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Antiproteinuric Effect of Sulodexide versus Losartan in Primary Glomerulonephritis

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Abstract

Introduction: Limited data are available for the use of sulodexide in primary glomerulonephritis (GN). Objective: We studied the efficacy of sulodexide compared to losartan in patients with primary GN. Design and Method: This was a prospective, open labelled, randomized control trial in patients with stable primary GN. Patients were randomized to receive either sulodexide or losartan to maximum tolerated doses for 12 weeks. Blood and urine investigations were measured at baseline and at 4-weekly intervals. Adverse effects were recorded. Results: 18 patients were recruited (10-sulodexide and 8-losartan). Their baseline characteristics were comparable. At end study, patients in both groups showed no significant reduction in proteinuria and there were no differences between groups at each visit. Nonetheless, there was a trend towards lower protein uria in the losartan but not in sulodexide group. There were no changes in the other parameters of renal function or of coagulation over time. No adverse events in particular clinical bleeding occurred. Conclusion: Sulodexide and losartan did not demonstrate any significant anti-proteinuric effect in primary GN. Nevertheless, there was a trend of better proteinuria reduction in losartan group. Furthermore, other renal parameters were not significantly affected by both drugs.

Keywords

Antiproteinuria, Losartan, Primary Glomerulonephritis, Sulodexide

1. Introduction

Glomerulonephritis (GN) is a renal disease characterized by inflammation of the glomeruli, or small blood ves-

sels in the kidneys. GN is broadly categorized into primary GN and secondary GN. Primary GN is due to intrinsic causes to the kidney while secondary GN is due to infection, drugs, diabetes mellitus or systemic disorders. Primary GN includes minimal change disease (MCN), focal segmental glomerulosclerosis (FSGS), primary membranous GN, immunoglobulin A nephropathy (IgAN) and various proliferative GN.

Little is known about the worldwide variation in incidence of primary GN. A systemic review had shown the incidence of primary GN to vary between 0.2/100,000/year and 2.5/100,000/year worldwide [1]. The commonest primary GN reported by the 3rd report of the Malaysian Registry of Renal Biopsy 2009 was MCN (33.4%), FSGS (29.3%) followed by IgAN (19.6%) and idiopathic membranous nephropathy (9.8%) [2]. GN is the third leading cause of end stage renal disease (ESRD) in United States [3] and fourth in the Malaysian population [4].

Proteinuria is the clinical hallmark of GN and is the most important predictor of outcome. It is also an independent determinant of the progression of chronic kidney disease (CKD)—the greater the proteinuria the more rapid decline of renal function [5]-[7]. These patients also have increased cardiovascular risk which is further aggravated by reduction of the glomerulofiltration rate (GFR) [8]. Hence, therapeutic intervention that reduces the level of proteinuria should impact the progression of proteinuric nephropathies.

As most primary GN is immune mediated, immunosuppressive therapy is an important first line treatment. The next therapeutic approach is the inhibition of the renin-angiotensin-aldosterone system (RAAS) by using angiotensin-converting enzymes inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARBs) and/or aldosterone receptor blockers. These have both antihypertensive and antiproteinuric properties and have been shown to significantly reduce the rate of progression of both diabetic and non diabetic nephropathies [9]-[12].

One of the pathogenic mechanisms leading to proteinuria in GN, involves an alteration in heparin sulfate (HS) expression in glomerular basement membrane (GBM). HS is a member of the family of glycosaminoglycans (GAGs) that is generally bound to a core protein to form a proteoglycan (PG). Alterations in HS expression in the GBM had been reported in many proteinuric renal diseases which include diabetic nephropathy, minimal change nephropathy and membranous GN [13]. The decrease of HS content causes a reduction on the permselectivity to negatively charged macromolecules such as albumin thus allowing protein leak into the urinary space.

Sulodexide is a highly purified mixture of GAGs composed of a fast-moving heparin like substance (80%) and dermatan sulphate (20%), with a low molecular weight, a high oral bioavailability and possesses antithrombotic and profibrinolytic activities [14]. This mixture of GAGs is highly purified from porcine intestinal mucosa by a patented process. It is concentrates in the renal parenchyma for a long time after administration [15]. It was shown to reduce proteinuria in patients with diabetes kidney disease (DKD) and non DKD [16]-[23].

