Medical therapeutics for pulmonary arterial hypertension: from basic science and clinical trial design to evidence-based medicine

Roxana Sulica and Michael Poon†

Pulmonary arterial hypertension is a severe disease with poor prognosis, caused by obliteration of the pulmonary vasculature as a result of pulmonary-vascular remodeling, active vasoconstriction and *in situ* thrombosis. Left untreated, pulmonary arterial hypertension results in right-ventricular failure and death. There has been dramatic progress in the treatment of pulmonary arterial hypertension during recent years. A remarkable number of randomized-controlled trials with agents known to target specific abnormalities present in pulmonary arterial hypertension have been completed. Most commonly, therapeutic efficacy was judged by the ability of the drug under study to improve exercise capacity and to decrease the rate of severe complications. Completed clinical trials have mainly evaluated patients with relatively advanced disease. Despite these advances, responses to therapy in pulmonary arterial hypertension are not uniformly favorable and frequently incomplete. In addition, the methods of delivery and the adverse effect profile of the currently available pulmonary arterial hypertension-specific drugs create further management difficulties. Based on newly identified pathobiologic abnormalities in the pulmonary vasculature, future studies are likely to focus on the discovery of new therapeutic targets. Clinical trial design will continue to evolve in an attempt to enable inclusion of patients with less advanced disease and evaluation of treatment combinations or comparisons of the currently approved drugs.

Expert Rev. Cardiovasc. Ther. 3(2), 347–360 (2005)

CONTENTS

†Author for correspondence
Mount Sinai School of Medicine, Director of Cardiology, Cabrini Medical Center, New York, NY 10003, USA
Tel.: +1 212 995 0869
Fax: +1 212 979 3474
mpoon@cabrininet.org

KEYWORDS:
antihistamin, bosentan, epoprostenol, exercise capacity, hemodynamics, iloprost, pulmonary arterial hypertension, sildenafil, sitaxsentan, treprostinil

Definition & classification

Pulmonary arterial hypertension (PAH) encompasses a heterogeneous group of disorders characterized by increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). PAH classification includes idiopathic PAH (IPAH; formerly primary pulmonary hypertension), familial PAH, PAH associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drug and toxins, and other conditions (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders and splenectomy), PAH associated with significant venous or capillary involvement and persistent pulmonary hypertension of the newborn [1].

Without intervention, PAH has a progressive course and poor prognosis. Estimated median survival of untreated IPAH patients is 2.8 years [2]. Survival is primarily determined by the level of the right-ventricular dysfunction and the most common cause of death is right-ventricular failure. Appropriate therapy may alter the natural course of the disease, but does not offer a definitive cure. To a certain degree, all forms of PAH share pathologic characteristics, clinical presentation, diagnostic modalities and therapeutic options. In PAH, the small pulmonary arteries are occluded by a combination of active vasoconstriction, *in situ* thrombosis and, most importantly, vascular proliferation and remodeling. PAH treatment is directed at all of these processes (FIGURE 1).

