

• CLINICAL RESEARCH •

Fenofibrate for patients with asymptomatic primary biliary cirrhosis

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Abstract

AIM: Primary biliary cirrhosis (PBC) is a chronic, cholestatic disease of autoimmune etiology, the histology of which shows a destruction of the intrahepatic bile duct and portal inflammation. Ursodeoxycholic acid (UDCA) is now used as a first-line drug for asymptomatic PBC (aPBC) because it is reported that UDCA decreases mortality and prolongs the time of liver transplantation. However, only 20-30% of patients respond fully to UDCA. Recently, lipoprotein-lowering agents have been found to be effective for PBC. The aim of this study was to examine the safety and efficacy of fenofibrate, a member of the fibrate class of hypolipidemic and anti-inflammatory agent via peroxysome proliferator-activated receptor α , in patients with aPBC.

METHODS: Fenofibrate was administered for twelve weeks in nine patients with aPBC who failed to respond to UDCA. UDCA was used along with fenofibrate during the study. The data from aPBC patients were analyzed to assess the biochemical effect of fenofibrate during the study.

RESULTS: The serum levels of alkaline phosphatase (ALP) (285 ± 114.8 IU/L) and immunoglobulin M (IgM) (255.8 ± 85.9 mg/dl) significantly decreased to 186.9 ± 76.2 IU/L and 192.9 ± 67.5 mg/dL respectively, after fenofibrate treatment in patients with aPBC ($P < 0.05$). Moreover, the titer of antimitochondrial antibody (AMA) also decreased in 4 of 9 patients with aPBC. No adverse reactions were observed in any patients.

CONCLUSION: Fenofibrate appears to be significantly effective in treating patients with aPBC who respond incompletely to UDCA alone. Although the mechanism of fenofibrate on aPBC has not yet been fully clarified, combination therapy using fenofibrate and UDCA might be related to the anti-immunological effects, such as the suppression of AMA production as well as its anti-inflammatory effect.

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INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic, cholestatic liver disease characterized by inflammation and progressive destruction of interlobular bile ducts, eventually leading to cholestasis, biliary cirrhosis and finally hepatic failure. The etiology of PBC is attributed to autoimmunity mainly due to the association with autoantibodies such as antimitochondrial antibodies (AMA), which present in 95% of PBC patients, and an increased level of immunoglobulin M (IgM). Regarding this therapy, orthotopic liver transplantation is selected for PBC patients with liver failure and intractable pruritus, while ursodeoxycholic acid (UDCA) has been widely used as a first-line drug for asymptomatic PBC (aPBC) to slow the disease progression^[1-3]. Although the biochemical data of the liver functions tend to normalize in 20-30% of patients with aPBC who are administered UDCA, the rest of the patients often progress to cirrhosis^[4,5]. Therefore, there is a need for a more effective treatment^[6].

PBC is often associated with lipoprotein abnormalities such as an elevation of serum cholesterol concentration^[7]. Recently, several studies focusing on lipoprotein-lowering drugs for PBC have been reported^[8-15]. Simvastatin, an HMG-CoA reductase inhibitor, was proven to be useful as a modulator of cholestasis and an immune response in PBC^[8]. Bezafibrate, a hypolipidemic agent, was also effective in PBC patients who failed to respond to UDCA^[9-15]. The mechanism of action of bezafibrate is believed to be the anti-inflammatory effects via peroxysome proliferator-activated receptor α (PPAR α), a member of the nuclear hormone receptor superfamily, and the expression of multiple drug resistance gene-3, both of which ameliorate hepatobiliary inflammation in PBC^[11,16-18]. Fenofibrate is a member of fibrate class agents as bezafibrate and works as a ligand of PPAR α , showing a potent triglyceride-lowering effect. Fenofibrate treatment for PBC has been addressed in very few studies^[19], including our previous abstracts which we presented at conferences^[20,21]. The effect of fenofibrate on PBC therefore has to be clarified and is currently being evaluated.

For this purpose, we studied the efficacy of fenofibrate on nine patients with aPBC who responded insufficiently to monotherapy of UDCA.