In addition to increasing the permselectivity of the GBM, sulodexide also inhibits mesangial cell proliferation [24] and exerts an antimitogenic effect on glomerular epithelial cells [25]. It reduces transforming growth factor-β expression and has an anti-thrombotic effect which helps to further reduce proteinuria [24] [26] [27].

The fast moving heparin (FMH) and dermatan sulphate (DS) accelerate the inhibition of thrombin by their interaction with ATIII and heparin cofactor II (HCII) and directly inhibit thrombin and thrombin generation by inhibiting the feedback activation of prothrombin. Sulodexide also prolongs the thrombin clotting time and the activated partial thromboplastin time (aPTT) [28] [29]. Several clinical trials have demonstrated the beneficial effect of sulodexide in the treatment of deep vein thrombosis [30] [31], venous leg ulcers [32] and intermittent claudication [33].

Most studies of the antiprotenuric effect of sulodexide have been carried out in patients with type 1 and/or type 2 diabetes mellitus. The antiproteinuric effect of sulodexide in proteinuric chronic primary GN is less well studied [34].

Most studies investigating the use of sulodexide as a novel antiproteinuric agent that works on perm selectivity of the GBM have been performed in patients with DKD and non DKD and many have reported that sulodexide had a significant antiproteinuric effect with or without added RAAS blockade [17] [18] [20]-[22]. However, there are no studies that have directly compared sulodexide and a RAAS blocker (e.g. losartan) as antiproteinuric agents. Hence we would like to perform a head-to-head comparison of this novel GAG with the ARB, losartan to evaluate the efficacy of sulodexide as an alternative antiproteinuric agent in primary GN.

Our primary objective was to evaluate the antiproteinuric effect of sulodexide compared to losartan, an ARB in primary GN. Our secondary objectives were to evaluate the effect of sulodexide compared to losartan on other parameters of renal function and determine the safety of sulodexide on parameters of coagulation.

2. Methodology

2.1. Patients and Method

This was a prospective open labelled randomized control trial involving patients with primary GN on follow up at the Nephrology Unit, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The study approved by the local Ethics & Research Committee (FF-454-2011).

Only patients with proteinuria of 0.3 g - 3.5 g/day and CKD stages 1 - 3 (eGFR > 30 ml/min/1.73m^2) with the diagnosis of primary GN included in this study. Patients on stable maintenance immunosuppressive therapy were included without altering the immunosuppressive drug. All patients had blood pressure of ≤ 150/90 mmHg and serum potassium of < 5.5 mmol/L at recruitment. Patients with known renal artery stenosis or allergy to study drugs were excluded from this study. Pregnant or lactating patients and patients with childbearing potential without effective method of birth control were also excluded from this study.

2.2. Randomization

Patients who met the eligibility criteria were recruited. Prior to randomization patients who were on RAAS blockers underwent a 4-week washout period. Other antihypertensive medications were continued. The patients were reviewed 2-weekly during the washout period and target systolic BP ≤ 150 mmHg and diastolic BP ≤ 90 mmHg were maintained. Other antihypertensive medications were added and/or dose adjusted until target blood pressure was achieved. Patients naïve to losartan and those who had undergone the RAAS blocker washout period were randomized into the sulodexide or losartan arms. Randomization was done in blocks of four. A short sequence of four probable alphabetical orders of AB combination were put in an envelope and pulled out as patients were recruited.

2.3. Study Protocol

At study entry, full blood count, coagulation profiles and blood samples for renal, liver and lipid profiles were taken. Spot urine sample urine Protein Creatinine Index (uPCI) was also taken. The treatment was for 12 weeks. Patients were reviewed at Weeks 0 (baseline), 2, 4 (V1), 8 (V2) and 12 (V3). At Weeks 4 (V1), 8 (V2) and 12 (V3)-blood pressure, uPCI and blood investigations listed above were taken each visit except for the estimated GFR (eGFR), coagulation and lipid parameters which were evaluated at the beginning (V0) and end of the study-Week 12 (V3). The eGFR was calculated by the Modification of Diet in Renal disease (MDRD) formula.

