risk for stroke (OR 0.81; 95% CI 0.69 to 0.95) (6), although this has yet to be corroborated in randomized, controlled trials. Elevated plasma tHcy (hyperhomocysteinemia) is almost universal among patients who have ESRD and require hemodialysis (7–12). Hyperhomocysteinemia has been linked with increased risk for both fatal and nonfatal cardiovascular events (3), as well as vascular access thrombosis (13,14), the most common cause for hospitalization of hemodialysis patients (15).

Strategies for normalizing plasma tHcy concentration in ESRD have included increasing dialysis membrane pore size (10,16) and pharmacologic doses of water-soluble vitamins, including folic acid, vitamin B6, and vitamin B12 (17,18). Although vitamin therapy has been shown to lower plasma tHcy by 15 to 47% (18–20), the majority of investigations failed to normalize plasma tHcy to levels observed in healthy control subjects with normal kidney function (9,17,18,20–22). This was highlighted in the recently completed Homocysteinemia in Kidney and End Stage Renal Disease (HOST) trial by the inability of high-dosage folic acid and B vitamins to normalize plasma tHcy or affect cardiovascular outcomes (23). The results of the HOST trial along with other large randomized, controlled trials of patients with normal kidney function, including the Heart Outcomes Prevention Evaluation 2 (HOPE-2) trial (24), Norwegian Vitamin Trial (NORVIT) (25), and Vitamin...
Intervention for Stroke Prevention (VISP) trial (26), have led to the suggestion that investigation of nonvitamin therapies are needed to determine whether decreasing tHcy reduces the risk for atherosclerosis and thrombosis and their associated complications (27).

Between 70 and 80% of plasma tHcy resides covalently bound \( \text{via} \) a disulfide bond to the single free cysteine residue on albumin (Cys\(^{34}\)-albumin), limiting its availability for dialytic clearance (28,29). An emerging strategy to lower tHcy is to increase its free fraction within the blood, thereby improving its removal by dialysis. This can be achieved by the addition of a pharmaceutical agent that is capable of forming a sulfhydryl bond within the plasma and that will exchange with Cys\(^{34}\)-albumin bound Hcy, allowing Hcy to pass through the dialytic membrane.

In a recent randomized study of hemodialysis patients (30), we examined the effect of prolonged oral administration of dimercaptosuccinic acid (DMSA) 2.5 mg/kg per d compared with matching placebo. At 8 wk, there was no statistically significant difference in tHcy between placebo and DMSA. Subsequently, \textit{in vitro} comparisons of a range of thiol agents led us to conclude that mesna (sodium 2-mercaptoethanesulfonic acid), a drug indicated to prevent hemorrhagic cystitis associated with ifosfamide chemotherapy, is a promising candidate. A dosage-finding pilot study was conducted in 10 hemodialysis patients to determine whether a single intravenous dose of 2.5 or 5.0 mg/kg mesna would lower tHcy (31). The results of that pilot study indicated that 5.0 mg/kg intravenous mesna rapidly and significantly decreased tHcy, because plasma levels were 21% lower with mesna than with placebo control (32). Furthermore, the residual effect of mesna on plasma tHcy was still significant 2 d later, before the next dialysis session, with plasma tHcy 2.3 \( \mu \text{mol/L} \) lower than placebo control. This suggested that routine 5.0 mg/kg mesna at the beginning of dialysis would have a cumulative effect and substantially decrease tHcy. Because a single dose of mesna administered in our pilot study caused a significant decrease in plasma tHcy, we designed this study to test the prolonged tHcy-lowering effect of 5.0 mg/kg mesna in a randomized, double-blind, placebo-controlled trial. The primary objective was to determine whether 5.0 mg/kg mesna at the commencement of each dialysis treatment thrice weekly for 8 wk would lower plasma tHcy while vigilantly monitoring for adverse effects.

Although mesna is used routinely as an adjunct to chemotherapy, adverse effects associated with its regular use in patients with ESRD are unknown; therefore, adverse effects associated with mesna therapy were intensely monitored during this trial. According to the product monograph, the most frequently reported adverse effects of mesna use include headache, nausea, vomiting, and diarrhea, and some patients have an allergic reaction to mesna. Mesna has been shown to deplete plasma thiols such as tHcy and cysteine in patients who undergo concomitant chemotherapy (33). As such, one theoretical concern is depletion of the intracellular antioxidant glutathione, although studies have shown that mesna depletes plasma cysteine, an essential precursor of glutathione synthesis, without affecting leukocyte glutathione (34).

