ELSEVIER

Atherosclerosis 152 (2000) 489–496

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Efficacy and safety of atorvastatin in hyperlipidemic, type 2 diabetic patients. A 34-week, multicenter, open-label study

Carlos A. Aguilar-Salinas [a,*], Francisco J. Gómez-Pérez [a], Carlos Posadas-Romero [b], Cuauhtémoc Vázquez-Chávez [c], Eduardo Meaney [d], Alfonso Gulías-Herrero [a], Luz E. Guillén [a], Alma Alvarado Vega [b], Enrique Mendoza Pérez [b], Luis Eduardo Romero-Nava [b], Rita Angélica Gómez-Díaz [c], Saúl Salinas-Orozco [c], Rafael Moguel [d], Germán Novoa [e]

[a] *Instituto Nacional de la Nutrición 'Salvador Zubirán' de la SSA (Secretaría de Salud), Mexico City, Mexico*
[b] *Instituto Nacional de Cardiología 'Ignacio Chávez' de la SSA, Mexico City, Mexico*
[c] *Hospital de Cardiologia, Centro Médico Nacional Siglo XXI del IMSS (Instituto Mexicano del Seguro Social), Mexico City, Mexico*
[d] *Hospital 1° de Octubre del ISSSTE (Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado), Mexico*
[e] *Parke-Davis, Mexico*

Received 22 March 1999; received in revised form 16 November 1999; accepted 13 December 1999

Abstract

Hyperlipidemia is common in type 2 diabetic patients and is an independent risk factor for cardiovascular disease. The aim of this trial was to evaluate the efficacy and safety of once-daily atorvastatin 10 — 80 mg for the treatment of hyperlipidemia in type 2 diabetics with plasma low-density lipoprotein cholesterol (LDL-C) levels exceeding 3.4 mmol/l (130 mg/dl). One hundred and two patients met the study criteria and received 10 mg/day atorvastatin. Patients who reached the target LDL-C level of ≤ 2.6 mmol/l (100 mg/dl) maintained the same dosage regimen until they had completed 16 weeks of treatment. Patients not reaching the target LDL-C underwent dose titration to atorvastatin 20, 40 and 80 mg/day at Weeks 4, 8 and 12, respectively. All 88 patients who completed the study attained target LDL-C levels and 52 (59%) of patients achieved the target goal at the starting dose of atorvastatin 10 mg/day. In this group the differences between baseline and post-treatment values for LDL-C were 4.3 ± 0.7 mmol/l (166 ± 26 mg/dl) versus 2.2 ± 0.4 mmol/l (87 ± 14 mg/dl) ($P < 0.0001$), respectively, a decrease of 47%. Similar trends were observed for total cholesterol, triglycerides, very low-density lipoprotein cholesterol and apolipoprotein B levels. The safety profile of atorvastatin in these patients was highly favorable and similar to those reported with other statins. Only one patient withdrew due to a possible drug-related adverse event. These data confirm the marked efficacy and safety of atorvastatin in type 2 diabetic patients with hyperlipidemia and the efficacy of atorvastatin 10 mg in helping patients attain their LDL-C goal.

Keywords: Atorvastatin; Type 2 diabetes mellitus; Hypercholesterolemia; Low-density lipoprotein cholesterol; Triglyceride

1. Introduction

Type 2 diabetes is frequently associated with elevations of plasma low-density lipoprotein cholesterol (LDL-C) and triglycerides, and reduced levels of high-density lipoprotein cholesterol (HDL-C) [1,2]. Although elevated levels of LDL-C are found with equal frequency in diabetic and non-diabetic patients, LDL particle composition is altered unfavourably in diabetics and is more likely to be atherogenic.These lipid abnormalities are recognized as major risk factors for the development of coronary heart disease (CHD) and underlie the 2–4-fold greater prevalence of CHD, cerebrovascular disease and peripheral vascular disease in diabetic compared with non-diabetic patients [3]. It has been estimated that 75–80% of deaths among the diabetic population are attributable to cardiovascular disease, particularly is-

* Corresponding author. Present address: Departamento De Diabetes y Metabolismo de Lipidos, Vasco de Quiroga 15, Mexico City 14000, Mexico. Tel.: + 52-5-5130002.