10.1586/14779072.3.2.347

ISSN 1477-9072

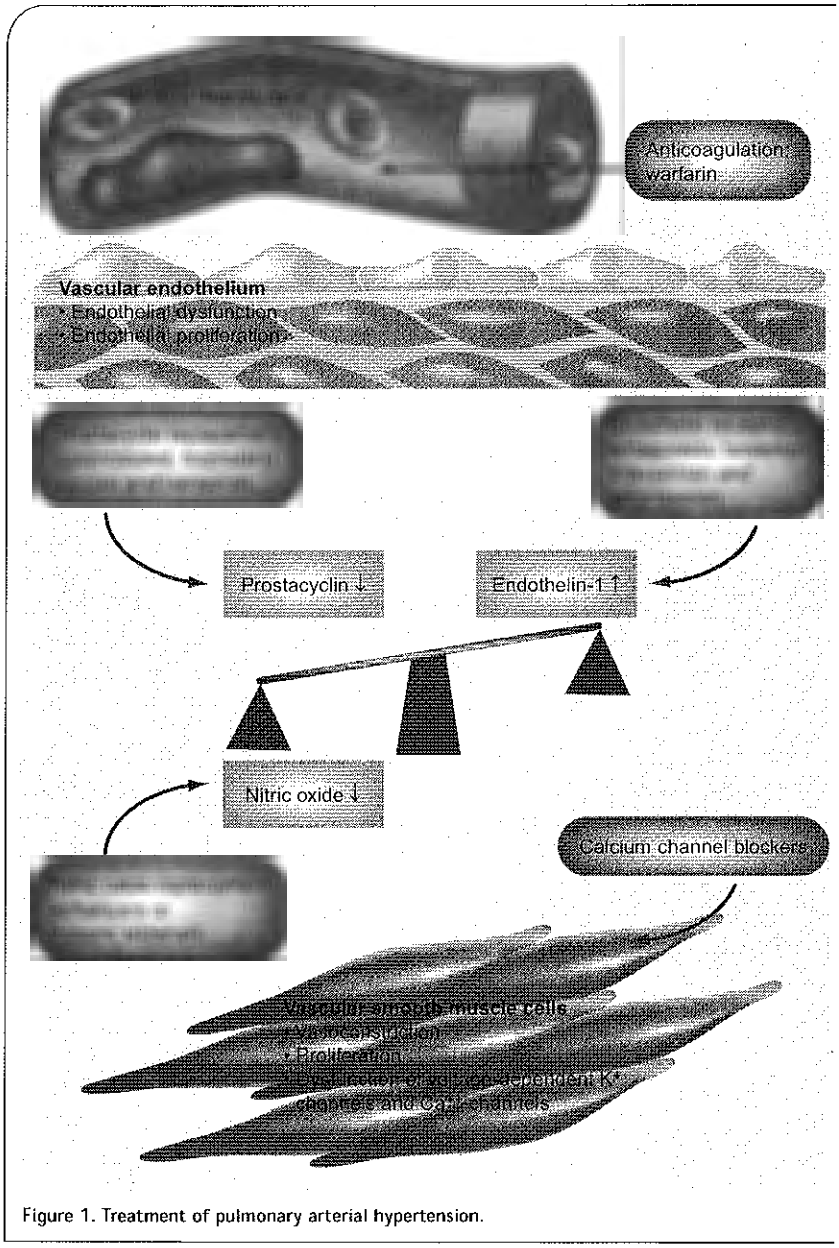

Figure 1. Treatment of pulmonary arterial hypertension.

Conventional treatment

Oral calcium channel blockers

Active vasoconstriction is detectable at right-heart catheterization during acute vasoreactivity testing. Patients who manifest acute vasoreactivity may have a good long-term response to oral calcium channel-blocker therapy [3]. Therefore, testing for acute vasoreactivity is recommended during initial evaluation in all patients with PAH [4]. During right heart catheterization, patients are administered short acting vasodilators such as inhaled nitric oxide (NO), intravenous epoprostenol or intravenous adenosine. Acute vasoreactivity is present if, after vasodilator challenge, the mean PAP decreases by at least 10 mmHg and to less than 40 mmHg, with preserved or increased cardiac output. This response is present in less than 10% of PAH patients, mainly IPAH and PAH associated with anorexigen use [5]. Initiation of oral calcium channel-blocker therapy is restricted to patients who manifest acute vasoreactivity and requires frequent monitoring to document long-term clinical efficacy. Indiscriminate use of oral calcium channel blockers in patients with PAH is strongly discouraged to avoid precipitation of hypotension and heart failure with potentially fatal consequences.

Oral anticoagulation

Although no randomized, double-blind, placebo-controlled trials of anticoagulation were performed in patients with PAH, two retrospective studies and one prospective report in patients with IPAH and PAH associated with anorexigen drug use have suggested improved outcome in patients receiving long-term warfarin therapy [3,6,7]. In the absence of contraindications, IPAH patients should receive long-term anticoagulant therapy, with a goal of keeping the international normalized ratio between 1.8 and 2.5. Some experts extend this recommendation to other forms of PAH, although this is controversial, particularly in cases with an increased risk of bleeding, such as PAH patients with scleroderma (erosive esophagitis), portopulmonary hypertension (gastrointestinal bleed) or congenital heart disease (hemoptysis).