Losartan and sulodexide doses were titrated up to the maximum tolerated dose as judged by blood pressure. Losartan dosages ranged from 50 - 100 mg daily and those for sulodexide from 100 - 200 mg daily. Patients were strongly advised to adhere to the study drugs given and to report any adverse reactions either by phone or during clinic visits. Patient compliance to study treatment was assessed by pill counts. Compliance was taken as adherence with medications ≥80% of the time.

2.4. Statistical Analysis

All data were recorded and analyzed using the statistical package Statistical Package for the Social Sciences version 20 (IBM SPSS, Armonk, NY: IBM Corp). Our sample size was small and was not normally distributed; hence non-parametric tests were used. Results were expressed as median with interquartile range (IQR). The differences between two groups were analyzed using the Mann-Whitney-U test. Related data across time were analyzed using both the Wilcoxon Rank test and the Friedman's analysis. Nominal and ordinal data were analyzed using Fisher's exact test. A p value of < 0.05 was considered significant.

3. Results

Eighty seven patients were screened and 34 patients were noted to be in complete remission with proteinuria < 0.3 g/day. Ten patients were excluded as they were not on stable immunosuppressive therapies. Eight patients had CKD above stage 3, 7 patients declined, 4 patients were non compliant to medications, 4 females had breast cancer and 2 females were pregnant. Hence only 18 patients were recruited with 10 patients randomized to receive sulodexide and eight patients to losartan.

Baseline demographics and clinical characteristics were tabulated in **Table 1**. Baseline laboratory investigations were tabulated in **Table 2**.

Median dose for sulodexide was 150 (100 - 200) mg daily and losartan was 75 (50 - 100) mg daily. The use of other concurrent medications including antihypertensive, statin, aspirin and immunosuppressive medication were the same between both groups. There was no significant difference of blood pressure across the study duration in both study groups.

Both groups did not show any significant reduction in proteinuria whether intragroup or intergroup and across all visits. Nonetheless, the losartan arm had a trend towards lower proteinuria at end study whilst in the sulodexide group, proteinuria levels remained static (**Figure 1**).

Other renal parameters results were tabulated in **Table 3**. There were no significant differences in all the parameters in between and within both groups.

Over the 12 weeks of treatment, there were no significant changes in the full blood count parameters nor prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (APTT) in patients in the sulodexide arm. There were also no clinical episodes of bleeding and no other adverse effects occurred.

4. Discussion

Primary GN is one of the common renal diseases that progress to ESRD. Besides immunosuppressive medications, RAAS blockade play an important role in the treatment of primary GN and reduction of proteinuria by reducing the intraglomerular pressure. A few randomized trials have shown that losartan has significant antiproteinuric effect in primary GN [35]-[39].

Table 1. Baseline demographics and clinical characteristics of the study groups.

Parameters	Sulodexide (n = 10)	Losartan (n = 8)	p value
Age (years)	48.5 (39.25 - 53.50)	53.0 (37.75 - 66.25)	0.573
Gender			
Male	1 (10%)	6 (75%)	0.013
Female	9 (90%)	2 (25%)	
Weight (kg)	58.2 (51.85 - 62.15)	66.0 (58.8 - 75.0)	0.460
Height (cm)	156.5 (154.0 - 163.8)	170.0 (155.0 - 175.0)	0.360
Body mass index (kg/m^2)	22.24 (21.40 - 25.85)	25.43 (23.82 - 28.14)	0.203
Blood pressure in mmHg			
Systolic BP	124 (110 - 137)	132 (130 - 143)	0.101
Diastolic BP	70 (70 - 72)	80 (70 - 90)	0.315
Primary Glomerulonephritis			
Ig AN	4 (40%)	4 (50%)	0.473
FSGS	6 (60%)	3 (37.5%)	
Membranous	0 (0%)	1 (12.5%)	
Age at diagnosis (years)	39 (34 - 44)	45 (30 - 51)	0.740
Disease duration (years)	7 (4 - 9)	7 (6 - 10)	0.573
Baseline Co-Morbidities			
Hypertension	4 (40%)	7 (87.5%)	0.066
Dyslipidaemia	6 (60%)	5 (62.5%)	1.000
Smoking	1 (10%)	0 (0%)	1.000

Results in median (IQR), IQR: interquartile range; IgAN: IgA nephropathy; FSGS: Focal segmental glomerulosclerosis; p value < 0.05 is significant.