A number of measures are recommended for the treatment of hyperlipidemia associated with diabetes. These include improved glycemic control, diet and weight modification, and control of other CHD risk factors, such as smoking and alcohol intake. If non-pharmacological strategies are not sufficient to control the lipid abnormalities, introduction of drug therapy may be warranted. Agents that are used to treat hypercholesterolemia or hypertriglyceridemia in non-diabetic patient groups, such as niacin and bile acid sequestrants, may not be suitable in patients with type 2 diabetes due to the possibility of aggravation of hypertriglyceridemia and/or insulin resistance [6]. In diabetic patients, drugs of choice to reduce LDL-C are the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) (some statins also reduce triglyceride levels), because they are generally well tolerated and do not adversely affect glycemic control. Data from subgroup analyses in recent cholesterol-lowering clinical trials using statin therapy indicate that the benefits of cholesterol lowering are at least as great in diabetic as in non-diabetic groups [7,8].

The results of a recent study have suggested that diabetic patients without CHD have as high a risk of a myocardial infarction as non-diabetic patients with CHD [9]. These data provide a rationale for treating cardiovascular risk factors in diabetic patients as aggressively as non-diabetic subjects in the high-risk CHD category. For diabetic patients without pre-existing CHD, the current American Diabetic Association (ADA) goal for LDL-C is <2.6 mmol/l (100 mg/dl) [3,10]. The recommendations of the ADA for the treatment of elevated LDL-C generally follow the guidelines of the NCEP [11], which state that diabetic subjects with clinical CHD and an LDL-C level of >2.6 mmol/l (100 mg/dl) after behavioural and glucose interventions should be treated with pharmacological agents. Despite the recommendations recent data suggest that only a small proportion of type 2 diabetic patients achieve and sustain target LDL-C levels of <3.4 mmol/l (130 mg/dl) to impact on cardiovascular morbidity [12–14].

Table 1
Baseline characteristics of all patients included in study ($n=102$)

Variable	n (% of total)
Sex	
Male	43 (42.2)
Female	59 (57.8)
Race	
Hispanic	101 (99.0)
White/caucasian	1 (1.0)
	Mean ± SD
Age (years)	58.9 ± 9.3
Weight (kg)	67.2 ± 11.7
Body mass index (kg/m^2)	26.6 ± 3.2
Duration of dyslipidemia (months)	50.4 ± 51.2
Duration of diabetes (months)	97.8 ± 80.9
Total cholesterol (mmol/l)	7.0 ± 1.1
LDL-C[a] (mmol/l)	4.6 ± 0.9
VLDL-C[b] (mmol/l)	4.6 ± 1.1
Triglycerides (mmol/l)	2.8 ± 1.9
Apolipoprotein B (g/l)	1.4 ± 0.28
Fasting plasma glucose (mmol/l)	7.6 ± 1.9
Fructosamine (mmol/l)	242.4 ± 62.5
HbA_{1C} (%)	7.6 ± 1.2

[a] LDL-C, low-density lipoprotein cholesterol.
[b] VLDL-C, very low-density lipoprotein cholesterol.

The objectives of this study were to assess the efficacy and safety of 10–80 mg atorvastatin for the treatment of hyperlipidemia in type 2 diabetes patients with LDL-C levels ≥ 3.4 mmol/l (130 mg/dl). Atorvastatin is a synthetic HMG-CoA reductase inhibitor which has been shown to be highly effective at lowering LDL-C and triglyceride levels in non-diabetic patients. In hyperlipidemic subjects, doses of atorvastatin from 10–80 mg once-daily have been shown to reduce LDL-C levels by 41–61% [15] and triglycerides by 23–45% [16].

2. Materials and methods

2.1. Patients

All patients were previously diagnosed with type 2 diabetes according to the criteria of the ADA and had to have $HbA_{1C}<10$ for at least 4 weeks prior to screening for the trial. Patient characteristics at baseline are detailed in Table 1. The trial included men and post-menopausal or non-pregnant women aged between 18 and 80 years who had a Body Mass Index of ≤ 30. Plasma LDL-C levels in these patients were >3.4 mmol/l (130 mg/dl) after the initial 6 weeks of isocaloric diet.