Specific pulmonary arterial hypertension treatment

Basic pathogenesis of pulmonary arterial hypertension

Vascular wall remodeling and proliferation are the hallmarks of pulmonary arterial obstruction in PAH [8]. Central to the pathogenesis of vascular remodeling is the dysfunction of the pulmonary vascular endothelium with an imbalance between endothelial mediators with opposing actions on the pulmonary vasculature [9–13]. There is an overexpression and/or activation of vasoconstricting, mitogenic and prothrombotic factors (endothelin [ET]-1, thromboxane and serotonin), while prostacyclin, NO and heparin-like substances, which promote vasodilatation and have antiproliferative and antithrombotic properties, are decreased. Specific PAH treatment entails either replacing deficient vasodilator factors or inhibiting mediators that induce vasoconstriction and vascular proliferation (FIGURE 1).

Specific pulmonary arterial hypertension therapeutic agents

Recent developments in the management of PAH focus on the introduction of new drugs with different intracellular mechanisms of action and the use of alternative routes of administration. In the USA, the agents approved by the US Food and Drug Administration (FDA) for the specific treatment of PAH are continuous intravenous epoprostenol (prostacyclin and prostaglandin I_2), continuous subcutaneous treprostinil (prostacyclin analog) and oral bosentan (ET receptor antagonist). Agents approved by the European Agency for the Evaluation of Medicinal Products are intravenous epoprostenol, oral bosentan and inhaled iloprost (prostacyclin analog). Other oral drugs recently investigated or currently studied in clinical trials include beraprost, sildenafil, sitaxsentan and ambrisentan.

Expert opinion

Evidence-based management

During the past 5 years, more than 2500 patients with PAH have been studied in a randomized, controlled fashion in more than ten completed major clinical trials. At least nine more randomized, controlled trials are planned or ongoing. TABLES 1–4 summarize the findings of the major clinical trials in PAH [14–36]. Sildenafil, a phosphodiesterase-5 inhibitor with pulmonary vasodilatory action, has also been evaluated in a 3-month double blind, placebo-controlled, multicenter, randomized trial in patients with PAH (63% IPAH, 30% PAH associated with connective tissue disease and 6% PAH associated with surgically corrected congenital heart disease) [37]. This trial included 278 patients with PAH in World Health Organization (WHO) functional Classes II to IV (39% Class II, 58% Class III and 3% Class IV) and evaluated three sildenafil doses (20, 40 and 80 mg three-times daily). The primary end point was the change from baseline in the 6-min walk test (6MWT) distance. There was a significant improvement in the exercise capacity as measured by the 6MWT, in hemodynamics and in WHO class for all three doses studied [37].

Multiple new findings in PAH pathobiology, genetics, diagnosis and therapy were assessed during the Third World Symposium on Pulmonary Arterial Hypertension (Venice, 2003) and proceedings of this meeting were published in a supplement to the Journal of the American College of Cardiology [38]. In addition, the American College of Chest Physicians has recently published evidence-based guidelines for PAH diagnosis and management [39]. Therapeutic choices in PAH depend on the etiopathogenic particularities of the disease and the severity of the functional impairment (FIGURE 2). A new treatment algorithm has been devised based on data from published randomized, controlled trials (FIGURE 3). This algorithm is mainly restricted to patients in WHO functional Classes III and IV and patients with IPAH and PAH due to the scleroderma spectrum of disease, who represented the majority of studied patients. Extrapolation of current recommendations to other PAH patient populations requires caution.

In the face of substantial achievements in the therapeutic armamentarium, PAH remains a disease with particularly poor prognosis, even among treated patients. Untreated IPAH patients from the National Institutes of Health registry had 1-, 3- and 5-year survival rates of 68, 48 and 34%, respectively [2]. Intravenous epoprostenol is the only PAH-specific therapy that has been shown to improve survival in a 3-month, randomized, controlled trial in IPAH [15], while newer drugs have been shown to reduce clinical deterioration during the same time interval [29–31]. IPAH is more responsive to treatment compared with other forms of PAH [21,31,34] and intravenous epoprostenol is still considered the most efficacious therapy available. Retrospective studies of IPAH patients treated with intravenous epoprostenol, demonstrated improved long-term outcome with 1-, 3- and 5-year survival rates of 85, 63 and 55%, respectively [19,20]. Response to available therapy is not universally favorable and there is no cure for PAH. Therefore, there is a continual need for discovery of novel therapeutic strategies.