MATERIALS AND METHODS

Patients and regimen

Nine patients with aPBC consisting of 2 males and 7 females were included in the prospective study. Ages were 50.3 ± 11.7 (mean \pm SD) yr ranging from 34 to 69 yr, and mean body mass 57.9 ± 5.6 (mean \pm SD) kg ranging from 50.0 to 64.6 kg. They were diagnosed to have aPBC according to laboratory and/or histological findings. All patients were negative both for anti-hepatitis C virus antibody and for hepatitis B surface antigen. All 9 patients with aPBC exhibited a poor therapeutic response to UDCA of 600 mg/d for 6 mo or more. Fenofibrate of 100 mg/d was administered for 4 patients (less than 60 kg in body mass) and of 150 mg for 5 patients (60 kg or more in body mass) for at least 12 wk. The study was approved by the local ethics committee, and informed consent was obtained from each patient included in the study.

Laboratory examination

During the study, any changes in dietary therapy were prohibited. In order to determine the drug compliance and safety, all patients were required to visit the hospital every 2 wk, and the serum blood chemistry including apolipoprotein was examined every 4 wk. Serum concentrations of total bilirubin, immunoglobulins G and M (IgG, IgM) as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyltransferase (γ GTP) were determined before the fenofibrate treatment as well after the treatment of 12 wk by routine laboratory procedures. AMA titers were measured using indirect immunofluorescence based on stomach/kidney frozen sections. Blood was sampled early in the morning during fasting, and a medical laboratory (SRL Co., Tokyo) centrally controlled the measurements up to 12 wk after the start of administration.

Statistical analysis

Differences in the means and proportions were evaluated by Chi-square test and Student's *t*-test. Baseline variables were assessed in the study, including AST, ALT, ALP, γ GTP, apolipoproteins, IgG, IgM and AMA titers. *P* value less than 0.05 was considered statistically significant.

RESULTS

Effect of fenofibrate on laboratory findings for hepatobiliary system and serum lipids

Table 1 and Figure 1 show the enzymatic changes in the hepatobiliary system identified up to 12 wk after the start of the combination therapy of fenofibrate and UDCA. The mean ALP value of 285.0 IU/L prior to fenofibrate therapy decreased to 186.9 IU/L at wk 12 after the initiation of the therapy, thus showing a statistically significant difference. The serum γ -GTP concentration also decreased after 12 wk of fenofibrate and UDCA treatment compared to that at initiation, although the difference was not statistically significant. The serum concentrations of AST and ALT did not change statistically regarding those obtained prior to and after 12 wk of treatment. The serum concentration of IgM of 255.8 mg/dL prior to the treatment was significantly reduced to 192.9 mg/dL at wk 12, whereas the concentration of IgG did not decrease. Regarding the titer of AMA, a reduction was identified in 4 of the 9 patients based on that obtained prior to and after 12 wk of treatment. As shown in Figure 2, the AMA titer of 320 decreased to 40, 320 to 80, 80 to 20 and 40 to 20 in 4 of 9 patients, respectively. The titers of AMA in the rest 5 patients remained unchanged. The serum levels of ALP of 571 IU/L and IgM of 236 mg/dL decreased to 306 IU/L and 154 mg/dL, respectively, in a patient whose AMA titer decreased from more than 320 to 40. Likewise, those of 276 and 159 decreased to 285 and 102 in a patient whose AMA titer decreased from more than 320 to 80, those of 215 and 375 decreased to 107 and 241 in a patient whose AMA titer decreased from 80 to 20, and those of 191 and 240 decreased to 114 and 180 in a patient whose AMA titer decreased from 80 to 20, respectively. Interestingly, all the four cases who showed a reduction of the AMA titer were females.

Table 2 shows the changes in serum lipids and apoprotein levels in all 9 patients. The concentrations of apo A-II (median value: 31.6 mg/dL) and apo C-II (median value: 3.9 mg/dL) increased statistically to 44.1 mg/dL and 4.5 mg/dL during fenofibrate therapy ($P < 0.005$), respectively. The concentrations of total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and Apo B lipoprotein tended to decrease while the high density lipoprotein-cholesterol (HDL-C), apo A-I and apo E levels tended to increase. However, the difference was not statistically significant.

