

Fenofibrate reduces osteonecrosis without affecting antileukemic efficacy in dexamethasone-treated mice

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ABSTRACT

Recent clinical trials in children with acute lymphoblastic leukemia (ALL) indicate that severe hypertriglyceridemia (>1000 mg/dL) during therapy is associated with an increased frequency of symptomatic osteonecrosis. Interventions to lower triglycerides have been considered, but there have been no preclinical studies investigating the impact of lowering triglycerides on osteonecrosis risk, nor whether such interventions interfere with the antileukemic efficacy of ALL treatment. We utilized our clinically relevant mouse model of dexamethasone-induced osteonecrosis to determine whether fenofibrate decreased osteonecrosis. To test whether fenofibrate affected the antileukemic efficacy of dexamethasone, we utilized a BCR-ABL⁺ model of ALL. Serum triglycerides were reduced by fenofibrate throughout the period of treatment, with the most pronounced, 4.5-fold, decrease at week 3 ($P < 1 \times 10^{-6}$). Both frequency (33% vs. 74%, $P = 0.006$) and severity (median necrosis score of 0 vs. 75; $P = 6 \times 10^{-5}$) of osteonecrosis were reduced with fenofibrate. Fenofibrate had no impact on BCR-ABL⁺ ALL survival ($P = 0.65$) nor on the antileukemic properties of dexamethasone ($P = 0.49$). These data suggest that lowering triglycerides with fenofibrate reduces dexamethasone-induced osteonecrosis while maintaining antileukemic efficacy, and thus may be considered for clinical trials.

Introduction

Hypertriglyceridemia occurs in 4-19% of children treated with glucocorticoids and/or asparaginase during therapy for acute lymphoblastic leukemia (ALL).¹⁻⁷ Although hypertriglyceridemia has been thought to be transient and relatively benign,^{1,2} recent studies suggest that patients with severe hypertriglyceridemia (>1000 mg/dL) during ALL therapy may be at increased risk of long-term complications, including symptomatic osteonecrosis.^{3,7,8}

Recent recommendations for pharmaceutical management of severe hypertriglyceridemia include the use of fibrates, specifically fenofibrate.⁹ In addition to being associated with fewer drug-drug interactions than statins,¹⁰⁻¹² fenofibrate specifically reduces serum triglycerides by as much as 50%, with minimal adverse reactions,¹³⁻¹⁵ whereas the main effect of statins is the decrease of serum low-density lipoprotein cholesterol.^{9,16,17} The active metabolite of fenofibrate, fenofibric acid, targets peroxisome proliferator activated receptor- α , leading to activation of lipoprotein lipase which increases lipolysis and elimination of triglyceride-rich particles,¹⁸ resulting in reduction of circulating serum triglycerides.^{19,20} Therefore, it has been suggested that fenofibrate could be useful in the management of acute hypertriglyceridemia, such as that observed during ALL therapy. However, there is no evidence that lowering triglyceride levels with fenofibrate can reduce risk of osteonecrosis. Moreover, with very effective ALL therapy, caution must be exercised before adding any new agents to treatment regimens, to avoid untoward drug interactions.

In these proof-of-principle experiments, we tested the hypothesis that lowering serum triglyceride levels with fenofibrate in dexamethasone-treated mice would

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result in decreased osteonecrosis and would not interfere with the efficacy of antileukemic therapy.

Methods

Treatment

Experiments were approved by the Institutional Animal Care and Use Committee of St. Jude Children's Research Hospital (SJCRC; Memphis, TN, USA); protocol numbers 423-100428 and 465-100549.