### Materials and Methods

#### Study Population

Patients were recruited from the hemodialysis units of London Health Sciences Centre (London, ON, Canada). Inclusion criteria were ESRD requiring thrice-weekly hemodialysis for a minimum of 3 mo and treatment with a high-flux, single-use, biocompatible (polysulfone) dialysis membrane. Exclusion criteria were age <18 yr; malnutrition (defined as normalized protein catabolic rate <1.0 g/kg/d) (35), malabsorption, or serum albumin <3.0 g/dl; planned major surgery or renal transplantation; clinically unstable (per attending nephrologist); life expectancy <6 mo; severe diabetic gastroparesis; untreated vitamin B\(_{12}\) deficiency; women of child-bearing potential who refused to practice contraception; and inability to provide informed consent.

The study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario and was conducted from January to March 2005. The study also received a no objection letter from the Therapeutic Products Directorate of Health Canada as required for clinical studies using off-indication pharmaceuticals in Canada, and the complete study protocol was conducted with adherence to the Declaration of Helsinki.

#### Intervention and Laboratory Tests

Eligible patients who provided written consent were supplied with a standard multivitamin supplement (Replavite; Landmark Medical Systems Inc., Richmond Hill, ON, Canada), including vitamin B\(_{12}\) 6 \( \mu \text{g} \), vitamin B\(_{6}\) 10 mg, and folate 1 mg, to be taken daily for a minimum of 4 wk before screening measurements of tHcy. Nonfasting, midweek, predialysis blood samples were drawn for tHcy to allow for matching. Study participants were then matched according to the following algorithm:

\[
\begin{align*}
\text{tHcy} &< 9 \text{\mu mol/L} \text{ matched within } \pm 3 \text{\mu mol/L} \\
\text{tHcy} &9 \text{ to } 12 \text{\mu mol/L} \text{ matched within } \pm 2 \text{\mu mol/L} \\
\text{tHcy} &12 \text{ to } 15 \text{\mu mol/L} \text{ matched within } \pm 1 \text{\mu mol/L} \\
\text{tHcy} &15 \text{ to } 25 \text{\mu mol/L} \text{ matched within } \pm 2 \text{\mu mol/L} \\
\text{tHcy} &25 \text{ to } 35 \text{\mu mol/L} \text{ matched within } \pm 3 \text{\mu mol/L} \\
\text{tHcy} &35 \text{ to } 45 \text{\mu mol/L} \text{ matched within } \pm 4 \text{\mu mol/L} \\
\text{tHcy} &>45 \text{\mu mol/L} \text{ matched within } \pm 5 \text{\mu mol/L} 
\end{align*}
\]

Each tHcy pair was randomly assigned to have one patient receiving active treatment (5.0 mg/kg mesna) and the other placebo (an equal volume of saline), using a computerized randomization program. This randomization plan ensured a balance in baseline tHcy and that each patient had a 50:50 chance of receiving active treatment or placebo within each pair. Study participants and all research personnel remained blinded to the treatment allocation, with the exception of a study pharmacist, until after the final statistical analyses were complete.

The evening before the scheduled hemodialysis treatment, pharmacy technicians prepared syringes of 5.0 mg/kg mesna (Pharmaceutical Partners of Canada Inc., Richmond Hill, ON, Canada) diluted in saline to a final concentration of 20 mg/ml or an equivalent volume of saline alone according to the randomization schedule, and syringes were stored at 4°C until administration. Within the first 30 min of starting hemodialysis, the dialysis nurse administered the contents of the syringe over 3 min into the venous drip chamber of the dialysis circuit. This continued at each dialysis treatment for 8 wk. At 4-wk intervals, midweek predialysis blood samples for tHcy were drawn, immediately placed on ice, centrifuged, and plasma-frozen at \(-70°C\) for batch processing at the completion of the study. Blood was sampled for all other biochemistry according to usual practice for hemodialysis patients. Plasma tHcy and mesna were measured by the chromatographic method of Jacobsen et al. (36) with minor modifications in solvent strength.
Clinical parameters were recorded three times weekly, including pre- and postdialysis weight, BP, pulse, and temperature, and were reviewed by a physician and/or a nurse practitioner at least once weekly. A study coordinator reviewed patients regularly to ensure correct administration of the study drug and monitor for potential adverse effects. Monthly tests of dialysis adequacy were performed as per routine.

