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A RANDOMISED, PROSPECTIVE, PARALLEL AND OPEN LABEL STUDY TO COMPARE EFFICACY AND SAFETY OF METFORMIN PLUS ROSUVASTATIN AND GLIMEPIRIDE PLUS ROSUVASTATIN IN PATIENTS OF COEXISTING NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND TYPE 2 DIABETES MELLITUS (T2DM)

Pharmacology

Dr. Prabhsimran kaur Junior resident, Department of Pharmacology, GMC Amritsar.

Dr.Gurpreet Kaur Randhawa Professor and Head, Department of Pharmacology, GMC Amritsar.

Dr.Surinder Kumar Salwan* Assistant Professor, Department of Medicine, GMC Amritsar. *Corresponding author

ABSTRACT

Background and Objectives: NAFLD and T2DM has global prevalence of 55.5% with currently no approved treatment. There is insufficient data for its pharmacotherapy. The sharing of risk factors, most common being the insulin resistance between NAFLD and T2DM, makes the antidiabetic drugs, with effect on insulin resistance, the potential treatment options. The aim was to compare efficacy and safety of antidiabetic drugs i.e. Metformin and Glimepiride with concomitant Rosuvastatin in NAFLD coexistent with T2DM.

Methods: Randomized, prospective, parallel and open-label study recruited 60 patients of concomitant NAFLD and T2DM after getting Institutional Review Board approval. Patients of either sex (20-60 years) with NAFLD (ultrasound diagnosed & raised AST 50-150 U/L) and T2DM(FBS> 126mg/dl) were recruited in medicine OPD after obtaining written informed consent. Chronic alcohol users and pregnancy cases were excluded. Patients were randomised into Group A[Rosuvastatin(10mg OD)+ Metformin(1gm BD)] & Group B[Rosuvastatin(10mg OD)+Glimepiride(3mg BD)]. Primary outcome was improvement in hepatic parameters and ultrasound grading of liver. Secondary outcomes were improvement in anthropometric, glycaemic and lipid parameters and assessment of safety.

Results: Group A caused significant($p<0.05$) reduction in hepatic parameters(S.Bilirubin & AST). Group A and B showed non-significant improvement($p>0.05$) in ultrasound grading of liver, respectively (24% vs 20% patients). Intergroup difference was significant($p<0.05$) for weight and BMI in Group A. Both groups showed highly significant($p<0.001$) reduction in glycaemic parameters and significant($p<0.05$) reduction in lipid parameters. Both treatments were safe.

Conclusion: Metformin plus Rosuvastatin seems to be more efficacious in NAFLD and T2DM over 90 days. These drugs could improve prognosis because of insulin sensitising action and additional benefits in cancers, cardiovascular diseases. Further studies are required to strengthen these findings which may help in finding a standard treatment for NAFLD and T2DM.

KEYWORDS

Biguanides, cirrhosis, insulin resistance, obesity, sulfonylureas

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and second common indication of liver transplantation. It is characterised by excessive hepatic fat accumulation, associated with insulin resistance. If left untreated it can progress to end stage liver disease and hepatocellular carcinoma.[1] The increasing global prevalence of NAFLD, amounting to 55.5% in T2DM, is placing a greater burden on healthcare resources.[2] India showed the prevalence of NAFLD of about 72.4% in northern states of India, with about 48% in Amritsar, district of Punjab, India.[3]

The coexistence of NAFLD and T2DM could be explained by its bidirectional relationship and the sharing of the risk factors such as obesity, insulin resistance and dyslipidaemia. The insulin resistance plays a pivotal role in pathogenesis of NAFLD and T2DM. The exacerbation of hepatic and peripheral insulin resistance in NAFLD and the release of pro-inflammatory cytokines and hepatokines promotes the development of T2DM. Likewise the coexistence of T2DM with NAFLD increases the likelihood of progression of NAFLD to NASH.[6]

Currently there is no approved treatment available for the concomitant NAFLD and T2DM. Lifestyle modification and weight loss are the mainstay of therapy but they are difficult to achieve and maintain. Hence the current gold standard treatment aims for the metabolic control to improve liver phenotype and glycaemic parameters.[6]

Antidiabetic drugs could have a role in decreasing progression of NAFLD because of their significant effect on insulin resistance, a common pathogenic link between NAFLD and T2DM.[7] Metformin, a biguanide, is the 1st line antidiabetic drug.[8] It is found to be useful in improving co-factors of NAFLD like body weight, transaminases or cholesterol levels and HbA_{1C} levels.[7] On the contrary, in some studies, Metformin has not shown improvement in histological or biochemical outcomes in NAFLD while some studies has shown its role in improvement of biochemical outcomes without improving histology of liver.[10,11] In addition, it has a protective role in cancers.[12] Further research is required to know its role in NAFLD.