All mice received prophylactic antibiotics in drinking water (herein referred to as "base-water"): continuous tetracycline (1 g/L; Sigma-Aldrich, St. Louis, MO, USA) and intermittent sulfamethoxazole/trimethoprim oral suspension (600/120 mg/L for 3.5 days/week; Aurobindo Pharma, USA, Inc., Dayton, NJ, USA). Mice were randomized to receive continuous dexamethasone (0.4 mg/mL sodium phosphate solution; Fresenius Kabi, Lake Zurich, IL, USA) in drinking water, herein referred to as "dexamethasone water" (3 mg/L in the osteonecrosis model and 4 mg/L in the BCR-ABL⁺ ALL model).²¹⁻²³

The folic acid-deficient diet (0.2 ppm folic acid; TestDiet, Richmond, IN, USA) was the "base-diet".²¹ Fenofibrate (Sigma Aldrich, St. Louis, MO, USA) was added to the base-diet for a final concentration of 0.2% fenofibrate (w/w) to make the "fenofibrate-supplemented diet" (TestDiet, Richmond, IN, USA). This dose had been used in prior experimental rodent models.²⁴⁻²⁶

Serum triglycerides were measured with an ABX Penta 400 instrument (Horiba, Montpellier, France) after the animals had fasted for 12 to 16 h (food was withheld; mice had free access to water).

Mice were randomized to one of four treatment groups: control (base-water and base-diet); fenofibrate-only (base-water and fenofibrate-supplemented diet); dexamethasone-only (dexamethasone-water and base-diet); or dexamethasone + fenofibrate (dexamethasone-water and fenofibrate-supplemented diet).

Osteonecrosis model

The protocol was modified from that previously described.^{21,22,27-29} At postnatal days 26 to 28, male Balb/cj mice (bred in-house at SJCRC) were randomized by body weight (13.5 g, 95% confidence interval [95% CI]: 13.0- 14.7) to 6 weeks of treatment. Fasting serum triglycerides were measured after 1, 3, and 6 weeks of treatment. At the end of treatment, white adipose tissue; and plasma dexamethasone and fenofibric acid levels were measured. Osteonecrosis and epiphyseal arteriopathy were evaluated and scored in both distal femora, by a board-certified veterinary pathologist (LJJ), as described previously.^{21,22,27-29} Details are provided in the *Online Supplementary Methods*.

BCR-ABL⁺ acute lymphoblastic leukemia model

The BCR-ABL (p185⁺, *Arf*^{-/-}) luciferase-positive cell line (BCR-ABL⁺) was generated.^{25,30-32} Female 8-week-old matched syngeneic mice (C57Bl/6J, *Arf*-wildtype; Jackson Laboratory, Bar Harbor, ME, USA) received intravenous injections of 2,000 BCR-ABL⁺ cells. Bioluminescent imaging was performed weekly,²³ to monitor leukemic burden. At day 3, mice were stratified by luminescent signal and body weight to treatment (n=10/treatment group). Fasting serum triglycerides were measured at day 24. Treatment ended at day 28: mice were maintained on base-diet/base-water until a humane endpoint or the end of study at day 63. Details are given in the *Online Supplementary Methods*.