Patients were excluded if they had type 1 diabetes, uncontrolled hypertension, severe renal dysfunction, nephrotic syndrome or dysproteinemias, fasting plasma triglycerides >10 mmol/l, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels $>1.5\times$ the upper limit of normal (ULN), or if their creatine phosphokinase (CPK) levels were $>3\times$ ULN. Consumption of any lipid-altering drug within the previous 4 weeks (6 months for probucol) prevented entry into the study. None of the study subjects had tendinous xanthomata.

The protocol was approved by an Ethics Committee of every Institution and every patient provided witnessed, written, informed consent prior to entering the study.

2.2. Study design

This was a multicenter, open-label, 34-week dose-titration study (Fig. 1). Patients attended an initial

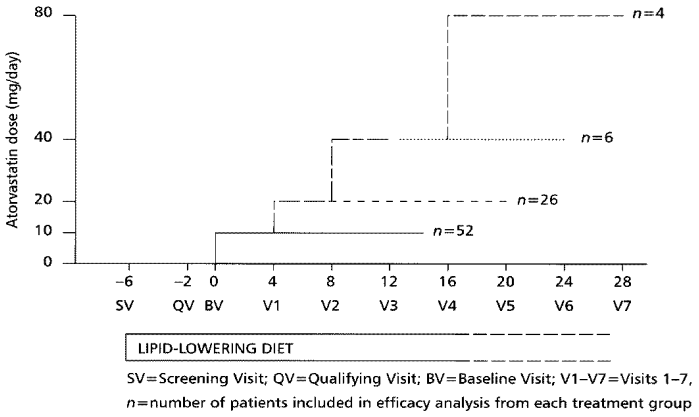

Fig. 1. Schematic figure of study design showing timings of patient visits, diet and dose titration periods.

screening visit followed by a qualifying visit 4 weeks later in which compliance with diet was assessed and blood samples were taken. Within 2 weeks patients returned for a baseline visit during which further blood samples were tested and drug treatment was initiated. Changes in lipid profile after periods of treatment with atorvastatin were compared against the mean laboratory parameters obtained during the qualifying (week −2) and baseline (week 0) visits.

Throughout the trial, including the pre-treatment period of 6 weeks, patients were required to comply with an isocaloric, standard lipid-lowering diet defined by a registered dietician of 50% carbohydrates, 20% protein, 30% fat and 30 g/day fiber. Dietary advice was given at the initial visit and compliance with the diet assessed at every subsequent visit (at 4-week intervals) using a 3-day food record. Drug compliance and efficacy, as well as laboratory parameters were also measured at every visit.

2.3. Dose titration

The starting dose of 10 mg/day was doubled every 4 weeks until either the desired LDL-C level ($\leq$2.6 mmol/l [100 mg/dl]) or a maximum dose of 80 mg atorvastatin once daily were achieved. Once patients had achieved their target LDL-C level, they maintained the same dose regimen for a further 16 weeks of treatment.

2.4. Efficacy parameters

At the end of the 16-week treatment period, efficacy parameters at the dose at which patients achieved the LDL-C target were compared with baseline values. In all cases, baseline values were averaged from measurements at the qualifying (Week −2) and baseline (Week 0) visits, whilst post-treatment values refer to the mean at Weeks 12 and 16 of treatment.

The primary efficacy parameters of the study were percentage changes in LDL-C and triglycerides from baseline. Secondary efficacy parameters included the percentage changes in total cholesterol, HDL-C, VLDL-C, and apolipoproteins A1 and B from baseline.

