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Comparative effectiveness of fish oil versus fenofibrate, gemfibrozil, and atorvastatin on lowering triglyceride levels among HIV-infected patients in routine clinical care

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Abstract

Objective—The goal of this study was to compare the effectiveness of fish oil, fenofibrate, gemfibrozil, and atorvastatin on reducing triglyceride (TG) levels among a large cohort of HIV-infected patients in clinical care.

Design—Retrospective observational cohort study

Methods—The primary endpoint was absolute change in TG levels measured using the last TG value pre-treatment and the first TG value post-treatment. A pre-post quasi-experimental design was used to estimate the change in TG due to initiating fish oil. Linear regression models examined the comparative effectiveness of treatment with fish oil versus gemfibrozil, fenofibrate, or atorvastatin for TG reduction. Models were adjusted for baseline differences in age, sex, race, $CD4^+$ cell count, diabetes, body mass index, protease inhibitor use, and time between TG measures.

Results—A total of 493 patients (mean age 46 years; 95% male) were included (46 receiving gemfibrozil, 80 fenofibrate, 291 atorvastatin, 76 fish oil) with a mean baseline TG of 347 mg/dL. New use of fish oil decreased TG (ΔTG -45 mg/dL 95% Confidence interval (CI):-80 to -11) in the pre-post study. Compared with fish oil (reference), fibrates were more effective (ΔTG -66;

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95% CI:-120 to -12) in reducing TG levels, whereas atorvastatin was not (ΔTG -39; 95% CI:-86 to 9).

Conclusion—In HIV-infected patients in routine clinical care, fish oil is less effective than fibrates (but not atorvastatin) at lowering triglyceride values. Fish oil may still represent an attractive alternative for patients with moderately elevated triglycerides particularly among patients who may not want or tolerate fibrates.

Keywords

fish oil; triglycerides; dyslipidemia; fibrates; HIV

Introduction

Triglyceride (TG) levels > 150 mg/dL are associated with increased risk of cardiovascular disease and levels > 500 mg/dL increase the risk of acute pancreatitis among individuals without HIV.[1] Hypertriglyceridemia is common among HIV-infected patients, likely due to many reasons including traditional risk factors, HIV virus itself, and antiretroviral therapy.[2-4] Guidelines from the Infectious Diseases Society of America and Adult AIDS Clinical Trials Group recommend considering fibrates for first-line therapy when TG values exceed 500 mg/dL.[5] Statins are often used for first-line therapy when TG values are 200-500 mg/dL, particularly in the setting of elevated low density lipoprotein (LDL) or non-high-density lipoprotein (non-HDL) levels.[5] Fish oil, containing omega-3 fatty acids, has fewer medication interactions than other treatments and has been shown to reduce TG levels among HIV-uninfected individuals.[6,7] However little is known about the effectiveness of fish oil for lowering triglyceride levels compared to other medications in routine care, and a role for fish oil in the care of HIV-infected individuals is not yet clearly defined.

Previous studies evaluating the use of fish oil for the treatment of hypertriglyceridemia among patients with HIV have usually been trials and were often limited by small sample size.[8-11] The majority of trials have not compared the impact of multiple lipid-lowering medications, although exceptions exist.[12] Comparing results across individual trials is difficult, as the eligibility criteria, doses utilized, follow-up time, and baseline characteristics (particularly baseline TG levels) vary across trials. Furthermore, even less information is available in routine clinical care settings where dosing, adherence, and patient characteristics may be much more variable than in a clinical trial and impact effectiveness. Thus, questions remain regarding the comparative effectiveness of pharmacotherapy options for hypertriglyceridemia among HIV-infected individuals.

The objectives of this study were to evaluate the impact of fish oil on lowering TG values in routine clinical care and to compare the effectiveness of fish oil, fenofibrate, gemfibrozil, and atorvastatin on lowering TG values in a large cohort of HIV-infected patients. This study is unique due to its relatively large sample size, geographic diversity and focus on the impact of medications as they are actually used in routine clinical care.