Table 2. Baseline laboratory parameters of the two study groups.

Parameters	Sulodexide (n = 10)	Losartan (n = 8)	p value
Haemoglobin (g/dl) (NR: 4.0 - 10.0)	12.3 (11.9 - 13.1)	13.5 (12.9 - 13.6)	0.068
Platelets ($\times 10^9$/L) (NR: 150 - 400)	298 (245 - 347)	257 (216 - 332)	0.360
Total white blood cells ($\times 10^9$/L) (NR: 4.0 - 10.0)	7.5 (6.4 - 9.4)	6.9 (4.6 - 9.8)	0.696
Se urea (mmol/L) (NR: 2.5 - 6.4)	4.5 (3.4 - 6.4)	5.1 (3.4 - 5.7)	0.897
Se creatinine (umol/L) (NR: 62 - 106)	67 (54.2 - 100.7)	96 (67.2 - 119.2)	0.101
Se potassium (mmol/l) (NR: 3.5 - 5.0)	4.1 (3.7 - 4.5)	3.8 (3.8 - 4.0)	0.315
Se uric acid (umol/l) (NR: 149 - 450)	353 (303 - 408)	472 (391 - 521)	0.550
Se albumin (g/L) (NR: 35 - 50)	43 (40 - 44)	42 (38 - 45)	0.829
uPCI (g/mmol creat) (NR: <0.02)	0.09 (0.04 - 0.15)	0.07 (0.05 - 0.08)	0.360
CKD			
Stage 1	6 (60%)	2 (25%)	
Stage 2	2 (20%)	4 (50%)	0.343
Stage 3	2 (20%)	2 (25%)	
eGFR (ml/min/1.7m^2)	93 (64 - 104)	63 (55 - 84)	0.203
Total cholesterol (mmol/L) (NR: <5.7)	5.39 (4.62 - 6.37)	5.02 (4.29 - 5.74)	0.370
HDL (mmol/L) (NR: >1.20)	1.75 (1.22 - 1.97)	1.36 (1.10 - 1.65)	0.673
LDL (mmol/L) (NR: <3.80)	3.06 (2.48 - 3.89)	2.83 (2.36 - 2.84)	0.374
Triglyceride (mmol/L) (NR: <1.40)	1.24 (0.85 - 1.74)	1.52 (1.15 - 1.73)	0.606

Results in median (IQR), IQR: interquartile range; uPCI: urine protein index; CKD: Chronic Kidney Disease; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; p value < 0.05 is significant.