2.5. Safety evaluation

Before entering the study patients underwent a complete physical examination with clinical laboratory evaluation including blood count, measurement of thyroid-stimulating hormone (TSH) and CPK levels, urinalysis, liver function tests (ALT and AST), glycemic profile (fasting plasma glucose, HbA_{1C} and fructosamine) and a pregnancy test. These tests were repeated at the end of the study. At each visit, liver function tests, glycemic profile and CPK levels were measured. Clinically important events were defined as: CPK $>5\times$ ULN at two consecutive measurements 1 week apart accompanied by muscle pain, tenderness or weakness; CPK $>10\times$ ULN at any time; ALT or AST $>3\times$ ULN at two consecutive measurements 1 week apart. Patients were excluded from the study if they developed severe hyperglycemia or any other significant deviation from safety tests. Other reasons for dismissal were lack of compliance to the drug or diet.

2.6. Laboratory analyses

The laboratory of the Departamento de Diabetes y Metabolismo de Lípidos of the Instituto Nacional de la Nutrición in Mexico performed all lipid and clinical laboratory measurements using standardized procedures. This laboratory is certified for standardization of tests by the External Comparative Evaluation of Laboratories Program of the College of American Pathologists. Blood samples were taken after an overnight fast ($\geq$9 h). All laboratory analyses were performed with commercially available standardized methods. Glucose was measured using the glucose oxidase method and HbA_{1C} using latex immunoagglutination inhibition (Bayer laboratories) [17]. Total serum cholesterol and triglycerides were measured using an enzymatic method (SERA-PAK®) (CV 3.3%). HDL-C levels were assessed using phosphotungstic acid and Mg^{2+} (CV 2.5%). LDL-C concentration was estimated by the Friedewald formula [18]. Direct LDL-C was determined by ultracentrifugation (β quantification) at Week 0, on completion of 16 weeks of treatment and in every patient in whom triglyceride levels were >4.5 mmol/l (400 mg/dl) [19]. Apolipoprotein B concentration was measured by an immunonephelometric method. Fructosamine concentration was measured using a reduction test with nitroblue tetrazolium (Bohringer–Mannheim).

2.7. Statistical analysis

Statistical analysis was performed with the SAS Statistical Package version 6.12 TS020. All differences between groups were evaluated using two-tailed paired t-tests.

Table 2
Relationship between baseline low-density lipoprotein cholesterol (LDL-C) level and atorvastatin dose required to achieve LDL-C goal

Atorvastatin dose (mg/day)	Baseline LDL-C level (mmol/l)
10	4.3 ± 0.7
20	4.7 ± 0.7
40	5.4 ± 0.6
80	6.2 ± 1.7

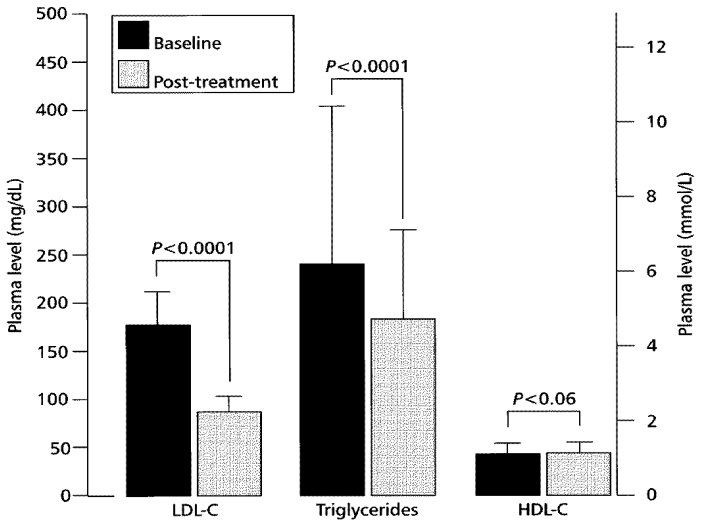

Fig. 2. Bar chart showing change (mean ± SD) in low-density lipoprotein cholesterol (LDL-C), triglycerides and high-density lipoprotein cholesterol (HDL-C) between baseline and after 16 weeks of treatment at the effective atorvastatin dose.