Methods

Data Source

The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort is a prospective longitudinal observational cohort of HIV-infected patients receiving clinical care from January 1995 to the present.[13] The CNICS data repository captures longitudinal comprehensive clinical data on the CNICS cohort from outpatient and inpatient encounters. Demographic, clinical, medication, and laboratory data are obtained from each site's electronic health record (EHR) and other institutional data sources. Laboratory data are uploaded directly from the Clinical Laboratory Systems at each site. Medication data are entered into the EHR by clinicians or prescription fill/refill data are uploaded directly from Pharmacy Systems and verified through medical record review. Patients from five sites were included in this analysis: University of Alabama at Birmingham (UAB), University of Washington (UW), University of California, San Diego (UCSD), University of California, San Francisco (UCSF), and the University of North Carolina (UNC).

Cohort Subjects

We conducted our analysis using two separate stages: 1) a quasi-experimental pre/post design of patients who initiated fish oil and 2) a classic comparative effectiveness new user cohort study with fish oil as the reference medication. The quasi-experimental pre/post design controls for within-subject time invariant confounders when evaluating the effectiveness of fish oil at reducing triglyceride levels within individuals.[14] The new user cohort design uses multivariate regression to adjust for differences in treatment group characteristics that may have a direct impact on the outcome. Furthermore, this study design can control for known biases associated with prevalent users (where differences in pre-treatment disease is unknown) by requiring pre-treatment triglyceride levels be available to adjust for differences in pre-treatment level between groups.[15] Individuals were included in the analyses if they met the following criteria: ≥18 years of age, initiated fish oil, fenofibrate, gemfibrozil, or atorvastatin between January 1, 2000 and December 31, 2009, had at least one TG result before (within 6 months) and after initiation of therapy, and were not on medications for dyslipidemia for at least 6 months prior to study entry. Atorvastatin was selected as the reference statin because it is one of the preferred agents for HIV-infected patients with dyslipidemia and is the statin most commonly utilized in the CNICS cohort.[5,16] Patients were excluded if the date they initiated lipid-lowering medications or their laboratory result date were missing, lipid-lowering medications were changed to alternative medications or additional lipid-lowering medications were added prior to the first post-treatment TG result, or if the post-treatment measure was >1 year after the pre-treatment measure. Patients were excluded if their baseline TG value was >810 mg/dL. A level of 810 mg/dL was selected as the upper limit to maintain comparability, as fish oil and atorvastatin were not routinely used in patients with TG levels >810. Patients were also excluded if their baseline TG value was <150 mg/dL as some medications (specifically atorvastatin) were used to treat other conditions besides hypertriglyceridemia.

Assessment of outcome and other baseline covariates

The primary outcome was the absolute change in TG level. The last TG value recorded pre-treatment was compared with the first TG value recorded post-treatment. The post-treatment TG level was obtained at least 6 weeks after treatment to ensure adequate time had elapsed for the therapy to take effect. Fasting status was not always routinely available. Baseline covariates included age, sex, race, height, weight, body mass index (BMI), HIV transmission risk factors, diabetes mellitus status, most recent $CD4^+$ cell count, most recent HIV-1 RNA copies, and antiretroviral therapy (ART) at TG therapy initiation (other ART/no ART vs. protease inhibitor [PI]-based vs. non-nucleoside reverse transcriptase inhibitor [NNRTI]-based regimen).

Statistical analysis

Multivariate analyses of variance were conducted to detect a difference in the absolute change in TG values in patients using fish oil adjusted for age (as a continuous centered variable), sex, race, baseline $CD4^+$ cell count (as a continuous centered variable), PI use, and duration between TG measures (as candidate confounder variables). In the self-controlled pre/post quasi-experimental analysis, we adjusted only for age, sex, race, baseline $CD4^+$ cell counts, PI use, and duration between TG measures in order to have a more precise estimate of the triglycerides-lowering effect of fish oil. Fish oil was used as the reference medication for the comparative effectiveness cohort analysis. Linear regression analyses were used to compare medications while adjusting for baseline differences in age, sex, race, $CD4^+$ cell count, PI use, diabetes, body mass index, and time between TG measures. We conducted sensitivity analyses among the subset known to be fasting. All statistical analyses were conducted using SAS Version 9.2 (SAS Institute Inc, Cary, NC). The Institutional Review Board of participating institutions as well as that of the University of Florida approved the study.