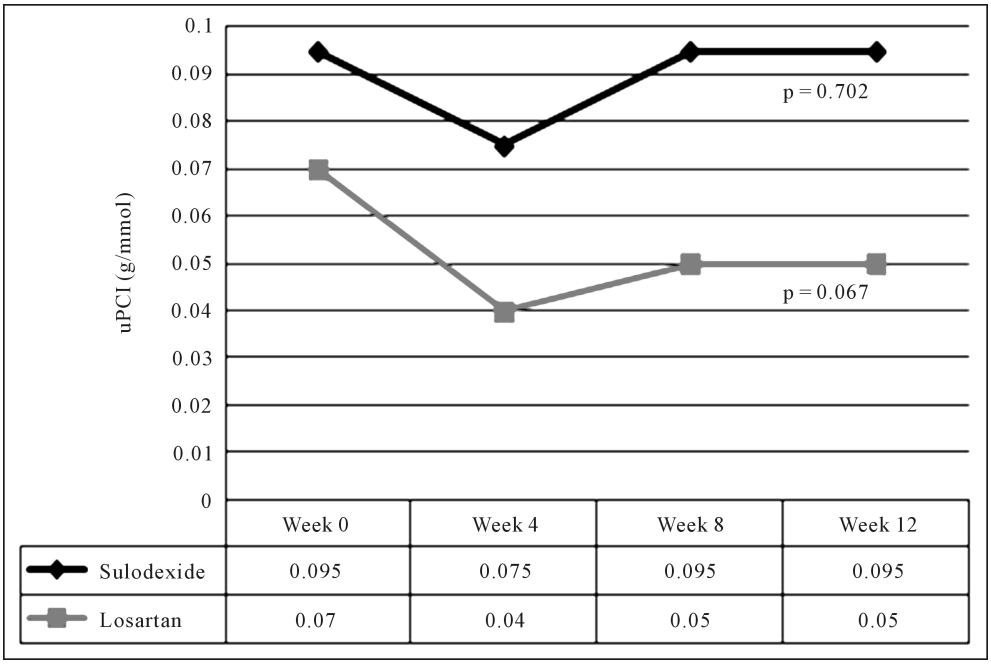

Figure 1. uPCI across the study period in both groups.

Table 3. Other renal parameters across the study period and in between the two groups.

		Week 0	Week 4	Week 8	Week 12	p value*
Se creatinine (umol/L)	Sulodexide	67 (54 - 100)	65 (53 - 105)	66 (55 - 114)	56 (46 - 110)	0.200
	Losartan	96 (67 - 119)	93 (71 - 110)	101 (69 - 113)	92 (71 - 99)	0.346
p (inter-Group)		0.101	0.122	0.146	0.101	
eGFR-(ml/min/1.7m^2)	Sulodexide	93 (64 - 104)	83 (63 - 110)	93 (52 - 106)	102 (56 - 125)	0.125
	Losartan	63 (55 - 84)	71 (55 - 84)	68 (62 - 84)	74 (64 - 83)	0.672
p (intergroup)		0.203	0.274	0.237	0.246	
Se potassium (mmol/l)	Sulodexide	4.1 (3.7 - 4.5)	4.1 (3.6 - 4.4)	4.1 (3.9 - 4.2)	4.0 (3.0 - 4.3)	0.882
	Losartan	3.8 (3.8 - 4.0)	4.0 (3.8 - 4.3)	4.1 (3.8 - 4.2)	4.2 (3.8 - 4.3)	0.658
p (inter-group)		0.315	1.000	0.768	0.829	
Se Uric acid (umol/l)	Sulodexide	353 (303 - 408)	360 (298 - 470)	367 (303 - 484)	335 (288 - 511)	0.615
	Losartan	472 (391 - 521)	440 (364 - 511)	461 (390 - 477)	408 (365 - 474)	0.700
p (inter-group)		0.055	0.203	0.237	0.408	
Se albumin (g/L)	Sulodexide	43 (42 - 44)	43 (41 - 43)	41 (41 - 44)	43 (42 - 44)	0.887
	Losartan	42 (38 - 46)	44 (41 - 47)	41 (39 - 47)	44 (42 - 46)	0.678
p (inter-group)		0.829	0.146	0.408	0.463	

Results in median (IQR), IQR: interquartile range; eGFR: estimated glomerular filtration rate; p value*: Intra-group analysis using Friedman's analysis; p value: intergroup using Mann-Whitney-U test; p value < 0.05 is significant.

In our study, there was no significant antiproteinuric property in both losartan and sulodexide groups. Nevertheless there was a trend towards significance of proteinuria reduction in the losartan group.

These rather disappointing results in losartan group can be explained by a short study duration of 12 weeks and a the lower median dose of 75 mg daily used due to patient intolerance as manifested by a lowish blood pressure. In DKD, it is a fact that RAAS blockers exert maximal antiproteinuric effects after 6 months of treatment [9] [12] [40] [41]. In several studies using losartan as antiproteinuric agent in non-DKD, losartan even at low doses of 25 - 50 mg were sufficient to significantly reduce proteinuria in primary GN as hypertension is not universal in early non-DKD [38]. Large multicenter trials have also demonstrated the optimum antiproteinuric dose of losartan to be 100 mg daily and that no beneficial effects were seen beyond this dose [42]-[44]. Furthermore, from the extensive experience with the use of RAAS blockers in DKD and more recently in non-DKD, the higher the baseline proteinuria, the greater the proteinuria reduction [5] [9] [11] [12]. Thus, the low baseline proteinuria, low median dose of losartan and short duration of our study may account for the lowered antiproteinuric performance of losartan in our study.