Table 1 Change in concentrations of laboratory data (mean \pm SD)

Laboratory Variable	Before therapy	4 wk	8 wk	12 wk
AST (IU/L)	29.9 \pm 8.1	50.0 \pm 36.3	46.6 \pm 24.9	46.9 \pm 28.3
ALT (IU/L)	31.1 \pm 13.2	48.6 \pm 35.2	57.0 \pm 38.9	48.4 \pm 42.5
ALP (IU/L)	285.0 \pm 114.8	238.5 \pm 88.4	200.6 \pm 76.7 ^a	186.9 \pm 76.2 ^a
γ -GTP (IU/L)	149.6 \pm 143.0	147.0 \pm 178.6	128.8 \pm 128.1	125.2 \pm 110.3
LDH (IU/L)	311.2 \pm 46.7	318.4 \pm 44.8	320.1 \pm 59.9	324.6 \pm 59.2
TB (mg/dl)	0.7 \pm 0.7	0.4 \pm 0.2	0.6 \pm 0.4	0.6 \pm 0.5
IgG (mg/dl)	1 431.4 \pm 285.3	-	-	1 415.0 \pm 316.1
IgM (mg/dl)	255.8 \pm 85.9	-	-	192.9 \pm 67.5 ^a

^a $P < 0.05$ (baseline-matched *t*-test) vs the serum concentrations prior to the treatment.

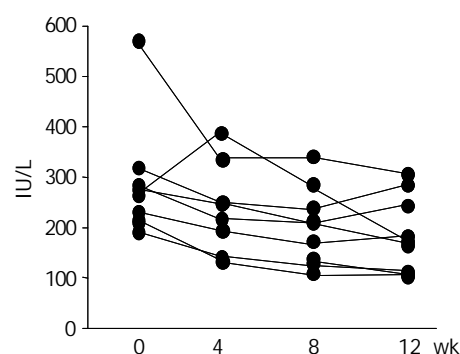


Figure 1 Change in the serum alkaline phosphatase levels during fenofibrate treatment.

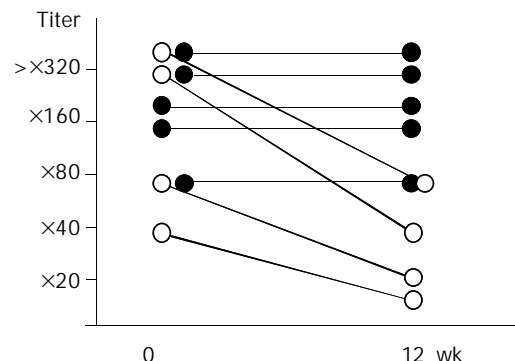


Figure 2 Change in antimitochondria antibody titers before and after fenofibrate treatment.

Table 2 Change in concentrations of serum lipids and apoproteins

Variables	Before	4 wk	8 wk	12 wk
TC (mg/dL)	206.3 \pm 26.5	186.3 \pm 22.9	189.9 \pm 27.7 ^a	192.1 \pm 30.1
TG (mg/dL)	126.0 \pm 50.1	119.5 \pm 76.2	102.8 \pm 52.3	103.6 \pm 53.0
HDL-C (mg/dL)	63.6 \pm 11.3	63.8 \pm 14.0	68.8 \pm 12.6	69.3 \pm 13.1
LDL-C (mg/dL)	115.7 \pm 22.1	99.3 \pm 29.3	105.6 \pm 28.0	105.2 \pm 25.1
Apo A-I (mg/dL)	159.0 \pm 17.9	154.7 \pm 19.4	158.3 \pm 17.9	172.1 \pm 24.3
Apo A-II (mg/dL)	31.6 \pm 6.5	39.5 \pm 7.0 ^a	40.7 \pm 4.6 ^a	44.1 \pm 4.9 ^a
Apo B (mg/dL)	95.1 \pm 22.9	84.1 \pm 31.4	81.0 \pm 26.5	84.1 \pm 23.1
Apo C-II (mg/dL)	3.9 \pm 1.7	4.6 \pm 2.0 ^a	4.2 \pm 1.6	4.5 \pm 1.5 ^a
Apo C-III (mg/dL)	9.7 \pm 3.8	9.5 \pm 4.2	8.9 \pm 2.9	9.8 \pm 3.6
Apo E (mg/dL)	4.3 \pm 1.0	4.3 \pm 0.8	4.4 \pm 0.8	4.6 \pm 0.9

TC: total cholesterol, TG: triglyceride, HDL-C: HDL-cholesterol, LDL-C: LDL-cholesterol, Apo: apoprotein. ^a $P < 0.05$ (baseline-matched *t*-test) vs the serum concentrations prior to the treatment.