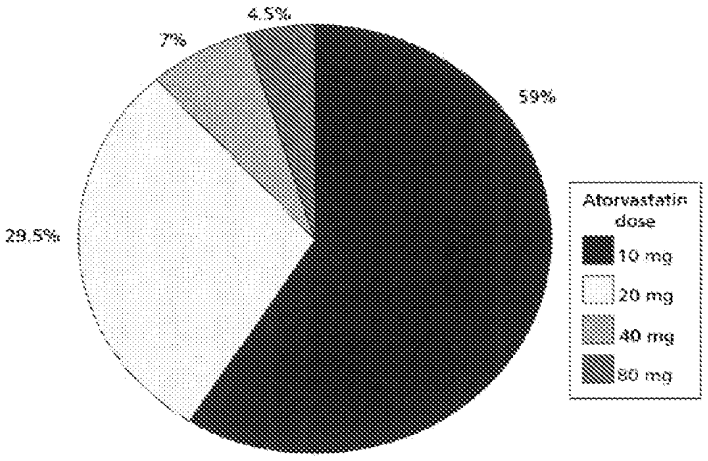

Fig. 3. Pie chart showing the proportions of patients requiring each of the atorvastatin doses in order to attain a low-density lipoprotein cholesterol goal of ≤100 mg/dl (2.6 mmol/l).

3. Results

3.1. Patients

One hundred and ninety-four patients were screened for the study. The characteristics and baseline measurements of the patients who entered the study are shown in Table 1. A total of 102 patients satisfied the inclusion/exclusion criteria and entered the trial. Eighty-eight patients completed the study; 14 patients were not considered in the final analysis due to lack of compliance ($n = 10$), withdrawal due to adverse events ($n = 2$) or administration difficulties ($n = 2$).

3.2. Efficacy

All 88 patients who completed the study attained the target LDL-C level of ≤2.6 mmol/l (100 mg/dl). Of these patients, 52 (59%) achieved their LDL-C goal with the 10 mg/day atorvastatin dose, 26 (29.5%) with the 20 mg dose, six (7%) with the 40 mg dose and four (4.5%) with the 80 mg dose. As expected the main determinant of the dosage needed to achieve the LDL-C goal was baseline LDL-C level (Table 2). When patients were stratified by their baseline LDL-C levels, 67 (76%) patients who finished the study had a baseline LDL-C of <5.2 mmol/l (200 mg/dl). Of these patients, 47 (70.1%) achieved their LDL-C goal with the 10 mg/day atorvastatin dose, 17 (25.4%) with the 20 mg/day dose and only three (4.5%) required a 40 mg dose or greater. Of the 21 patients finishing the study whose baseline LDL-C was ≥5.2 mmol/l (200 mg/dl), 14 (66.7%) required 20 mg/day or less to achieve the LDL-C goal. The highest dose (80 mg/day) was required in only three cases.

A 16-week treatment period of atorvastatin (10, 20, 40 or 80 mg) in 88 patients with type 2 diabetes resulted in a mean reduction from baseline in plasma LDL-C of 50% (4.6 ± 0.9 mmol/l [177 ± 34 mg/dl] to 2.2 ± 0.4 mmol/l [87 ± 16 mg/dl], $P < 0.0001$) and a mean reduction in triglyceride levels of 18% (2.7 ± 1.8 mmol/l [240 ± 164 mg/dl] to 2.1 ± 1.1 mmol/l [183 ± 95 mg/dl], $P < 0.0001$) (Fig. 2). During this period there was no significant change in Body Mass Index. The majority of patients achieved the target level of ≤2.6 mmol/l (100 mg/dl) at the 10 mg dose of atorvastatin ($n = 52$, 59.1%) (Fig. 3). A total of 26 (29.5%) patients required titration to 20 mg/day; six (6.8%) required titration to 40 mg/day, and only four (4.5%) required titration to 80 mg/day.