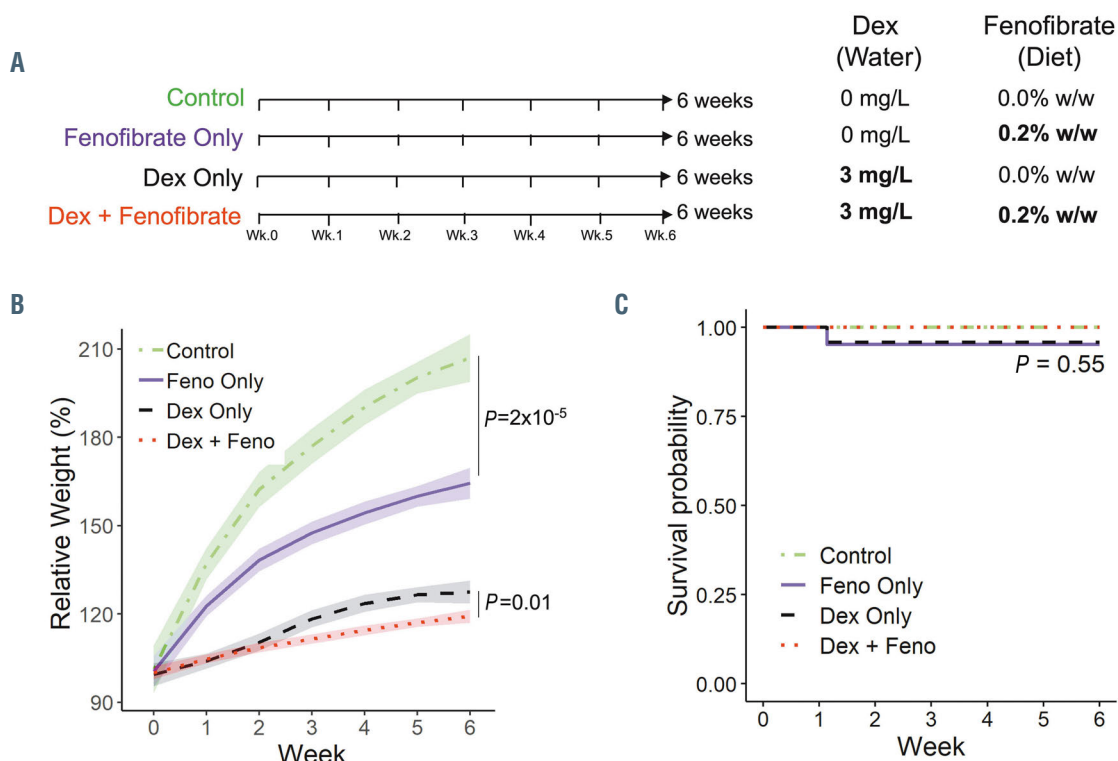


Figure 1. Experimental design, body weight, and survival in dexamethasone-induced osteonecrosis. (A) Experimental design: male Balb/cj mice were placed on 6 weeks of continuous treatment with dexamethasone, fenofibrate, or both. (B) Body weight relative to week 0 is shown as a median with 95% confidence interval (95% CI). Control mice and mice treated with fenofibrate (Feno) only weighed more than those treated with dexamethasone (Dex) only or Dex + Feno from weeks 1-6 of treatment ($P < 1 \times 10^{-6}$). (C) Survival did not differ by treatment group. The survival rate was 100% in the control group (12/12) and the group treated with Dex + Feno (33/33), whereas it was 98% in both the Dex Only (23/24) and Feno Only (20/21) groups ($P=0.55$).

Statistical analysis

The frequency of osteonecrosis/arteriopathy was compared using the χ^2 test. Log-rank testing was used for survival comparisons. For continuous variables, the two-tailed Mann-Whitney test was used (two groups); the Kruskal-Wallis test with Dunn correction was used for multiple comparisons (three or more groups). All continuous statistics are expressed as the median with 95% confidence interval. The R program (version 3.5.1)³³ or GraphPad Prism³⁴ was used for the statistical analyses and visual representation. *P* values <0.05 were considered statistically significant for all analyses.

Results

Fenofibrate in experimental osteonecrosis

Consistent with previous observations,^{21,22,28,29} mice that received dexamethasone (i.e., animals in the dexamethasone-only and dexamethasone + fenofibrate treatment groups) gained less weight over time compared to those not treated with dexamethasone (control and fenofibrate-

only treatment groups) (Figure 1B). Fenofibrate supplementation suppressed weight gain over the course of treatment. By week 6 of treatment, control mice had gained 50% more weight than mice treated with fenofibrate only ($P=2 \times 10^{-5}$) and mice treated with dexamethasone only had gained 10% more weight than those treated with dexamethasone + fenofibrate ($P=0.01$) (Figure 1B). There was no difference in survival between groups ($P=0.55$) (Figure 1C).