**Sample Size and Statistical Plan**

The primary outcome of the study was tHcy at week 8. The sample size was calculated as follows. In prospective studies of dialysis patients, each 1-μmol/L increase in tHcy was accompanied by an increased risk for thrombosis of vascular access (fistula or graft) of 4% (13) and increased risk for myocardial infarction or death of 1% (37). As such, an effect size of 5.0 μmol/L would have significant clinical relevance. In our previous study of DMSA versus placebo, we observed an SD of the difference in tHcy at 8 wk of 7.3, comparable to an SD of 6.7 used in a study with similar design of N-acetylcysteine (NAC) by Friedman et al. (38). We used the sample size calculation for paired data (39): \( N_d = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times SD^2}{\delta^2} \). The sample size calculation was based on an estimated mean difference of 5.0 μmol/L and an SD of the differences of 7.3 with a level of significance of 0.05. A sample size of 36 patients (18 pairs) would have 80% power to detect this difference. The sample size was increased to 48 patients (24 pairs) to allow for a dropout rate of 25%.

Paired \( t \) test was used to compare means between mesna and placebo groups on an intention-to-treat basis. Four-week interim blood sampling was designed to allow for additional analyses if there were significant dropouts. All analyses were repeated using unpaired tests and multivariable modeling to adjust for baseline tHcy and vitamin levels, in the case of significant dropout. All analyses were performed using SPSS 11.0 (SPSS Inc., Chicago, IL). A two-tailed \( P < 0.05 \) was required for significance.

**Results**

Forty eight patients met eligibility criteria; agreed to participate in the study; and had nonfasting, predialysis tHcy measured. One patient with a screening tHcy of 8.5 μmol/L and another with a screening tHcy of 43.1 μmol/L could not be matched according to the predetermined algorithm (see the Materials and Methods section); therefore, those patients were randomly assigned unpaired. The remaining 46 patients were matched and randomly assigned as 23 complete pairs.

Three patients (one placebo, two mesna) withdrew consent or died after randomization but before commencing the study drug; therefore, no data were available for these patients for the intent-to-treat analysis. Unfortunately, with matching, loss of one patient results in loss of the pair, reducing the power of the final analysis for the primary outcome. One patient who was receiving placebo died, and three additional patients (one placebo, two mesna) withdrew before the first laboratory testing at 4 wk, leaving 41 patients (16 pairs, nine unmatched patients) for interim analysis. An additional seven withdrew before completing the full 8 wk of the study. The remaining 33 patients (11 pairs, 11 unmatched patients) completed the full 8-wk study. The trial profile is depicted in Figure 1.

There were no baseline differences between the groups, as listed in Table 1. Matched randomization resulted in near-identical baseline levels of tHcy. No patients were below the lower level of the reference interval for vitamin B₁₂ or folate, and adherence to the study schedule throughout the trial was excellent, with <1% of the doses of study drug missed or given outside the 30-min window. Adverse events were reported by 33.3 and 45.8% of the study and placebo groups, respectively (\( P = 0.45 \)). The most common adverse event was dysgeusia, experienced by 16.7% of the study group, compared with 8.3% of the placebo group (\( P = 0.67 \)), and led to withdrawal from the study by two participants. Three patients experienced worsening glycemic control, all of whom were receiving placebo. One patient developed pruritus and rash that was temporally related to the study medication on two consecutive occasions and was withdrawn from the study. No serious adverse events were attributable to mesna. Although mesna is administered as a pH-neutral compound, the molecule itself is an acid and therefore in theory may cause acidosis. Serum bicarbonate levels after treatment were not significantly different between mesna and placebo control groups (Table 1).

Levels of tHcy remained virtually unchanged between baseline and 4 and 8 wk for both the placebo and mesna groups; therefore, the primary analysis comparing tHcy between groups at 8 wk was not statistically significant. Using paired analysis, the mean tHcy at 8 wk in the placebo group was 24.9 μmol/L compared with 24.3 μmol/L in the mesna group (mean difference 0.63; 95% CI −3.9 to 5.2, \( P = 0.76 \)). Unpaired analysis yielded similar results: 23.7 μmol/L in the placebo group versus 24.9 μmol/L in the mesna group (mean difference −1.25; 95% CI −6.5 to 4.0; \( P = 0.63 \)). Because only 11 pairs completed the study, it was underpowered at 8 wk. We therefore performed interim analysis at 4 wk, at which time the study was adequately powered having 16 pairs. Using a paired analysis, the mean tHcy at 4 wk were 26.3 and 24.5 μmol/L for placebo and mesna, respectively (mean difference 1.88; 95% CI −0.8 to 4.6; \( P = 0.16 \)). For unpaired
analysis, tHcy was 24.8 μmol/L in the placebo group and 24.8 μmol/L in the mesna group (mean difference 0.02; 95% CI −4.2 to 4.2; P = 0.99). Multivariable adjustments for baseline characteristics did not alter the analysis. Plasma mesna seemed to reach steady state by 4 wk. Trough concentrations of mesna at 4 and 8 wk were 104.8 ± 51.8 and 106.2 ± 38.4 μmol/L, respectively. Mesna was also detectable in plasma 1 wk after completion of the study at a concentration of 24.3 ± 29.2 μmol/L.