Rate of change of each variable between AMA-reduced group and AMA-unchanged group

The rate of change of each variable between the AMA-reduced group and the AMA-unchanged group was compared before and after the combination therapy of fenofibrate and UDCA. As shown in Table 3, the IgM concentrations dropped to $35.4 \pm 0.6\%$ in the AMA-reduced group and $7.1 \pm 1.8\%$ in the AMA-unchanged group, showing a statistically significance between the two groups. Interestingly, however, the values of ALP, γ -GTP and apo A-II dropped at a similar rate in two groups.

Table 3 Rate of change in the valuables between AMA-reduced group and AMA-unchanged group

Factors	AMA-reduced group	AMA-unchanged group	t-test
ALT (IU/L)	61.6 ± 124.8^1	52.0 ± 109.2	0.905
ALP (IU/L)	-33.4 ± 24.8	-33.8 ± 16.0	0.978
γ -GTP (IU/L)	-2.8 ± 73.4	-5.3 ± 39.8	0.950
IgM (mg/dL)	-35.4 ± 0.6	-7.1 ± 11.8	0.010
Apo A-II (mg/dL)	52.0 ± 17.3	37.4 ± 38.6	0.573
Apo C-II (mg/dL)	29.5 ± 13.8	10.6 ± 10.1	0.089

¹Changing rate (%) (mean \pm SD).

Adverse effects

In all the nine patients, no subjective symptoms such as systemic malaise, anoxia, were observed. No deterioration of the liver function tests was identified in any cases as shown in Table 1. The blood urea nitrogen and creatinine levels did not change either after fenofibrate administration.

DISCUSSION

Primary biliary cirrhosis presents as a chronic cholestatic disease involving predominantly middle-aged women with a very frequent association with AMA. In addition, PBC has been found to be often associated with other autoimmune diseases^[22-27]. Therefore, PBC is thought to be an autoimmune disease and most therapies have thus been directed at altering the immune response. So far, the use of corticosteroid, azathioprine, cyclosporine^[28], D-penicillamine^[29], methotrexate^[30,31], colchicines^[31,32] has been studied for patients with PBC.

However, none of these drugs appeared to offer any significant benefits while they tended to induce adverse effects such as osteoporosis, or pulmonary toxicity^[24]. Recently UDCA appeared to be a drug which most effectively treated patients with PBC^[1-3] through cytoprotective and choleretic effects and alterations in the bile pool by competition for uptake by ileal bile acid receptors. However, a considerable number of patients with PBC still clinically respond insufficiently to UDCA alone, and now a new problem has emerged concerning which agent should be used for these patients.

Several clinical studies on lipoprotein-lowering agents such as simvastatin^[8] and bezafibrate^[9-15] for PBC patients who failed to respond to UDCA have so far been conducted, and the results have been found to be of value. In addition, fenofibrate, a member of such fibrate class agents as bezafibrate, has recently been found to be an expected agent for PBC because of its stronger activity of an anti-inflammatory effect via PPAR α ^[33], and more potentiality in reducing TG and LDL-C levels^[34] than that of bezafibrate. Early attempts of the apoprotein-lowering agents focused on treating concomitant conditions of hypertriglyceremia or hypercholesterolemia. Therefore, we conducted a study on the efficacy of fenofibrate in nine patients with aPBC.

Indeed, serum concentrations of TC and TG decreased and the concentration of HDL-C increased in all the 9 patients with aPBC, however, these changes were not statistically significant. As for apoprotein, apo AII and apo C II, which are major protein constituents of HDL, were significantly increased in the study. As a result, lipoprotein, an indicator for the risk of developing atherosclerotic disease was improved after fenofibrate treatment in PBC patients in our study^[17,35].