In mice treated with dexamethasone, fenofibrate significantly reduced serum triglyceride levels as early as week 1, from 130.1 mg/dL (95% CI: 85.2- 201.1) to 37.4 mg/dL (95% CI: 17.1- 60.3), a 3.5-fold decrease ($P=0.0004$). Fenofibrate supplementation continued to suppress dexamethasone-induced hypertriglyceridemia at week 3 (4.5-fold decrease, $P<1 \times 10^{-6}$) through to the end of treatment at week 6 (3.5-fold decrease, $P=5 \times 10^{-6}$). There was no difference in triglyceride levels at weeks 1 and 3 between mice treated with fenofibrate only and those treated with

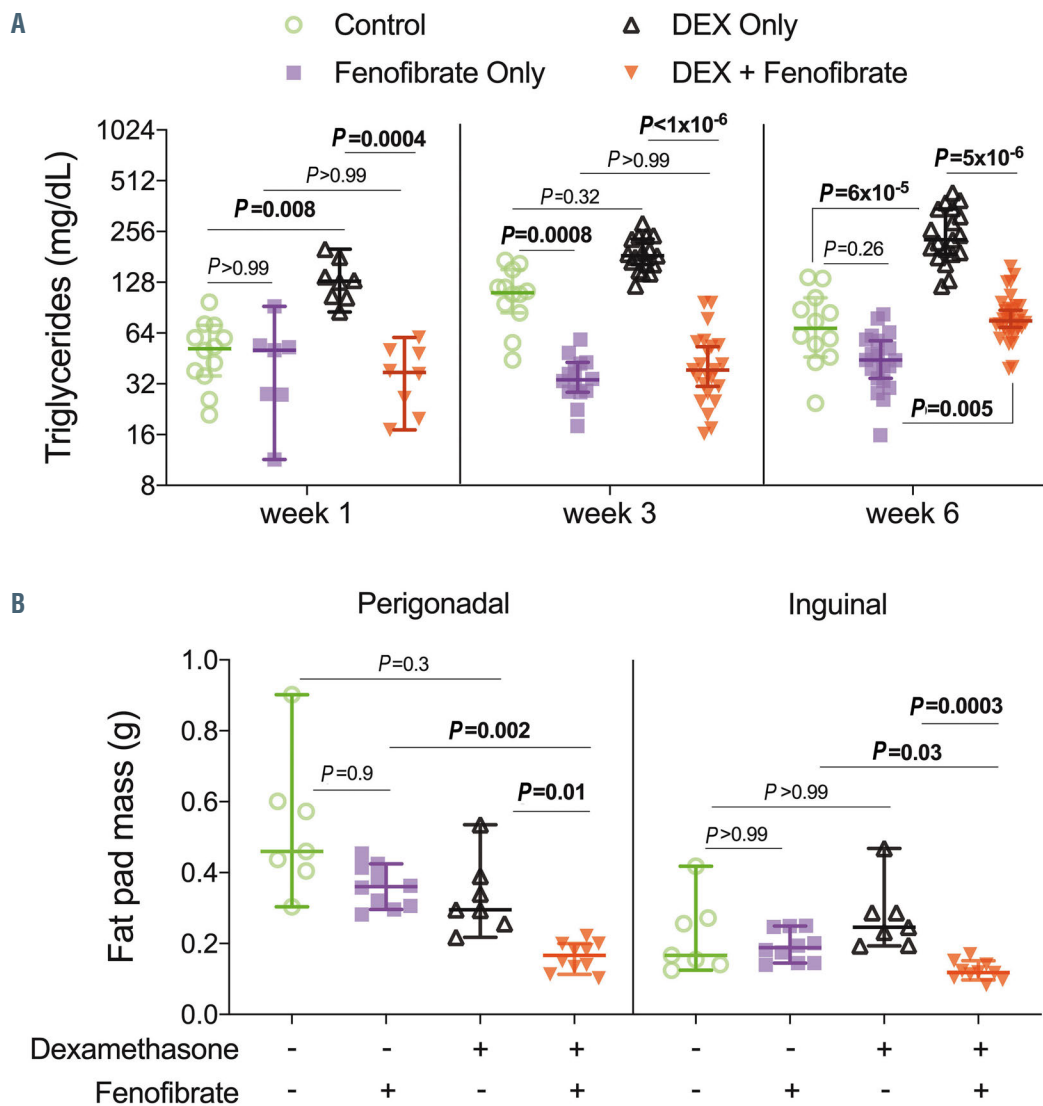


Figure 2. Fenofibrate reduces serum lipids and fat depots in dexamethasone-treated mice. (A) Median (with 95% confidence interval) fasting serum triglyceride levels at weeks 1, 3, and 6 of treatment. Week 1, n=8-12/group; week 3, n=12-27/group; week 6, n=12-31/group. (B) Perigonadal and inguinal fat pads at week 6; n=8-10/group. *P*-values shown between relevant groups: control versus fenofibrate only; control versus dexamethasone (DEX) only; fenofibrate only versus DEX + fenofibrate; DEX only versus DEX + fenofibrate.