Glimepiride is found to bring effective glycaemic control because of its insulin releasing action.[13] The reduction in HbA_{1c} with Glimepiride monotherapy is better than insulin and many antidiabetic drugs. Studies have shown that glimepiride can be hepato-protective because of its antioxidant property but requires further research to know its role in NAFLD.[15] Conclusively, Metformin and Glimepiride seem to be promising drugs because of their role in NAFLD manifestations and diabetes.

An important concern for T2DM is cardiovascular disease that requires treatment for dyslipidaemia. Statins are the 1st choice treatment for T2DM patients with dyslipidaemia, because of their role in lowering low density lipoproteins (LDL).[15] Statins have a beneficial role in managing dyslipidaemia, prevention of atherosclerosis, reduction in transaminases but its effect on LDL control is insufficient as monotherapy. Combination of Statins with antidiabetics is preferable because of risk of new onset diabetes. Rosuvastatin has shown decreased glucose levels in some studies but the current literature gives a conflicting view about the effects of Rosuvastatin in diabetes.[16]

Therefore, in present study, two antidiabetic drugs, Metformin (1st line) and Glimepiride (2nd line) are compared in combination with a statin, Rosuvastatin for their role in patients of NAFLD with coexistent T2DM over a period of 90 days. Primary outcome was improvement in ultrasound grading of liver. Secondary outcomes were improvement in anthropometric, glycaemic, hepatic and lipid parameters and assessment of safety.

MATERIAL AND METHODS

A randomized, parallel, prospective, open label, comparative study between Rosuvastatin plus Metformin and Rosuvastatin plus Glimepiride in patients with coexisting NAFLD and T2DM was conducted in the Department of Pharmacology in collaboration with Department of Medicine, Guru Nanak Dev Hospital attached to Government Medical College, Amritsar. Before starting the study, approval of Institutional Ethics Committee was taken. Sampe size was determined using mean values from previous literature with alpha of

0.05 and power of 80%. Patients (n=60) of either sex and age 20-60 years with NAFLD diagnosed by ultrasound liver with abnormal aminotransferase levels were recruited. AST 50-150 U/L (1 to 3 times the upper limit of normal) and with newly diagnosed T2DM were recruited in the study after taking their written informed consent. Patients with chronic drug or alcohol abuse [daily intake (> 20g in females & 30 g in males)], hereditary disorders like Wilson's disease or long-term use of steatogenic medications like methotrexate, amiodarone and tamoxifen), comorbidities like coronary heart disease, myocardial infarction, angina, peptic ulcer disease, pregnant and lactating females were excluded from the study. Patients were randomly divided into 2 groups- A and B consisting of 30 patients each. Randomisation was carried out with the help of random numbers generated by computer software programmer (Random number generator). Group A received Rosuvastatin (10 mg OD) plus Metformin (1 gm BD) and Group B was given Rosuvastatin (10 mg OD) plus Glimepiride (3 mg BD) orally for 90 days. Follow up was done every 15 days for 90 days for assessment of anthropometric parameters, liver function tests, lipid profile, fasting blood sugar, HbA1c, HOMA-IR and ultrasound of liver. All the parameters were recorded, tabulated and analysed using 't' test; paired `t`-test for intragroup comparison and unpaired `t` test for intergroup comparison.

RESULTS

The study groups were comparable (p>0.05) at baseline (Day '0') among various parameters.