To date, large trials of sulodexide have been conducted only in hypertensive patients with type 2 diabetes mellitus (DM) [20]-[22]. Its use in proteinuric chronic GN is very recent and followed the failure of the SUN-Micro-trial in which sulodexide at the optimal dose of 200 mg daily did not further reduce microalbuminuria [21]. The SUN-Macro-trial which was terminated prematurely by the sponsor had already recruited more than 2000 hypertensive type 2 DM patients with a mean follow-up of 11 months [22].

Several published studies, which included only a small number of patients, had previously investigated the effect of sulodexide on proteinuria in chronic non-DKD [17]-[19] [45]. Almost all these studies on non-DKD involved the use of sulodexide with an ACE-I or ARB. To our knowledge, there has been no head-to-head comparison between sulodexide versus a RAAS blocker in proteinuric renal disease, diabetic or non-diabetic. We believed this was the first study to investigate the antiproteinuric property of sulodexide as a sole antiproteinuric agent in primary GN.

A recent multicenter study by Kitae Bang *et al.* of sulodexide involved 77 patients with IgA nephropathy who despite RAAS blockade remained proteinuric. They were randomized to receive placebo, sulodexide 75 mg dai-

ly or sulodexide 150 mg daily. At the end of 16 weeks only those on sulodexide 150 mg daily had a significant reduction in proteinuria [17].

In a retrospective review, BY Yang *et al.* reported their experience with 20 patients with IgA nephropathy treated with sulodexide 50 mg daily as add-on therapy to optimized RAAS blockade. The investigators found a significant reduction of proteinuria and also noted the higher the baseline levels of proteinuria the greater the reduction [18].

As our study was a head-to-head comparison of sulodexide to losartan, it was not appropriate to compare our results with those of the above studies, which evaluated sulodexide as add-on therapy to RAAS blockade in proteinuric non DKD.

The median dose of sulodexide used was 150 mg daily (100 - 200 mg). In the literature, no previous study had specifically addressed the optimal dose of SDX in primary GN. In earlier study, Gambaro G *et al.* demonstrated a significant reduction of proteinuria with increasing oral doses of sulodexide from 50 mg to 100 mg to 200 mg daily [20]. In a recent study of patients with IgA nephropathy, sulodexide at 150 mg daily had significant antiproteinuric effects up to 4 months of treatment and maximized at 6 months [17]. Another study by Byeong Yun Yang *et al*. reported that even lower sulodexide doses of 50 mg daily as add-on to ACE-I/ARB resulted in ≥ 50% reduction in IgA nephropthy [18]. The shorter study duration of 12-week could explain the lack of antiproteinuric efficacy of sulodexide in our study.

Serum creatinine and eGFR were stable throughout the study period of 12 weeks and there were no differences seen within or between the two treatment groups. There was even a slight improvement in the serum creatinine and eGFR in both groups. These findings are consistent with other reports of the use of sulodexide in IgA nephropathy [17] [18] as well as in diabetic nephropathy [20]. Studies of losartan in primary GN also reported similar findings to ours [13] [37].

Serum uric acid has emerged as a risk marker for progression of CKD [46]. Hyperuricaemia increases blood pressure, proteinuria, renal dysfunction and renal scarring [46]. The changes of serum uric acid levels in our study patients were not significant in both groups. So far, there have been no reports on changes of serum uric acid in the earlier sulodexide studies [17]-[20]. In contrast, losartan has been proven to reduce serum uric acid and delay renal progression in patients with DKD [47]. There were no changes seen in the serum haemoglobin, platelet count, protrombin time, INR and aPTT after 12 weeks of treatment in our study. This is consistent with findings from numerous trials with sulodexide for renal disease including D.I.N.A.S [20]. No adverse events such as rash, diarrhea, musculoskeletal symptoms, epigastric pain and vomiting were observed in our study.

5. Conclusion

Sulodexide and losartan did not demonstrate any significant anti-proteinuric effect in primary GN. Nevertheless, there was a trend of better proteinuria reduction in losartan group. Furthermore, other renal parameters were not significantly affected by both drugs. These findings may be due to lower dose of study drugs, shorter study duration and low baseline proteinuria in both groups. We found both drugs were safe and well tolerated by patients. A larger and longer study is indicated to confirm our findings.

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Conflict of Interest

None declared.

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