**Discussion**

Elevated plasma tHcy is consistently observed in hemodialysis patients despite vitamin supplementation sufficient to normalize it in most patients with adequate renal function (17). Dialysis patients have an extremely high incidence of cardiovascular morbidity and mortality; elevated plasma tHcy may represent a modifiable cardiovascular risk factor in this resistant population (11). The current therapy for decreasing plasma tHcy is supplementation with folic acid, vitamin B6, and vitamin B12 (40) despite that this treatment consistently fails to lower tHcy in the majority of patients to achieve a normalized plasma tHcy level and overwhelming or extensive progression of disease. In addition, adverse effects of high-dosage folic acid may have offset the benefit of lowering Hcy. These results are consistent with other, recently completed, large-scale trials involving patients with a history of stroke (VISP trial [26]) or cardiovascular disease (NORVIT [25] and HOPE-2 trial [24]) that found no effect on primary outcomes. In light of recent evidence, supplementation with folic acid and B vitamins does not benefit cardiovascular morbidity. It should be noted that B vitamin supplementation confers benefit toward reduction of cerebrovascular events, as seen in the HOPE-2 trial (24), subgroup analysis of the VISP trial (42), and a recent meta-analysis of large randomized trials (43). It should also be noted that lowering plasma tHcy with vitamins has a positive effect on cognitive function (44). Because the results of large randomized trials have been conflicting, the notion of Hcy as a causal marker of atherosclerosis remains controversial.

Recent efforts to lower tHcy have focused on administering thiol-containing pharmaceutical agents to enhance its free dialyzable fraction. These trials have had variable results. In a similar study design, our group found no effect of oral DMSA, 2.5 mg/kg per d for 8 wk (30). Similarly, Friedman et al. [38] observed a small, insignificant effect of oral NAC, 1 g twice daily for 4 wk. Conversely, Scholze et al. [45] observed a large, significant, intradialytic drop in tHcy with a parallel improvement in pulse pressure and endothelial function after a single 5.0-g intravenous dose of NAC. Our group recently developed an in vitro assay to test the efficacy of thiol pharmaceuticals to exchange with protein bound Hcy before performing in vivo clinical trials (31). This assay indicated that among several thiols tested, mesna and NAC exchange with protein bound Hcy but that mesna is more effective on a concentration basis. A dosage-finding pilot study demonstrated that a single 5.0-mg/kg intravenous dose of mesna caused a rapid, significant decrease in plasma tHcy (32). Furthermore, tHcy remained significantly lower 2 d later, suggesting a cumulative tHcy-lowering effect would be observed upon routine dosing.

This is the first study to investigate the effect of multiple-dose intravenous mesna on plasma tHcy in hemodialysis patients. Despite promising results from our pilot study, we found no effect of thrice-weekly 5.0-mg/kg mesna for 8 wk on tHcy. A lack of effect could be explained by the inverse relationship between plasma tHcy and the cellular efflux of Hcy (unpublished observation); therefore, any decrease in plasma tHcy caused by mesna may be countered by an increased input to the plasma compartment. The dosage of mesna used in this study may be inadequate to overcome the increased endogenous rate of Hcy production, a consequence of increasing Hcy clearance. The single dose of mesna used during our pilot study achieved