Results

Four hundred ninety-three patients met the study's eligibility criteria (80 receiving fenofibrate, 46 gemfibrozil, 76 fish oil and 291 atorvastatin) with a mean baseline TG value of 347 mg/dL (median 309 mg/dL; IQR: 215-415). The patients were primarily male (95%) with a mean age of 46 years. Patients receiving gemfibrozil were slightly younger than patients on other lipid-lowering medications, however this difference was not statistically significant (Table 1). The mean $CD4^+$ cell count at the time of dyslipidemia therapy initiation was significantly lower for gemfibrozil users compared to the other therapies. Patients on fish oil and atorvastatin had significantly lower baseline triglyceride levels compared to those on fibrates. Diabetes was present at baseline in significantly more fenofibrate and atorvastatin users. Patients on fish oil were more likely to be on a PI-based regimen compared to the other therapies. The average time period between the pre and post TG laboratory measurements was 5 months (median 5 months; IQR: 3.2-7 months) (Table 1). The time period between the pre and post TG measurements did not differ significantly between therapies. The median time between TG therapy initiation and post TG measurement was 3.1 months and did not differ between groups.

The mean decrease in TG values for patients who initiated fish oil was 40 mg/dL in unadjusted analyses [IQR: -73, -7], p=0.02. A total of 9% (7/76) of patients on fish oil received a target TG value <150 compared with 18% (14/80) on fenofibrate, 22% (10/46) on gemfibrozil, and 28% (80/291) on atorvastatin. After adjusting for age, sex, baseline $CD4^+$ cell count, PI use, and duration of time between pre and post triglycerides, the change in TG values was 71 mg/dL [-126, -15], p=0.01 (Table 2).

In the comparative effectiveness analyses, significantly greater reductions were seen in gemfibrozil (-80, 95% CI: [-150, -10], p=0.02) compared to fish oil. Gemfibrozil and fenofibrate demonstrated similar reductions in TG values with overlapping confidence intervals, although fenofibrate did not demonstrate a statistically significant greater reduction compared to fish oil (-49, 95% CI: [-108, 11, p=0.1). Atorvastatin was not associated with a statistically significant greater reduction in TG values compared to fish oil (-33, 95% CI: [-81, 15], p=0.2). (Table 3) In sensitivity analyses conducted among the subset with known fasting values, similar patterns of findings were found, although with the small sample size, none were significant. For example, gemfibrozil was associated with greater average reductions than fish oil (-81, 95% CI: [-187-25], and this was of similar magnitude to the findings in the main analysis, although these differences were no longer significant in the smaller subset analysis.

Absolute and percent changes in TG values by baseline ART regimens are shown in Table 4. These results are exploratory in nature, as the study was underpowered to detect differences in TG values secondary to ART regimens. Fish oil demonstrated an absolute reduction in TG values of 124 mg/dL in the NNRTI-based regimen group; however, the small number of patients in the group does not allow conclusions to be drawn. Heterogeneity was also seen in reductions associated with gemfibrozil among those on PI-based regimens vs. NNRTI-based regimens however again, numbers were small and these findings are not conclusive.

Discussion

Fish oil led to a significant reduction in triglyceride values. Fibrates were associated with greater reductions in TG values compared to fish oil in HIV-infected patients in routine clinical care. The reduction in TG values associated with atorvastatin compared with fish oil was not statistically significant.

Fenofibrate and gemfibrozil demonstrated similar substantial reductions in TG values. Gemfibrozil was used less frequently, suggesting clinicians' preferentially use fenofibrate, consistent with general population trends across the US for much greater fenofibrate use without increasing use of gemfibrozil.[17] Fenofibrate may have a lower risk of rhabdomyolysis than gemfibrozil in combination with statins and the advantage of daily dosing versus twice daily.[18,19] Of the other statins commonly used in HIV-infected patients, pravastatin and rosuvastatin, the latter has previously been shown to have similar reductions in TG values compared to atorvastatin, while pravastatin has less reduction in TG values.[16,20] Although niacin is another treatment option for hypertriglyceridemia, it was not included in this study due to its rare use and small sample size within the CNICS Cohort.

