Calcification of the medial layer of arteries, often termed Monckeberg’s arteriosclerosis, is common in CKD and present in most patients with ESRD (1). Although it likely has detrimental long-term consequences, it is generally a chronic, asymptomatic condition. However, in a few patients, medial calcification leads to occlusion of small arteries and arterioles, resulting in an acute, life-threatening presentation of skin and subcutaneous necrosis previously known as calciphylaxis but now more accurately termed calcific uremic arteriolopathy (CUA). This disease continues to mystify investigators and challenge physicians, who must rely on treatments that are more mythical than evidence based. It is hoped that a recently established international collaborative network (2) will provide more objective data in the future.

Why CUA develops in only a very small percentage of ESRD patients despite the prevalence of medial arterial calcification in these patients is unclear. Vessel occlusion appears to involve intimal hyperplasia, inflammation, and thrombosis (3,4), but which is the initiating event and how this relates to the medial calcification that is invariably present remain unknown. Case-control studies have provided few specific clues other than altered mineral metabolism (5–7). However, a recent study in Japan identified warfarin therapy as a potent risk factor (7), confirming the suspicions of many investigators (4). Warfarin may promote CUA by blocking carboxylation and activity of matrix gla protein, a potent inhibitor of vascular calcification (8), and the anticoagulant proteins C and S. On the basis of these studies, treatment usually consists of correcting hyperphosphatemia, lowering serum calcium levels (by parathyroidectomy or adding cinacalcet, discontinuing vitamin D compounds, and reducing dialysate calcium concentration), and discontinuing warfarin in addition to aggressive wound therapy.

The uncertain pathogenesis and the lack of randomized controlled trials leave physicians with therapies based on mechanistic assumptions and small case reports. One such therapy that is now commonly used in CUA is sodium thiosulfate (STS). This therapy stems from observations published over 3 decades ago that STS could prevent recurrent kidney stone formation (9). Its use was subsequently proposed for tumoral calcinosis in renal failure (10) and the first report of its use for CUA appeared almost a decade ago (11).

Several case reports and small series have followed with mixed results in terms of benefit. Although there are no data proving efficacy of STS in CUA in humans, STS does reduce medial arterial calcification in a model of uremic vascular calcification in rats (12) and in an ex vivo model of calcification in cultured rat aortas (13). However, neither is a model of CUA.

How thiosulfate might reverse CUA is unclear and a number of mechanisms have been proposed, primarily involving complexation with calcium ions or dissolution of calcium deposits. Despite a widely held assumption to the contrary, thiosulfate does not chelate calcium ions and neither inhibits hydroxyapatite formation nor dissolves vascular calcifications in vitro (13). Hydroxyapatite formation and vascular calcification are pH dependent within the pathophysiologic range, with alkalosis favoring calcification (14), and acidosis reduces arterial calcification in uremic animals (15). However, thiosulfate is not an acid and it does not alter pH when added to blood ex vivo (12) and the inhibition of calcification in cultured vessels occurred without a change in the pH of the culture medium (13). The expansion acidosis that STS does produce in vivo is too mild to have much of an effect on calcification (12). Lastly, an antioxidant action that targets inflammation and intimal hyperplasia has been proposed based on the fact that thiosulfate can be oxidized to sulfate. However, sulfate was just as effective as thiosulfate in inhibiting calcification in cultured vessels (13), thus ruling out an antioxidant effect.

Despite an absence of efficacy data in humans, an uncertain mechanism, and unknown safety, STS continues to be used to treat CUA. This is possible because STS is approved and available for the treatment of cyanide toxicity. In this issue of CJASN, Nigwekar et al. present a large series of 147 patients who completed treatment with STS for CUA, by far the largest to date, which helps to fill this information gap (16). Although detailed information was available in only 43 patients, this study is still several times larger than any previous study. The major finding of this study was that the treatment was safe and well tolerated, with the caveat that there was no control group. Laboratory data showed the expected increase in the serum anion gap as well as a decrease in serum calcium. The latter persisted after therapy and presumably reflects other measures that were undertaken such as decreased
calcium intake, decreased dialysate calcium concentration, discontinuation of vitamin D compounds, initiation of cinacalcet, and parathyroidectomy. The decrease in serum parathyroid hormone, which was of borderline significance, is not surprising given that 72% of the patients either underwent parathyroidectomy or were started on cinacalcet. There was a decrease in postdialysis weight that persisted after therapy and most likely reflects the illness of the patients rather than an effect of STS. Nausea and vomiting occurred in about a third of patients but were rarely intractable, and no deaths were attributable to STS.

Because patients could be identified only through the use of STS and not the diagnosis of CUA, there is unfortunately no control group. Because it is unlikely that a randomized controlled trial will ever be performed, any evidence of efficacy must be gleaned from historical comparisons. This is always problematic, particularly because CUA is now recognized earlier, more aggressive wound therapy is utilized, and cinacalcet is now available. Although 1-year mortality was lower in the current series (35%) compared with a previously published series of patients not treated with STS (55%) (5), there was no difference when patients with similar, milder disease were compared, suggesting no benefit. There are other limitations that also affect the analysis of the data. Because a histologic diagnosis was made in fewer than half of the patients, CUA may not have been present in some of them. In addition, the potential exclusion of hospitalized (and presumably sicker) patients may have introduced a selection bias. Thus, the efficacy of STS cannot be answered by this study and is still questionable.

Despite the limitations of this study, the authors are to be congratulated for this difficult undertaking and providing us with useful data from the largest series to date. Although efficacy is not established by this study, the authors clearly demonstrate that the treatment is safe and well tolerated. In the absence of controlled trials and a clear understanding of its pathophysiology, treatment of CUA will remain in the realm of mythology. Although we do not know whether STS works and by what mechanism, we can at least rest assured that it is safe.

Disclosures

W.C.O. has received grants from Amgen, Genzyme, and Synageva, and grants and royalties from Baxter Healthcare.

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Published online ahead of print. Publication date available at www.cjasn.org.