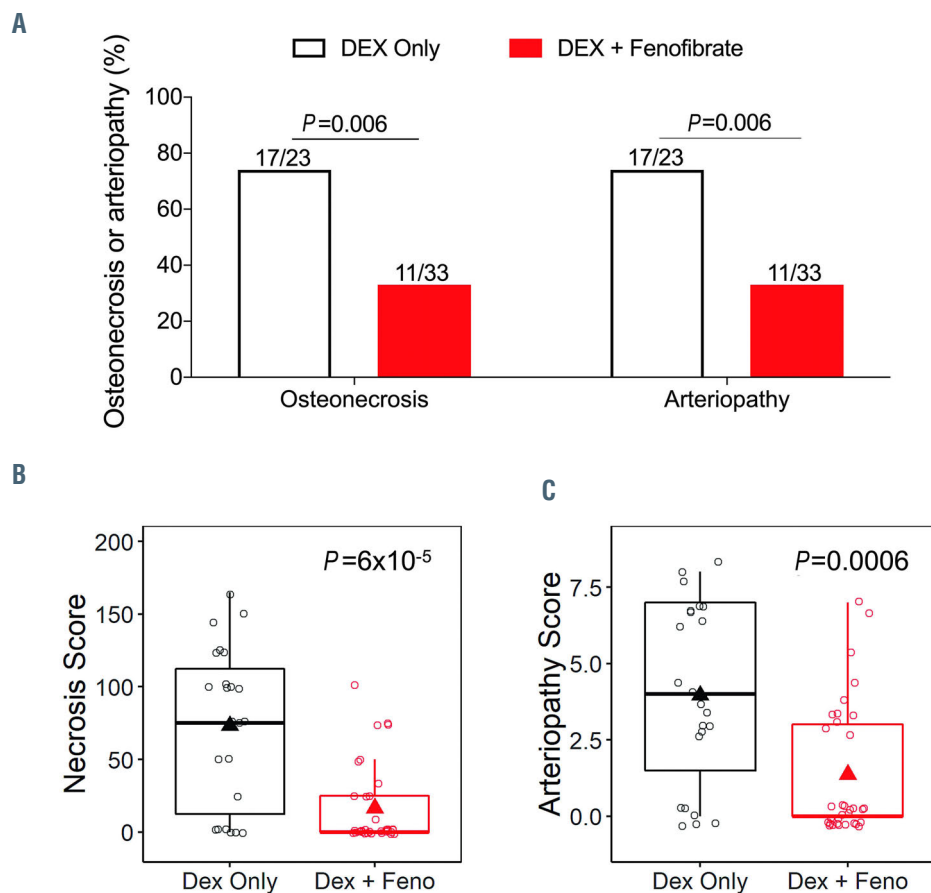


Figure 3. Fenofibrate reduces the frequency and severity of osteonecrosis and arteriopathy in dexamethasone-treated mice. (A) Frequency of osteonecrosis or arteriopathy, compared with the χ^2 test. (B) Necrosis scores (possible range of 0 [no osteonecrosis] to 200 [equivalent to 100% necrosis in both hind limbs]) and (C) arteriopathy scores (possible range of 0 [no arteriopathy] to 8 [thrombotic arteriopathy in both limbs]) were reduced with fenofibrate. Median with 95% confidence interval (box and whiskers) and mean (triangle). Note that no control mice or mice treated with fenofibrate only developed osteonecrosis or arteriopathy. Dex: dexamethasone; Feno: fenofibrate.

fenofibrate + dexamethasone ($P>0.99$ at each time point). By week 6, triglycerides were higher in the mice treated with fenofibrate + dexamethasone than in those treated with fenofibrate only ($P=0.005$); however, levels were comparable to those in control mice ($P>0.99$) (Figure 2A).