Table I: Comparison of parameters of Group A and B at baseline (Day '0')

Parameters	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
SBP (mmHg)	139.67 ± 12.46	143.35 ± 11.82	0.149
DBP (mmHg)	91.00 ± 10.52	94.40 ± 10.53	0.216
BMI (kg/m^2)	29.55 ± 3.25	29.66 ± 2.85	0.893
WHR	0.88 ± .04	0.87 ± .04	0.699
S. Bilirubin (mg/dl)	1.02 ± .53	1.00 ± .29	0.889
SGOT (U/L)	43.24 ± 15.98	43.90 ± 10.29	0.850
SGPT (U/L)	50.01 ± 16.11	50.70 ± 12.08	0.853
ALP (IU/L)	170.30 ± 46.45	155.23 ± 28.15	0.134
Albumin (g/dL)	3.43 ± .86	4.48 ± 6.72	0.401
FBS (mg/dl)	188.67 ± 22.26	189.70 ± 17.08	0.841
HbA_{1c} (%)	9.67 ± 1.17	9.78 ± 1.37	0.753
S. Insulin (mIU/L)	10.29 ± 2.80	11.04 ± 2.96	0.322
HOMA IR	4.84 ± 1.51	5.22 ± 1.77	0.376
T. Cholesterol (mg/dL)	206.27 ± 25.15	198.43 ± 17.16	0.164
Triglycerides (mg/dL)	217.90 ± 58.95	222.80 ± 60.40	0.752
HDL (mg/dL)	36.29 ± 9.68	33.93 ± 8.28	0.315
LDL (mg/dL)	127.66 ± 23.82	119.94 ± 11.82	0.117

BMI - Body Mass Index	ALP - Alkaline Phosphatase
SGOT - Aspartate transferase	FBS - Fasting Blood Glucose
SGPT - Alanine transferase	HDL - High density Lipoproteins
HOMA IR - Homeostatic model assessment- Insulin resistance	LDL - Low Density Lipoproteins
	WHR - Waist hip ratio

Liver function tests

Both groups have shown significant improvement in hepatic parameters but Group A was significantly better (p<0.05) in improving serum bilirubin and SGOT over 90 days (Table 3)

Ultrasound grading of liver

Both groups showed comparable improvement in grading of liver on ultrasound over 90 days (Group A -24% patients and Group B- 20% patients; p>0.05). There was no worsening of grading of liver in any patient. (Table II)

Anthropometric Parameters

At the end of 90 days, a highly significant reduction (p<0.001) was seen in weight (kg) and BMI (kg/m2) in Group A. (Table III)

Glycaemic parameters

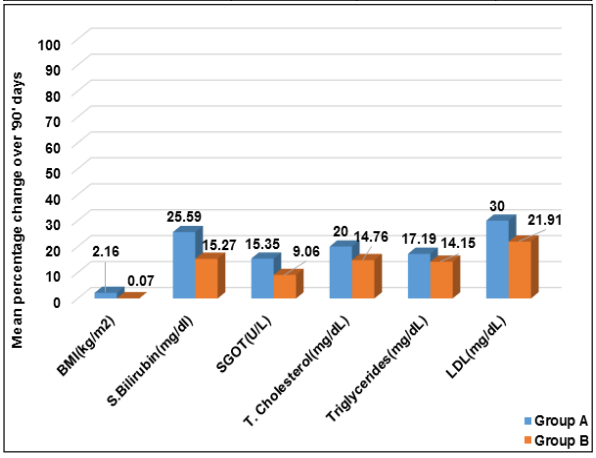
A highly significant (p<0.001) reduction was seen over 90 days in both the groups in diabetic parameters i.e. FBS, HbA1c, serum insulin and HOMA IR. The intergroup difference was non-significant (p>0.05). (Table III)

Lipid parameters

Both groups showed highly significant (p<0.001) improvement in the lipid parameters over 90 days. Group A showed statistically significant reduction in lipid parameters (all except HDL). (Table III)

Table II: Intergroup Comparison For Change Of Ultrasound Grading Of Liver Over '90' Days In Group 'a' And 'b'

Grade	Number of patients(%)		p- value
	Group A	Group B	
Grade 2 to Grade 1	5(17)	5(17)	0.743
Grade 3 to Grade 2	2(7)	1(3)	
TOTAL	7(24)	6(20)	



Graph I: Shows Parameters For Which Intergroup Difference For Mean Percentage Change Was Significant Between Group 'a' And 'b' Over A Period Of '90' Days