Table 1. Major randomized controlled clinical trials with intravenous epoprostenol in patients with PAH.

Trial	n	PAH	WHO class (%)			Route	Duration (months)	Dose of active drug achieved (ng/kg/min)	Control*	Primary end point	Treatment effect						Ref.
			II	III	IV						6MWT (m)	H/dyn	WHO class	Symptoms	QOL	Survival	
Rubin (1990)	24	IPAH	9	65	26	Iv.	2	N/A	Conv. therapy	H/dyn	+45 (mean)	Better	N/A	Better	N/A	No change	[14]
Barst (1996)	81	IPAH		75	25	Iv.	3	9.2	Conv. therapy	H/dyn	+47 (mean)	Better	Better	Better	Better	Better	[15]
Badesch (2000)	111	SPAH	5	78	17	Iv.	3	11.2	Conv. therapy	6MWT	+94 (median)	Better	Better	Better	N/A	No Change	[16]

*None of these studies were placebo-controlled for ethical reasons; patients in the active group received intravenous epoprostenol in addition to conventional therapy, while the control group was represented by patients receiving conventional therapy alone.
6MWT: 6-min walk test; Conv.: Conventional; H/dyn: Hemodynamics; IPAH: Idiopathic pulmonary arterial hypertension; Iv.: Intravenous; N/A: Not applicable; PAH: Pulmonary arterial hypertension; QOL: Quality of life; SPAH: Scleroderma pulmonary arterial hypertension; WHO: World Health Organization.

Table 2. Other clinical trials with intravenous epoprostenol in patients with PAH.

Trial	Findings	Comments	Ref.
Barst 1994 Shapiro 1997	Effect on survival	Improved long-term survival in IPAH patients treated with epoprostenol compared with historic controls	[17,18]
Retrospective reviews: McLaughlin (2002) Sitbon (2002) Kuhn (2003)	Long-term outcome (3–5-year follow-up) and predictors of response to therapy	Baseline hemodynamics and right-ventricular function predict response to therapy. Patients who improve at 3–12-month follow-up have better long-term prognosis. Patients with scleroderma PAH have worse long-term prognosis, even if treated with intravenous epoprostenol. Treated patients had better survival compared with historic controls or to expected survival derived from the NIH equation	[19–21]
McLaughlin (1998)	Insights into mechanism of action	With epoprostenol, long-term decrease in PVR is more pronounced compared with the acute response, suggesting an effect on pulmonary vascular remodeling	[22]
Rich 1999	Dose adjustment	Intravenous epoprostenol rate should be adjusted to avoid deleterious hyperdynamic cardiovascular effects	[23]
Case series: McLaughlin 1999 Robbins 2000 Horn 2000 Krowka 1999 Rosenzweig 1999	Use of intravenous epoprostenol in other forms of PAH	Hemodynamic and symptomatic improvement with intravenous epoprostenol in patients with other forms of PAH	[24–28]

IPAH: Idiopathic pulmonary hypertension; NIH: National Institutes of Health; PAH: Pulmonary arterial hypertension; PVR: Pulmonary vascular resistance.

Alternative approaches to therapy with currently available drugs

Several therapeutic strategies aimed at improving the control of the disease or the risk–benefit ratio of the treatment were employed in small clinical trials and retrospective series.