In dexamethasone-treated mice, fenofibrate reduced white adipose tissue: perigonadal fat (representative of visceral fat) was reduced from 0.30 g (95% CI: 0.22- 0.54) to 0.17 g (95% CI: 0.11- 0.20; $P=0.01$) and inguinal fat (representative of posterior subcutaneous fat) was reduced from 0.25 g (95% CI: 0.19- 0.47) to 0.12 g (95% CI: 0.10- 0.15; $P=0.0003$) (Figure 2B).

As expected, only mice that received dexamethasone developed osteonecrosis and/or arteriopathy (Figure 3). The frequency of both osteonecrosis and arteriopathy was 74% in mice treated with dexamethasone only *versus* 33% in those treated with dexamethasone + fenofibrate ($P=0.006$) (Figure 3A). Not only was the frequency of osteonecrosis and arteriopathy reduced over 2-fold with fenofibrate, but the severity of these conditions was significantly reduced. In the mice treated with dexamethasone only, the necrosis score was reduced from 75 to 0 with fenofibrate supplementation ($P=6\times 10^{-5}$) (Figure 3B) and the arteriopathy score was reduced from 4 to 0 ($P=0.0006$) (Figure 3C).

In mice treated with dexamethasone + fenofibrate, there was a correlation between the triglyceride level at week 3 and osteonecrosis: mice that developed osteonecrosis had a median triglyceride concentration of 67.5 mg/dL (95% CI: 21.1-96.9) *versus* 37.2 mg/dL (95% CI: 30.9-53.1) in osteonecrosis-negative mice ($P=0.03$) (Online Supplementary Figure S1A). By the end of treatment, there

was no difference in triglyceride levels by osteonecrosis status ($P>0.99$) (Online Supplementary Figure S1B).

At the end of treatment, there was no difference in plasma dexamethasone levels between mice treated with dexamethasone only (26.6 nM, 95% CI: 20.0-58.3 nM) and those treated with dexamethasone + fenofibrate (20.5 nM, 95% CI: 16.7- 25.9 nM; $P=0.1$) (Online Supplementary Figure S2A). The levels of fenofibric acid were significantly lower in animals treated with dexamethasone + fenofibrate (1.9 $\mu\text{g/mL}$, 95% CI: 1.6-2.4 $\mu\text{g/mL}$) than in those treated with fenofibrate only (6.7 $\mu\text{g/mL}$, 95% CI: 6.1-8 $\mu\text{g/mL}$, $P<1\times 10^{-6}$) (Online Supplementary Figure S2B).

Fenofibrate in experimental BCR-ABL⁺ acute lymphoblastic leukemia

In a BCR-ABL⁺ dexamethasone-sensitive model of murine ALL, (Figure 4A), all mice that did not receive dexamethasone succumbed to disease by day 35 (Figure 4C), and animals in both the groups treated with dexamethasone only and dexamethasone + fenofibrate lived longer than those that did not receive dexamethasone ($P<1\times 10^{-6}$). Mice were monitored for relapse until the end of follow-up at day 63. There was no difference in disease burden between the dexamethasone-only *versus* dexamethasone + fenofibrate treatment groups, as indicated by survival ($P=0.49$) (Figure 4C), spleen weight ($P>0.99$) (Online Supplementary Figure S3A), and white blood cell count ($P>0.99$) (Online Supplementary Figure S3B). Among the dexamethasone-treated mice, fenofibrate decreased triglyceride levels from 89.9 mg/dL to 29.0 mg/dL ($P=0.001$) (Figure 4D).