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 11)</th>
<th>Mesna (n = 11)</th>
<th>P</th>
<th>Placebo (n = 19)</th>
<th>Mesna (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.4</td>
<td>65.3</td>
<td>0.65</td>
<td>67.6</td>
<td>64.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>81.8</td>
<td>81.8</td>
<td>0.98</td>
<td>68.4</td>
<td>80.0</td>
<td>0.57</td>
</tr>
<tr>
<td>Serum folate (ng/ml)</td>
<td>24.1</td>
<td>24.1</td>
<td>0.54</td>
<td>24.1</td>
<td>24.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>526.4</td>
<td>526.3</td>
<td>0.99</td>
<td>495.1</td>
<td>510.0</td>
<td>0.87</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.22</td>
<td>3.46</td>
<td>0.07</td>
<td>3.33</td>
<td>3.42</td>
<td>0.34</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.7</td>
<td>79.5</td>
<td>0.25</td>
<td>85.3</td>
<td>79.0</td>
<td>0.54</td>
</tr>
<tr>
<td>tHcy (μmol/L)</td>
<td>23.3</td>
<td>23.0</td>
<td>0.46</td>
<td>22.7</td>
<td>24.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Urea reduction ratio</td>
<td>73.5</td>
<td>75.5</td>
<td>0.54</td>
<td>74.0</td>
<td>74.4</td>
<td>0.88</td>
</tr>
<tr>
<td>Posttreatment serum bicarbonate (mEq/L)</td>
<td>24.6</td>
<td>25.3</td>
<td>0.34</td>
<td>24.2</td>
<td>25.0</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*To convert folate in ng/ml to nmol/L, multiply by 2.266; vitamin B12 in pg/ml to pmol/L, multiply by 0.738; albumin in g/dl to g/L, multiply by 10; total homocysteine (tHcy) in μ mol/L to mg/L, divide by 7.397.*
a peak concentration of approximately 300 µmol/L and declined to approximately 100 µmol/L after dialysis. In this study, we observed a mean trough plasma mesna concentration of 106.2 ± 38.4 µmol/L at 8 wk. Trough concentrations of mesna did not differ between weeks 4 and 8, suggesting that mesna did not accumulate. We speculate that dialysis of mesna itself or its oxidation in the prepackaged syringes (despite precautions taken) may have attenuated any lowering of tHcy.

Mesna(7,13),(994,994) is indicated for prevention of ifosfamide-induced hemorrhagic cystitis during chemotherapy. Several studies have demonstrated that mesna depletes plasma thiols such as cysteine and tHcy in patients who undergo chemotherapy. Stofer-Vogel et al. (46) were the first to report that oral and intravenous mesna deplete the thiol amino acid cysteine by enhancing its urinary excretion. Similarly, Lauterburg et al. (33) and Pendyala et al. (34) showed depletion of tHcy by intravenous infusion of mesna to patients who were undergoing concurrent chemotherapy with ifosfamide. Because this is the first study to evaluate the effect of routine mesna on plasma tHcy in patients with ESRD, we conservatively chose a dosage of 5.0 mg/kg. For prevention of hemorrhagic cystitis, mesna is administered at a dosage of 2 to 8 g/m² per d (47). These dosages result in plasma Cmax, ranging between approximately 120 and 365 µmol/L. Previous studies that evaluated the effect of mesna on plasma thiols in patients who received chemotherapy with ifosfamide used much higher dosages of mesna and administered it as a continuous intravenous infusion.

This trial did not have a sufficient number of patients to detect the planned 5.0-µmol/L difference in tHcy at 8 wk, despite the observed SD of 6.4 being similar to the 7.3 used in the sample size calculation. According to our matched pair design, dropout of one patient from either the placebo or the mesna group would result in the loss of one complete pair. Nevertheless, the study was adequately powered at 4 wk for interim analysis, at which time there was no significant difference in tHcy.

Thiol exchange is a novel strategy for treatment of elevated tHcy in hemodialysis patients. Despite the negative result of this trial, previous literature reports suggested that mesna is a good candidate for thiol exchange and depletion of plasma tHcy. A number of groups have reported that parenteral vitamin B₉₂ significantly lowers plasma tHcy concentrations in dialysis patients and that in some cases this treatment normalizes plasma tHcy (48–53). Thiol exchange could be an important adjunctive therapy to parenteral B₉₂ to lower plasma tHcy of patients who remain at risk.

**Conclusions**

The homocysteine theory remains unproved in dialysis patients, and its evaluation requires a safe, effective therapy for long-term normalization of tHcy. Although this trial indicates that 5.0 mg/kg mesna fails to lower tHcy in dialysis patients, mesna has a favorable adverse effect profile, and the literature supports its ability to exchange with protein-bound Hcy. Further studies are necessary to determine whether a larger dosage of mesna or different regimens for its administration will lower tHcy in dialysis patients.

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**Disclosures**

B.L.U., D.J.F., J.D.S., and A.A.H. have applied for a patent for the use of mesna to lower tHcy in patients with ESRD.

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