The effect of atorvastatin on the lipid profile showed a dose-dependent trend although this was not tested statistically (Table 3). After 16 weeks of treatment at the effective dose, patients showed mean decreases in plasma LDL-C of 47.1, 53.0, 59.9 and 53.0% at daily

Table 3
Percentage change in the lipid profile and clinical characteristics between baseline and post-treatment values[a]

	Percent change (%)			
	10 mg ($n = 52$)	20 mg ($n = 26$)	40 mg ($n = 6$)	80 mg ($n = 4$)
Total cholesterol	−34.5	−39.4	−43.9	−47.3
Triglycerides	−13.6	−19.3	−22.1	−52.4
LDL-C	−47.1	−53.0	−59.9	−53.0
HDL-C	2.3	5.0	5.8	12.5
VLDL-C	−29.3	−36.4	−32.1	−60.0
Apo A1	−5.5	−4.4	−1.7	2.2
Apo B	−34.9	−40.0	−42.1	−45.6
Glucose	7.0	11.5	11.6	23.4
HbA1	2.4	9.0	9.7	−0.7
Fructosamine	26.4	16.0	12.5	20.1

[a] Titration to the higher dose only occurred in non-responders. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.

Table 4
Percentage changes in (mean ± SD) lipid profiles and clinical characteristics between baseline after 16 weeks of treatment at the effective atorvastatin dose[a]

Variable	n	Baseline	Post-treatment	Change (%)	P
		Mean ± SD	Mean ± SD		
Total cholesterol (mmol/l)	88	7.0 ± 1.2	4.3 ± 0.6	−37.2	<0.0001
Triglycerides (mmol/l)	88	2.7 ± 1.9	2.1 ± 1.1	−17.7	<0.0001
LDL-C (mmol/l)	88	4.6 ± 0.9	2.3 ± 0.4	−50.0	<0.0001
HDL-C (mmol/l)	88	1.1 ± 0.3	1.1 ± 0.3	3.8	ns
VLDL-C (mmol/l)	88	1.7 ± 1.2	0.9 ± 0.6	−33.1	<0.0001
Apo A1 (g/l)	88	1.36 ± 0.22	1.29 ± 0.20	−4.6	<0.0001
Apo B (g/l)	88	1.44 ± 0.29	0.88 ± 0.17	−37.4	<0.0001
Glucose (mmol/l)	88	7.57 ± 1.87	8.21 ± 2.37	9.4	<0.001
HbA1 (%)	88	7.7 ± 1.3	7.9 ± 1.5	4.7	ns
Fructosamine (mmol/l)	88	242.8 ± 57.1	288.4 ± 56.6	22.3	<0.0001

[a] Baseline = mean of qualifying and baseline visits; post-treatment = mean of Weeks 12 and 16 of treatment period at effective atorvastatin dose; ns, not significant; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B; apolipoprotein B.

doses of 10, 20, 40 and 80 mg atorvastatin, respectively. At the same doses plasma triglyceride levels were reduced by 13.6, 19.4, 22.2 and 52.4%, respectively. The variable effects of the 80 mg dose may be explained in part by the low sample size ($n = 4$).

Mean values for the secondary efficacy parameters revealed that VLDL-C was significantly reduced from baseline by 33.1% from 1.7 ± 1.2 mol/l to 0.9 ± 0.6 mol/l ($P < 0.0001$) (Table 4). Apolipoprotein B levels were reduced from baseline by 37.4% from 1.44 ± 0.29 g/l to 0.88 ± 0.17 g/l ($P < 0.0001$). Patients showed a small but significant decrease in apolipoprotein A1 levels (4.6%, $P < 0.0001$). There was a trend toward increased plasma HDL-C (3.8%), but this did not reach significance in this patient group ($P < 0.06$). Importantly, the lack of effect on HbA_{1C} indicates that the patients remained under adequate diabetic control.

3.3. Safety

The safety analysis included all patients entering the study ($n = 102$). Adverse events that may have been related to drug treatment were mild-to-moderate and reported by 8 (7.8%) patients. Two patients withdrew from the study because of adverse events. Only one was possibly attributable to the study drug in a patient who experienced a mild generalized rash after 4 weeks of 10 mg/day atorvastatin. A brain tumor was diagnosed during the first week of treatment in other case. No correlation between the incidence of potentially drug-related adverse events and drug dosage was observed in this study. There were no incidents of myopathy or liver dysfunction. No persistent elevations in ALT, AST or CPK, defined as clinically important, were reported during the course of the study.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.