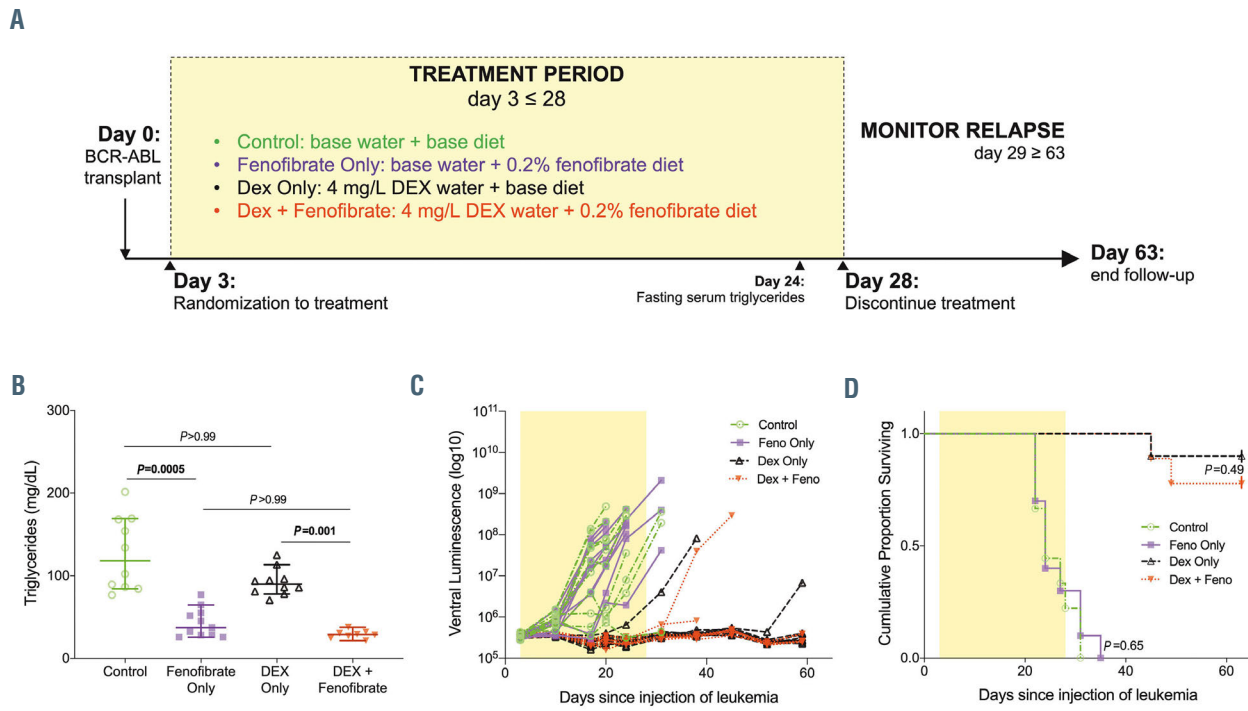


Figure 4. Fenofibrate does not affect efficacy of dexamethasone in BCR-ABL⁺ acute lymphoblastic leukemia. (A) Experimental design. DEX water: continuous dexamethasone in drinking water; base-water: drinking water; base-diet: folic acid-deficient diet. (B) Ventral luminescence was measured weekly. (C) A log-rank test of survival data shows *P*-values for the comparisons between the various groups: control mice, mice treated with fenofibrate only, dexamethasone (DEX) only and DEX + fenofibrate. $P < 1 \times 10^{-6}$ between DEX-treated groups (DEX only and DEX + fenofibrate) versus no DEX treatment (control and fenofibrate only). The shaded yellow area indicates time on therapy. (D) Fasting serum triglyceride levels at day 24 (3 weeks after BCR-ABL transplant). *N* = 9-10/group.

Discussion

Although the etiology of osteonecrosis is not completely understood, the involvement of lipid metabolism has been well documented.³⁵⁻³⁷ However, there have been few studies investigating whether pharmacologically lowering triglycerides prevents osteonecrosis.³⁸

We found that fenofibrate supplementation successfully managed dexamethasone-induced hypertriglyceridemia (Figure 2) and was associated with reductions in the frequency and severity of osteonecrosis (Figure 3). The correlation between week 3, but not week 6 triglyceride levels (Online Supplementary Figure S1), and osteonecrosis suggest that management of triglycerides is especially important early in the progression of the disease. Although there was an increase in triglyceride levels between mice treated with fenofibrate + dexamethasone and those treated with fenofibrate only by week 6 (Figure 2A), fenofibrate was able to maintain triglyceride levels comparable to those in control mice, even with prolonged continuous exposure to dexamethasone.