Table III: Intergroup Difference For Mean Percentage Change In Anthropometric, Hepatic, Glycaemic And Lipid Parameters Over '90' Days Between Group 'a' And 'b'

S. No	Parameters	Investigations	GROUP A % Change (Mean ± SD)	GROUP B % Change (Mean ± SD)	p-value
1	Anthropometric	Weight (kg)	2.31 ± 1.85 (p<0.001)	0.12 ± 1.78 (p>0.05)	**<0.001 ** **
		BMI (kg/m^2)	2.16 ± 2.06 (p<0.001)	0.07± 1.77 (p>0.05)	**<0.001 ** **
		WHR	0.42 ± 1.02 (p<0.05)	0.03 ± .82 (p>0.05)	>0.05
2	Hepatic	S. Bilirubin (mg/dl)	25.59±20.08 (p<0.001)	15.27±13.53 (p<0.001)	**<0.05***
		SGOT (U/L)	15.35±9.56 (p<0.001)	9.06 ± 7.52 (p<0.001)	**<0.05***
		SGPT (U/L)	12.19±10.07 (p<0.001)	8.51 ± 6.36 (p<0.001)	>0.05
		ALP (IU/L)	5.74 ± 5.96 (p<0.001)	3.24 ± 3.66 (p<0.001)	>0.05
		S. Albumin (g/dL)	19.20±18.23 (p<0.001)	13.51±16.61 (p<0.05)	>0.05
3	Glycaemic	FBS (mg/dl)	16.47±6.30 (p<0.001)	18.57 ± 5.44 (p<0.001)	>0.05
		HbA_{1c} (%)	12.97±7.27 (p<0.001)	14.74 ± 6.60 (p<0.001)	>0.05
		S. Insulin (mIU/L)	6.45 ± 5.01 (p<0.001)	7.79 ± 4.82 (p<0.001)	>0.05
		HOMA-IR	21.98±7.91 (p<0.001)	23.60 ± 8.18 (p<0.001)	>0.05
4	Lipid	T. Cholesterol (mg/dL)	20.0 ±4.85 (p<0.001)	14.76 ± 4.40 (p<0.001)	**<0.001 ** **
		Triglycerides (mg/dL)	17.19 ± 5.54 (p<0.001)	14.15 ± 5.11 (p<0.001)	**<0.05***
		HDL (mg/dL)	19.16±17.12 (p<0.001)	14.33±12.51 (p<0.001)	>0.05
		LDL (mg/dL)	30.0 ±9.92 (p<0.001)	21.91 ± 8.83 (p<0.001)	**<0.05***

DISCUSSION

Hepatic Parameters

Group A showed significantly better reduction in the levels of mean serum bilirubin and Aspartate aminotransferase (SGOT) over a period of 90 days as compared to Group B, respectively i.e. serum bilirubin [0.32 ± 0.42 vs 0.17 ± 0.18; p<0.05] and SGOT [7.03 ± 5.32 vs 3.93 ± 2.95; p <0.05] (Table I). It is in agreement with the reduction seen in SGOT levels (8.74 ± 9.42; p= <0.001) with Metformin alone and (60.6 ± 98.5 to 24.1 ± 9.0; p<0.001) with Rosuvastatin alone in 12 weeks observed by Rana H et al. (2016) in a study conducted at Lucknow (n=98).[17] It is supported by another study conducted by Li et al. (2013) which showed the mean SGOT reduction from 28.88 ± 14.08 to 22.03 ± 10.27; p<0.05 in 24 weeks and mean reduction of serum bilirubin (8·8 ± 4·4; p<0.05) in a study conducted by Cefalu et al. (2013) with Glimepiride.[11,25] In contrary to the above study, Kinoshita T. et al (2020) conducted a study and observed an increase in SGOT from 32.3 ± 2.5 to 32.7 ± 2.6 in 28 weeks with Glimepiride.[26]

The improvement seen in hepatic parameters in Group A could be attributed to Rosuvastatin which is known to improve liver enzymes and Metformin, owing to beneficial effects of weight loss on liver enzyme levels.