This study demonstrates the difficulty in achieving TG goals with monotherapy in HIV-infected patients.[21] The reduced response to dyslipidemia therapies in HIV-infected patients has been demonstrated previously.[22] Only 23% achieved TG < 150 mg/dL post-treatment. This number would be lower if patients with TG > 810 mg/dL had not been excluded, as these patients are unlikely to reach goal with monotherapy.

Although combination therapy was not the focus of this study, fish oil represents a particularly attractive option, as it is well tolerated and appears devoid of drug-interactions.[12,23] Guidelines recommend caution when using statins and fibrates in combination due to the increased risk of toxicity, however in clinical practice their combined use is not uncommon. Statin therapy has the strongest evidence for reducing cardiovascular risk, while the evidence supporting fibrate and fish oil therapy is moderate.[1,5] Clinical trials have shown conflicting results for cardiovascular risk reduction with fibrates, but there seems to be a benefit in patients with high triglycerides and low HDL cholesterol.[24-27] Fish oil has demonstrated efficacy in reducing cardiovascular risk, particularly as secondary prevention.[28,29] Additional studies are needed to determine the impact of fish oil on reducing TG values in combination with other medications among those individuals who do not reach their targets on monotherapy.

This study found a much smaller reduction in TG values associated with fish oil than earlier trials which demonstrated reductions ranging from 15-46%[8-11,30] While this may be due in part to differences in patient populations and the extent of baseline hypertriglyceridemia in participants, we suspect that much of this difference is due to the way fish oil is used in clinical care settings compared with clinical trials. Dosage information was not available for the majority of patients included, however, among the subset of patients taking fish oil in the entire CNICS cohort (N=720) with complete dosage data (N=97, 14%) 61% of patients had a dose of 2 g or less and only 2% had a dose of 4 g or greater. In contrast, while data was also incomplete, among those with doses for gemfibrozil and fenofibrate, most were on standard or high doses (e.g. 600 mg gemfibrozil BID, varies based on brand for fenofibrate). Mean atorvastatin dose was 22 mg. Doses utilized in randomized clinical trials of HIV-infected patients have typically used higher doses, 3-6 g, compared to the doses used in clinical care in this cohort. Furthermore, a dose effect with greater impact from higher doses has previously been suggested.[30] The relatively low doses used in clinical care suggest the effectiveness of fish oil in this study may be underestimated, but reflective of how it is used in clinical practice. Variations in the amount of omega-3 fatty acids contained in the various fish oil brands likely also contributed to the findings.

The range of eligible baseline TG values was restricted to maintain comparability across treatments, however baseline TG values were still significantly higher in patients receiving fibrates. This may underestimate the comparative effects of fish oil and atorvastatin since the baseline TG value is an effect measure modifier. Previous randomized trials have demonstrated that the higher the baseline TG value, the greater the therapeutic response.[30,31,32]

Strengths and limitations

Strengths of this study include the large sample size, geographic diversity and comprehensive clinical data. This study examined the change in triglyceride levels associated with individual therapies in clinical care with minimal exclusion criteria. Our findings are generalizable to similar populations of patients in routine care who represent a broader range of characteristics than patients who typically enroll in clinical trials. The restriction of baseline TG values <810 mg/dL resulted in baseline TG values of approximately 350 mg/dL, therefore the generalizability of these findings is limited to those with moderate hypertriglyceridemia.

As with any observational study, there may be unmeasured confounders for which adjustment is not possible. The study lacks information regarding adherence, genetic factors, diet, and exercise. The advantage of the pre/post design is it controls for within-subject time independent confounders. Lipid values were measured in clinical care so we could not confirm fasting status, but have no reason to suspect that fasting status would vary between therapies. In addition, despite the greater variability in non-fasting triglyceride values, their importance is increasing appreciated given their association with CVD.[33] Contradictory to a previous pharmacokinetic study, gemfibrozil showed a greater reduction in TG values in patients receiving a PI-based regimen.[34] The sample size of the study population did not allow inference to be made when hypertriglyceridemia treatments were stratified by ART classes. Furthermore, it is well known that antiretroviral medications differ in their effects on lipid profiles not only between classes, but also within antiretroviral medication classes. Finally, because fish oil is available over-the-counter, it is certainly possible that additional patients were taking fish oil and this was not captured. Most, but not all of the fish oil captured was prescription fish oil so findings may be somewhat less generalizable to OTC fish oil use.