Combination therapy

Since multiple and complex pathogenetic mechanisms are implicated in the development and progression of pulmonary hypertension, various combinations of drugs with already proven benefit may represent alternative therapeutic strategies in PAH. Prostacyclins, ET receptor antagonists and drugs acting through a NO-dependent pathway (such as sildenafil, a phosphodiesterase inhibitor) have different intracellular signal transduction pathways with potential synergistic effect. A small multicenter clinical trial on the combined use of epoprostenol and bosentan, initiated simultaneously, suggested that bosentan may provide a small additional hemodynamic benefit to severe PAH patients who require epoprostenol treatment [40]. In retrospective studies of patients on chronic epoprostenol or treprostinil, the addition of bosentan was safe and increased vasodilatory efficacy, which allowed for prostacyclin dose reduction or even discontinuation [41–43]. Small series have demonstrated acute and chronic benefit from combined use of various prostacyclins (intravenous epoprostenol, subcutaneous treprostinil and inhaled iloprost) and oral sildenafil [44–47]. A multicenter trial investigating the effect of combined oral sildenafil and intravenous epoprostenol is currently ongoing. The possibility of unexpected interactions between these drugs and the absence of efficacy and safety data in large clinical trials preclude recommendation of routine use of combination PAH therapy.

Transition from intravenous epoprostenol to oral bosentan or subcutaneous treprostinil

Continuous intravenous epoprostenol administration, although known to improve exercise capacity, symptoms, hemodynamics and right-ventricular function in severe PAH and to offer survival benefit in IPAH patients, requires a complicated delivery system. It may be associated with potentially life-threatening side effects, such as line-related sepsis and thrombosis or rebound pulmonary hypertension and acute right heart failure from inadvertent discontinuation. Newer PAH drugs have also been shown to have beneficial effects on exercise capacity, symptoms, hemodynamics and clinical events in patients with severe PAH. Small published series from centers with extensive experience in PAH management have demonstrated the feasibility and safety of transitioning selected patients from intravenous epoprostenol to other therapeutic alternatives, such as subcutaneous treprostinil and oral bosentan [43,48,49]. In addition, a current multicenter trial is evaluating the safety of transitioning PAH patients from intravenous epoprostenol to subcutaneous treprostinil. At the present time, however, the authors caution against indiscriminate discontinuation and substitution of intravenous epoprostenol with other available drugs. There is no guarantee that, in the case of clinical deterioration, reinstitution of previous therapy will reverse disease progression, which may have fatal consequences. Larger clinical investigations are warranted to establish enrollment criteria and transitioning methods to assure both the efficacy and safety of such an approach.

Use of alternative methods of delivery

The main difficulty with subcutaneous treprostinil therapy is the development of pain and reactions at the infusion site [29]. To avoid this side effect of treprostinil, intravenous

and inhalatory routes of administration were recently investigated. Treprostinil has a longer half-life compared with epoprostenol, which decreases the risk of rebound pulmonary hypertension and right heart failure in the case of abrupt discontinuation. In comparison to intravenous epoprostenol, intravenous treprostinil administration alleviates the need for a large infusion pump, drug reconstitution and the use of ice packs. Continuous intravenous treprostinil administration has been evaluated for safety and efficacy in a multicenter trial, both as transition from intravenous epoprostenol and as *de novo* therapy [50]. Intravenous treprostinil was associated with an improvement in exercise performance and hemodynamics, with added advantages of safety and convenience [50]. It has recently received FDA approval for this route of administration.

In a recent report from Germany, inhaled treprostinil demonstrated substantial pulmonary vasodilatory efficacy in acute administration, as well as symptomatic and functional benefit in chronic use in a small number of PAH patients [51].