Ultrasound liver

We observed that 24% patients had shown improvement of ultrasound grading in Group A and 20% patients in Group B over a period of 90 days with no statistical difference in between (p=0.743) (Table II). No similar study could be found comparing the effects of concomitant therapies assessed in the present study on ultrasonography grading. A study conducted by Rana H et al. (2016) at Lucknow (n=98) showed that Rosuvastatin had shown significant improvement (p<0.05) in ultrasound while there was no improvement with Metformin over a period of 12 weeks.[17] In a study conducted by Loomba R et al. (2009) at California (n=86), Metformin had shown improvement in liver histology.[18]

No study could be found for the effect of Glimepiride on ultrasonography in NAFLD but a study conducted by Kato H et al. (2015) at Japan (n=20), showed that there was no improvement in intrahepatic lipid content with Glimepiride over a period of 24 weeks.[19]

Anthropometric parameters

WEIGHT

The mean weight reduction seen with Group A (1.77 ± 1.42; p<0.001) (Table I) was in line with the studies on Metformin and Rosuvastatin monotherapy i.e. Rana et al. (2016) (n=98) in a study at Lucknow showed mean weight reduction of 2.67± 0.89 (p<0.001) with Metformin and 2.47 ± 0.98 (p<0.001) with Rosuvastatin in 12 weeks. The weight reduction in Group B (0.15 ± 1.44; p>0.05) (Table I) was less which is in accordance with the available literature.[13] Glimepiride showed the mean weight reduction of 2.01 kg in 12 months (p<0.05) in study conducted by Martin et al. (n=520).[20] On the contrary, See T et al. (2003) (n=32) observed an increase in mean weight with Glimepiride, from 65.01 ± 8.94 kg to 68.25 ± 9.80 kg after 12 weeks (p = 0.023).[19] Hence, Group A was better in reducing weight in the present study.

BMI

This study observed that Group A has shown statistically better effect in improving BMI as compared to Group B, respectively i.e. 0.62 ± 0.59 (p<0.001) vs 0.04 ± 0.52 (p>0.05) (Table 3).

Group A has better effect in reducing BMI which could be due to Metformin and Rosuvastatin. Metformin is known to cause weight loss due to its effects on insulin resistance and appetite regulatory centre and few studies have shown the correlation of lipid reducing effect of Rosuvastatin with weight reduction.[23] Group B has shown less reduction (0.04 ± 0.52; p>0.05) in mean BMI which could be attributed mainly to Rosuvastatin and to a lesser extent to Glimepiride which is known to have weight neutralising/reducing effect.[13]

Glycaemic parameters

The intergroup difference for the mean change in FBS and HbA_{1c} at Day '90' in the present study is non-significant (p>0.05) (Table 3) which is in concordance with a study conducted by Yoon et al. (2011) at Korea, in which the mean reduction in FBS and HbA_{1c} due to Metformin and Glimepirideat Day '90' was comparable (p>0.05) .[26]

The reduction in HOMA-IR in present study in Group A and B over a period of 90 days, respectively i.e. 21.98 ± 7.91 (p<0.001) vs 23.60 ± 8.18 (p<0.001) (Table 3) was non-significant between the groups; p =0.439. It is in line with the mean HOMA- IR reduction seen with Metformin (32.5% reduction in HOMA-IR, p = 0.01) and reduction from 5.0 ± 0.8 to 3.8 ± 0.6, p = 0.005 with Glimepiride in a study conducted by Nagasaka et al. (2003) at Japan (n=28).

Both Group A and Group B decreased significantly the FBS, $HbA_{1c,}$ insulin resistance in 90 days, which can be attributed to Metformin and Glimepiride mainly. Rosuvastatin has no impact on diabetic profile as seen in a study conducted by Kim et al. (2013) at Korea (n= 379,865), where Rosuvastatin didn't show any significant effect on fasting glucose levels and insulin resistance.[27]

Lipid Parameters

Group A caused significantly better mean reduction in the lipid parameters over a period of 90 days as compared to Group B, respectively i.e. [Total cholesterol (34.73 ± 15.97 vs 29.53 ± 9.73; p<0.001), triglycerides (32.00 ± 18.91 vs 30.86 ± 17.36; p<0.05 and LDL (34.39 ± 16.92 vs 26.06 ± 9.76; p<0.05)] (Table I). It is in line with a study conducted by Najim H et al. (2013) at Iraq (n=50) in which mean % change caused by Metformin in total cholesterol (p<0.001), triglycerides (p<0.05) and LDL (p<0.05) was significant as compared to Glimepiride.[27]