Another limitation was the doses of medications were not always available. It is possible that the doses of fenofibrate, fish oil, and atorvastatin used were lower than optimal and may have been titrated after the post-treatment results. This concern is less likely with gemfibrozil, as there is only one commonly used dose. However, the point of this study was to examine the effectiveness of triglyceride lowering medications as they are actually prescribed in clinical care. We focused on the initial time period after initiation of these medications as clinical inertia and lack of medication titration is a frequent occurrence[35] and a shorter time-frame lessened the likelihood that large changes in BMI or other factors would occur and impact results. Finally, this study focused only on the impact on triglyceride levels. In addition to lowering triglyceride levels, these medications may have other potential impacts such as changes in LDL subfractions which require further study.[36]

Conclusions

Among HIV-infected patients with moderate hypertriglyceridemia in clinical care, fibrate therapy remained the most effective at reducing TG levels. Fish oil had a much more modest impact on TG levels, likely in part due to the frequent use of low doses in the usual care setting. However, when considering risks and benefits, fish oil may be an attractive option

for HIV-infected patients with moderately elevated TG, particularly among patients who may not want or tolerate fibrates. Additional studies are needed to further determine the appropriate indications and the lipid-lowering effects of fish oil in HIV-infected patients.

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Table 1

Demographic and clinical characteristics by therapy (N=493); data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort 2000-2009[b]

Characteristics	Fenofibrate (n=80)	Gemfibrozil (n=46)	Fish Oil (n=76)	Atorvastatin (n=291)	P value
Age (years)					0.4
<40	17 (21)	14 (31)	18 (24)	64 (22)	
40-49	39 (48)	24 (52)	36 (47)	127 (44)	
≥50	24 (31)	8 (17)	22 (29)	100 (34)	
Sex					0.1
Male	76 (95)	45 (98)	76 (100)	273 (94)	
Female	4 (5)	1 (2)	0	18 (6)	
Race					0.1
White	52 (65)	25 (55)	51 (67)	177 (61)	
Black	12 (15)	13 (28)	6 (8)	63 (22)	
Hispanic	14 (17)	6 (13)	15 (20)	36 (12)	
Other	2 (3)	2 (4)	4 (5)	15 (5)	
Body mass index (kg/m^2)[c]					0.2
<18.5	2 (2)	3 (7)	6 (8)	15 (5)	
18.5-25	20 (25)	13 (30)	24 (31)	95 (33)	
25.1-30	37 (47)	22 (51)	31 (41)	101 (35)	
>30.0	21 (26)	5 (12)	15 (20)	78 (27)	
Diabetes					0.05
Yes	13 (16)	1 (2)	5 (7)	33 (11)	
No	67 (84)	45 (98)	71 (93)	258 (89)	
Pre-index TG (mg/dl)	467	440	366	295	<0.01
Post-index TG (mg/dl)[a]	351	273	326	254	<0.01
HIV risk factor					0.004
MSM	43 (54)	32 (70)	48 (63)	190 (65)	
IDU	2 (3)	3 (6)	6 (8)	15 (5)	