Any addition to ALL therapy must be thoroughly assessed to ensure that it does not interfere with the highly effective modern drug regimens. For our purposes, we utilized a model of BCR-ABL⁺ ALL known to be sensitive to dexamethasone treatment. Fenofibrate supplementation did not cause observable differences in the efficacy of dexamethasone in the treatment of experimental BCR-ABL⁺ ALL (Figure 4).

In our experimental models, the dosage of both dexamethasone and fenofibrate were well tolerated (Figure 1C) and resulted in plasma levels of the drug/metabolites in the

clinical range.^{13,39,40} Although the plasma concentration of fenofibric acid was lower in mice treated with dexamethasone + fenofibrate than in those treated with fenofibrate only (Online Supplementary Figure S2B), it was still effective in reducing dexamethasone-induced hypertriglyceridemia (Figure 2A) and osteonecrosis (Figure 3), while not affecting BCR-ABL⁺ ALL treatment (Figure 4). Statins have been suggested as possible agents to reduce osteonecrosis⁴¹⁻⁴³ but because they have potent interactions with CYP3A and with SLCO1B1 (enzymes involved in the metabolism and disposition of multiple ALL drugs), their likelihood of drug interactions makes them less desirable agents to use in patients with ALL.

Dexamethasone treatment is associated with hypertriglyceridemia.^{1,3,44} It has been shown that elevated levels of serum triglyceride-rich lipoproteins contribute to endothelial dysfunction and subsequent atherosclerosis.⁴⁵ We hypothesized that dexamethasone-induced arteriopathy and subsequent osteonecrosis are related to hypertension caused by endothelial dysfunction.^{27,46} We therefore suspect that the mechanism by which fenofibrate reduced the incidence of osteonecrosis and arteriopathy was by lowering the dexamethasone-induced elevation of triglyceride-rich lipoproteins and thereby mitigating the effects of endothelial dysfunction.

In children with ALL, there are no specific guidelines for managing triglyceride levels during glucocorticoid and/or asparaginase treatment. However, conservative use of fibrates has been successful in managing triglycerides in specific cases, with no reported adverse events.^{5,5,47} In general, the use of fibrates in children is limited to cases of extreme hypertriglyceridemia to prevent pancreatitis, pri-

marily in individuals with familial lipid disorders.^{20,48-50} Fibrates have been shown to reduce triglycerides effectively in children, by between 39% and 54%.^{49,51} As seen in adults, data suggest that fibrates are well tolerated in children, with the most frequently reported adverse reactions being gastrointestinal disturbances and muscle cramps.^{15,14,20,49} However, transient increases in liver function tests have been reported in a small number of cases,^{48,51} indicating a potential for hepatotoxicity when used in combination with other hepatotoxic chemotherapeutic agents.

Although fibrates have been included in a case-by-case basis to manage hypertriglyceridemia during ALL therapy^{5,5,47} there has been no systematic analysis of the effect of lipid-lowering interventions and long-term outcomes in ALL survivors. Our proof-of-principle preclinical experiments show that fenofibrate treatment is a potential intervention to reduce dexamethasone-induced osteonecrosis in ALL, without carrying the risk of substantial drug interactions and without any untoward effect on the efficacy of ALL therapy. Our findings support the rationale for controlled clinical trials with fenofibrate in chemotherapy-related hypertriglyceridemia.

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Disclosures

No conflicts of interest to disclose.

Contributions

ERF: conceptualization of experiments; ERF, MAP, DAJ, XC, LL, SEK, MVR and LJJ: methodology and data collection; ERF, MVR and LJJ: formal analysis; ERF, MVR and LJJ wrote the original manuscript. All authors reviewed and approved the manuscript.

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