Fenofibrate has been shown to regulate the expression of various kinds of lipids and proteins, and cell proliferation through the activation of PPAR α ^[36,37]. However, apart from the lipoprotein-lowering effect, its pleiotropic effects have recently received much attention ranging from inhibited production of interleukin (IL)-1, IL-6, IL-1- and IL-6-induced prostaglandin E2 as well as cyclooxygenase (COX)-2 expression to the induction of apo A-II through the inhibition of the nuclear factor (NF)- κ B signalling by activation of PPAR α ^[38,39]. Furthermore, fenofibrate could inhibit the expression of intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, which play a role in the adhesion of monocytes through apo A-II induction or NF- κ B inhibition

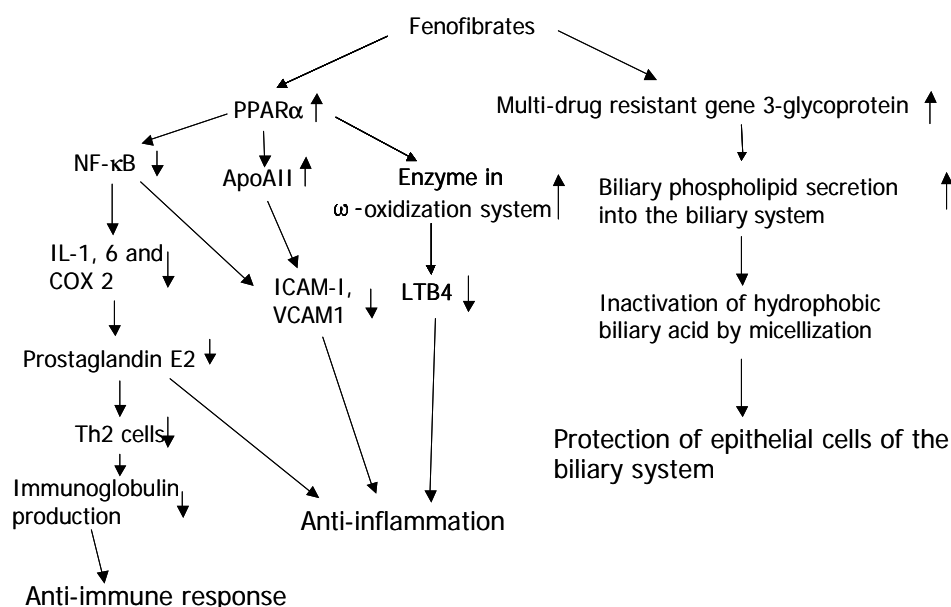


Figure 3 Possible mechanisms of action for fibrates on PBC.

[40]. These findings suggest that fenofibrate can inhibit not only the lipid metabolism but also the inflammatory reaction through PPAR α . It is therefore likely that the PPAR α activation-mediated anti-inflammatory effects of fenofibrate, such as the inhibited expression of NF- κ B, IL-1, IL-6, COX-2 and prostaglandin E2 might contribute to an improvement of PBC. Apo A-II could inhibit the expression of such adhesion molecules as ICAM-1 and VCAM-1 which are believed to be progression factors in cases of PBC, because adhesion molecules induce lymphocytes into epithelial cells of hepatobiliary ducts. From another point of view, as reported by Iwasaki *et al* [11], improvement of PBC might also occur because the canalicular phospholipid translocator, encoded by multi-drug resistant gene-3 (MDR3) expressed by bezafibrate administration, was exclusively present on the canalicular membrane, increases the secretion of biliary phospholipids and inactivating hydrophobic bile acid by micellization to protect hepatocytes and epithelial cells of bile ducts [18] (Figure 3). Thus, MDR3 messenger RNA and the canalicular phospholipid translocator (MDR3-P glycoprotein) of fibrates are strictly PPAR α dependent. Although the different sensitivities to PPAR α between fenofibrate and bezafibrate have not yet been clarified, a possible reason is that fenofibrate could selectively act on PPAR α only, while bezafibrate could act on PPAR α , γ as well as δ [33].