Characteristics	Fenofibrate (n=80)	Gemfibrozil (n=46)	Fish Oil (n=76)	Atorvastatin (n=291)	P value
Heterosexual	30 (37)	9 (20)	13 (17)	80 (28)	
Other	5 (6)	2 (4)	9 (12)	6 (2)	
$CD4^+$ cell count (cells/mm^3)					0.001
0-200	7 (9)	11 (24)	15 (20)	36 (12)	
201-350	18 (22)	20 (43)	15 (20)	67 (23)	
>350	55 (69)	15 (33)	46 (60)	188 (65)	
HIV-1 RNA (copies/ml)					0.1
0-9,999	70 (87)	43 (94)	69 (91)	265 (91)	
10,000-99,999	10 (13)	3 (6)	3 (4)	19 (7)	
≥100,000	0	0	4 (5)	7 (2)	
Antiretroviral therapy regimen					0.001
PI-based	34 (43)	18 (39)	48 (63)	107 (37)	
NNRTI-based	18 (22)	9 (20)	10 (13)	62 (21)	
Other ART	10 (13)	12 (26)	6 (8)	47 (16)	
None	18 (22)	7 (15)	12 (16)	75 (26)	

[a] Average time period between the pre and post TG laboratory measurements was 5 months.

ART, antiretroviral therapy; MSM, men who have sex with men; IDU, injection drug use; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[b] Restricted to baseline TG value >150 mg/dl and <810 mg/dl.

[c] There was missing data for BMI in atorvastatin group (n=2)

Table 2

Unadjusted and adjusted TG changes in fish oil users (N=76)[a,b]

	TG Change	95% CI	P value
Unadjusted change	-40	(-73, -7)	0.02
Unadjusted percentage change (%)	-8	(-17, 0)	0.06
Adjusted change[a]	-71	(-126, -15)	0.01
Adjusted percentage change (%)	-18	(-33, -4)	0.01

[a] Adjusted for age, sex, race, baseline $CD4^+$ cell count, protease inhibitor use, and time between triglyceride measures

[b] Restricted to baseline TG value >150 mg/dl and <810 mg/dL

Table 3

Adjusted absolute and percent change in triglyceride values comparing fish oil to other therapies[a,b]

Characteristics	TG Change (95% CI)	P value	% change	P value
Fenofibrate vs. Fish oil	-49 (-108, 11)	0.11	-16 (-31, 0)	0.04
Gemfibrozil vs. Fish oil	-80 (-150, -10)	0.02	-19 (-37, -1)	0.04
Gemfibrozil or fenofibrate vs. Fish oil	-60 (-114, -5)	0.03	-17 (-31, -3)	0.02
Atorvastatin vs. Fish oil	-33 (-81, 15)	0.18	-4 (-16, 9)	0.56

[a] Adjusted for age, sex, race, baseline $CD4^+$ cell count, diabetes, body mass index, protease inhibitor use, and time between triglyceride measures

[b] Restricted to baseline TG value >150 mg/dl and <810 mg/dl

Table 4

Crude absolute and percent change in triglycerides levels by ART regimen (Descriptive)

	Fenofibrate (n=80)	Gemfibrozil (n=46)	Fish Oil (n=76)	Atorvastatin (n=291)
PI-based ART				
N	34	18	48	107
Pre-index (mg/dl)	481	453	367	312
Post-index (mg/dl)	367	234	341	274
Crude absolute change (mg/dl)	-114	-219	-26	-38
Crude percent change (%)	-24	-48	-7	-12
NNRTI-based ART				
N	18	9	10	62
Pre-index (mg/dl)	509	370	326	306
Post-index (mg/dl)	370	323	202	239
Crude absolute change (mg/dl)	-139	-47	-124	-67
Crude percent change (%)	-27	-13	-38	-22
PI or NNRTI ART				
N	52	27	58	169
Pre-index (mg/dl)	491	425	360	310
Post-index (mg/dl)	368	264	317	261
Crude absolute change (mg/dl)	-123	-161	-43	-49
Crude percent change (%)	-25	-38	-12	-16
Other ART regimen				
N	10	12	6	47
Pre-index (mg/dl)	461	434	446	288
Post-index (mg/dl)	362	246	533	244
Crude absolute change (mg/dl)	-99	-188	+87	-44
Crude percent change (%)	-22	-43	+19	-15
No ART				
N	18	7	12	75
Pre-index (mg/dl)	399	506	352	267
Post-index (mg/dl)	295	352	263	245
Crude absolute change (mg/dl)	-104	-154	-89	-22
Crude percent change (%)	-26	-30	-25	-8

ART, antiretroviral therapy