In a study conducted by Nagasaka et al. (2003) at Japan (n=28), Glimepiride has showed non-significant reduction in lipid parameters in 12 weeks i.e. [Total Cholesterol (214 ± 6 to 210 ± 6 mg/dl, p= 0.125); Triglycerides (123 ± 10 to 120 ± 10 mg/dl, p= 0.387) and HDL (54 ± 3 to 53 ± 3 mg/dl, p = 0.438).[29] Glimepiride monotherapy causes lesser reduction in lipid parameters as compared to what is seen in the present study. The additional improvement in lipid parameters in Group B could be due to the improving effect of Rosuvastatin given concomitant with Glimepiride in Group B.

The significant reduction in lipid parameters in Group A can be due to both Rosuvastatin and Metformin. Rosuvastatin is known to have beneficial role on lipids while AMPK (AMP-activated protein kinase) activation by Metformin exerts beneficial effects on lipid metabolism by decreasing fatty acids and cholesterol synthesis.[31]

Safety Profile

On analysis of adverse effects in the present study, both the groups had comparable safety profile. None of the groups had shown any serious adverse effect or the need to discontinue the treatment. Adverse effects observed with Group A were tiredness (n=6, 20%), headache (n=5, 16.6%), muscle aches (n=4, 13.3%), abdominal pain (n=2, 6.7%) and nausea (n=3, 10%) (Table III). Group B showed adverse effects of weight gain (n=10, 33.3%), headache (n=4, 13.3%), muscle aches (n=3, 10%), dizziness (n=2, 6.7%) and nausea (n=1, 3.3%) (Table III). A metanalysis conducted at China by Li Y et al. (2013) found that out of 9 studies included, only 4 studies have mentioned about the adverse effects of Metformin which were gas, bloating and mild abdominal pain (n=17, 8.5%) and none of the patients had to discontinue the treatment due to intolerance.[11] Another metanalysis conducted by Zhu H et al. (2013) at China, had shown more episodes of hypoglycaemia with Glimepiride (p<0.001) and more of gastrointestinal effects such as diarrhoea and abdominal pain with Metformin (p<0.05).[29]

Table IV: Comparison Of Adverse Effect Profile Of Patients In Group 'a' And 'b' Over '90' Days Of Treatment

Adverse Effects	Group A	Group B
Weight gain	-	10(33.3)
Tiredness	6(20%)	-
Headache	5(16.6 %)	4(13.3 %)
Muscle aches	4(13.3%)	3(10%)
Abdominal pain	2(6.7%)	-
Dizziness	-	2(6.7%)
Nausea	3(10%)	1(3.3%)
Total number	20	20

Limitations:

As with the majority of the studies, this present study is subjected to few limitations. They are possibly because of small sample size (n=60) and time constraint (3 months). Other diagnostic tests such as CT, MRI and liver biopsy were not used in the present study because of the financial constraint.

INTERPRETATION AND CONCLUSION

It can be concluded that Group A showed statistically better improvement in hepatic (S. bilirubin and SGOT), weight, BMI, and lipid parameters (all except HDL). Group A and B showed comparable improvement in FBS, HbA_{1c}, HOMA-IR and ultrasound grading of liver. Both groups had comparable safety profile with no serious adverse effects. Hence, Metformin plus Rosuvastatin seems to be more efficacious than Glimepiride plus Rosuvastatin in NAFLD coexistent with T2DM over a period of 90 days.

Along with the lifestyle interventions and dietary modifications which are difficult to achieve, the discussed concomitant therapies could be potential and effective treatment option for the coexisting NAFLD and T2DM. In addition to known insulin sensitising benefits of antidiabetics and improving effects of Rosuvastatin on aminotr ansferases and dyslipidaemia, the additional benefits of these drugs in hepato-protection, cardiovascular disease and cancers could help in improving the prognosis of the disease. The small sample size, shorter duration of this study and the open label design might have led to some of the conclusions. Further studies are required to strengthen these findings, which may pave a pathway for development of standard treatment guidelines for NAFLD with T2DM.

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Conflict of interest: Nil

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