The emerging question is whether fenofibrate's anti-immunological effect is truly mediated via PPAR α or its receptor-independent anti-inflammatory effects. Our results demonstrated that fenofibrate did not only improve dyslipoproteinemia but also significantly reduce serum ALP and IgM levels. It was of great interest that a reduction of AMA titer was also observed in 4 of 9 patients. The immunological response of PBC patients to fenofibrate therapy thus raises another question, namely, how is the AMA production regulated by PPAR α in PBC? Is the AMA production interrelated in the inflammation or lipid synthesis? Kurihara *et al* reported 5 cases of aPBC who responded to the combination therapy of bezafibrate and UDCA [9], however, the AMA titer remained unchanged in all cases. Nevertheless, there was a reduction of IgM as well as ALP, γ GTP and TC. Similarly, Iwasaki *et al* described that IgM decreased significantly, but the AMA titers were not affected in all 5 PBC patients treated with bezafibrate [11]. In contrast, Fukuo *et al* showed 6 cases of aPBC who responded to bezafibrate with a decreased AMA titer [10]. Nakai *et al* did not analyze the AMA titer among 23 patients with PBC treated with a combination therapy of bezafibrate and UDCA, while they confirmed a decrease in the IgM concentration [12]. Although no relationship between IgM concentration and AMA titer was observed in these papers, our study demonstrated that IgM concentration closely correlated with the reduction of AMA titer, whereas the decrease of ALP and γ -GTP levels was not correlated with the AMA reduction. Interestingly, immunoglobulins, the secretory products of stimulated B lymphocytes, were characteristically elevated, with a distinct focus on IgM in PBC. One possibility to explain the reduction of IgM by fenofibrate treatment for PBC is that the decreased production of prostaglandin E2 via PPAR α suppressed the Th2 lymphocytes that induce B cells, thus leading to the reduced production of immunoglobulin [41]. However, our study showed that fenofibrate treatment for PBC resulted in a decrease in IgM level, while IgG level was unchanged. Fenofibrate may also possess an additional or synergistic potential for lowering IgM levels as observed in the ALP and γ GTP levels. The exact cause of hyperglobulinemia in PBC, however, remains to be elucidated.

Regarding the adverse effect of fenofibrate, diabetes arteriosclerosis intervention study (DAIS) showed that micronized fenofibrate at 200 mg (equivalent to 300 mg of the

standard formulation) was administered for 3 yr to type 2 diabetic patients in order to observe its inhibitory effect on the progression of coronary arterial stenosis. As a result, no difference in the safety between fenofibrate and placebo was observed [42]. In addition, studies of human first-generation cultured cells and HepG2 cells suggested that serum aminotransferase levels were transiently elevated and then normalized or returned to pretreatment levels [43]. The increase in the aminotransferase level after treatment with fenofibrate was not considered to be clinically significant. As fenofibrate could activate the aminotransferase gene expression, thus leading to a mild and transient elevation of aminotransferase through mechanisms of PPAR α involving increased levels of reactive oxygen species and intracellular glutathion depletion, thus leading to mitochondrial dysfunction and perturbation of intracellular Ca⁺⁺ homeostasis and also to cell death [43,44]. A dosage of 100 mg or 150 mg per day of fenofibrate in the 9 patients studied, which is half the commonly administered dose, was thus administered to poor responders to UDCA, and a blood examination was performed every 2 wk. No adverse effect was observed either clinically or biochemically in all the 9 patients in our study.

Administration of fenofibrate in combination with UDCA was safe and useful for patients with aPBC. This finding confirms our belief that fenofibrate's beneficial effects are mediated only through its lipoprotein-lowering effect. The mechanism underlying the long term efficacy of fenofibrate for symptomatic PBC remains to be elucidated [15]. The expansive array of ligands, target genes, and metabolic processes regulated by nuclear receptors such as PPAR α , β , γ within hepatocytes, and ever-changing internal milieu, has made a completely comprehensive regulatory scheme virtually impossible to depict graphically [44]. Nuclear receptors-regulated gene products may create or disable a protein ligand or regulate the import or export of another nuclear receptor, which might be related to the production of IgM or AMA. There are likely many more mechanisms of action for fenofibrate on PBC still awaiting further discovery.

In conclusion, fenofibrate can be well tolerated by all patients with aPBC, while it has no remarkable side effects. This agent is beneficial for the treatment of aPBC. However, further studies are needed to elucidate the effect of fenofibrate on PBC and to determine its long-term biochemical and histological efficacy.

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