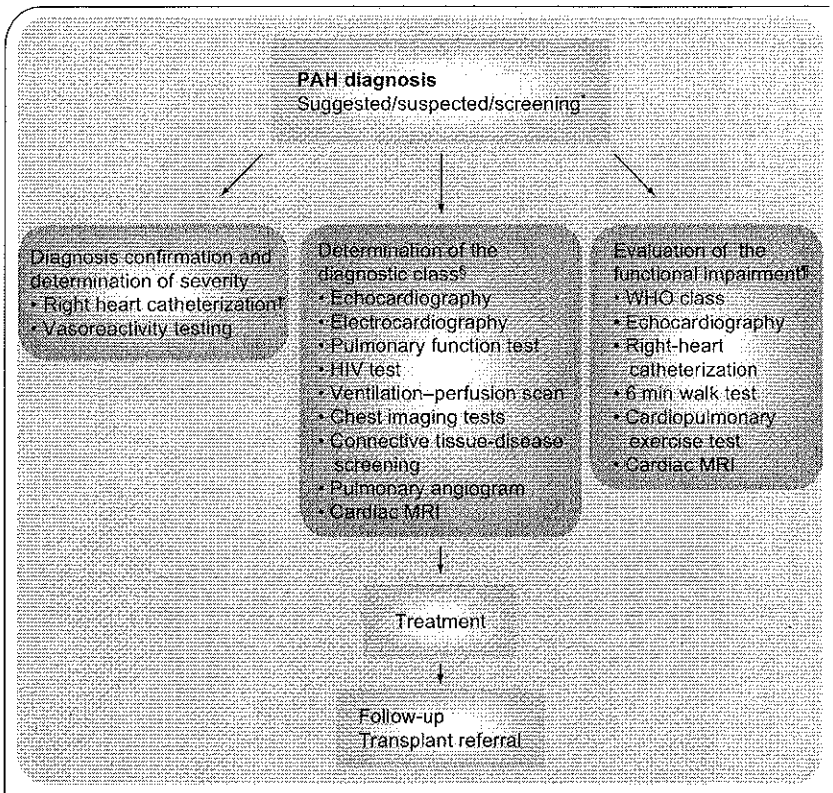

Figure 2. PAH management. Investigations used to characterize the disease process.
*Strongly consider early referral to specialized centers.
†Right heart catheterization is required to confirm the diagnosis of PAH. Vasoreactivity testing by inexperienced operators may place patients at unduly increased risk.
§Type and extent of work-up varies on individual basis, but all patients with suspected PAH diagnosis should undergo a battery of essential tests, which include echocardiography, chest radiography, ventilation-perfusion scan, HIV testing and screening for connective tissue disease, and pulmonary function test with oximetry.
¶Prior to institution of therapy, it is essential to evaluate functional parameters with prognostic significance, such as exercise capacity and right-ventricular function.
MRI: Magnetic resonance imaging; PAH: Pulmonary arterial hypertension; WHO: World Health Organization.

Head-to-head comparisons between currently available drugs

With the advent of multiple therapeutic options for PAH patients, questions of relative efficacy, safety and therapy of choice are likely to arise. Head-to-head comparison trials are the most meaningful and accurate method of detecting efficacy and safety differences among various PAH treatments with already proven benefit. Experimental data from tissue culture and animal studies are not necessarily predictive of human response, and data from individual clinical trials cannot be directly compared. An example is represented by ET receptor antagonists. There are two types of ET receptors: ET_A receptors, located in the vascular smooth muscle cells, and ET_B receptors, found on both endothelial (ET_{B1} subtype) and smooth muscle cells (ET_{B2} subtype) [52]. ET binding to receptors located on the vascular smooth muscle cell (ET_A and ET_{B2}) induces vasoconstriction and smooth muscle-cell proliferation [53,54]. The relative contribution of ET_A and ET_{B2} receptors to the ET-mediated vasoconstriction depends on the species, experimental conditions and vascular bed studied. ET_{B1} receptors mediate vasodilatation and are responsible for ET clearance from the circulation [55]. Three ET receptor antagonists were recently evaluated in PAH trials: bosentan, a mixed ET_A/ET_B receptor antagonist already approved for clinical use, and the selective ET_A receptor antagonists, sitaxsentan and ambrisentan. Theoretically, selective blockade of the ET_A receptors may be more advantageous compared with nonselective ET_A/ET_B antagonism, by preserving ET_{B1}-mediated vasodilatation and ET clearance. However, in isolated pulmonary arteries and in animal models, combined ET_A/ET_B receptor blockade was superior to selective ET_A antagonism in reducing vasoconstriction and in improving right-ventricular hypertrophy and animal survival, respectively [56,57]. In randomized clinical trials in patients with PAH, all three ET receptor antagonists improved exercise capacity, hemodynamics, symptoms and WHO functional class [33–36]. It is impossible to accurately compare their relative efficacy on the basis of the available trials, because the PAH patient populations and trial designs were different. However, conducting large-scale head-to-head comparison studies would require more refined methodology and increased

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.