Background: Sildenafil, a short-acting phosphodiesterase-5 inhibitor (1), is safe and may benefit patients with primary pulmonary arterial hypertension (2– 8). However, it requires many daily administrations. We describe a patient with end-stage primary pulmonary arterial hypertension who improved while taking tadalafil, a long-acting phosphodiesterase-5 inhibitor (9). Case Report: A 72-year-old woman was hospitalized for progressive cardiopulmonary failure. Five years earlier, primary pulmonary arterial hypertension was diagnosed and the patient was hospitalized for hydropic decompensation and hypoxemia. Since then, she had been receiving permanent oxygen therapy and had also taken digoxin, amlodipine, furosemide, potassium canrenoate, and acenocoumarol. At the most recent hospitalization, the patient had dyspnea (New York Heart Association class IV) and 4 pitting edema of the legs up to the thighs, which had progressed over the previous 3 months. The patient's blood pressure was 110/70 mm Hg, her pulse was 102 beats/min, her respiratory frequency was 32 breaths/min, and her temperature was 36.8 °C. During oxygen therapy (fraction of inspired oxygen, 35%), arterial PO2 was 55 mm Hg. Electrocardiography showed sinus rhythm and right ventricular hypertrophy. Chest radiography showed cardiomegaly without signs of pulmonary edema. Doppler echocardiography showed dilation of right chambers with severe tricuspidal regurgitation and estimated peak systolic pulmonary pressure of 105 mm Hg. Chest spiral computed tomography excluded pulmonary arterial embolism. Despite administration of intravenous diuretics and optimization of oxygen therapy, the patient's condition did not substantially improve. Epoprostenol therapy was attempted but was stopped because the patient had symptomatic arterial hypotension despite a low infusion rate. Therefore, with the patient's informed consent, we administered tadalafil (20 mg orally every other day) in addition to background therapy. After 2 weeks of tadalafil therapy, the patient improved remarkably (New York Heart Association class III); the only untoward effect was slight arterial hypotension that promptly regressed with amlodipine withdrawal. Blood pressure was 116/66 mm Hg, pulse rate was 84 beats/min, and respiratory frequency was 20 breaths/min. Leg edema was remarkably reduced. The patient's arterial PO2 was 70 mm Hg during oxygen therapy (fraction of inspired oxygen, 0.28%). Doppler echocardiography showed a notable reduction of the estimated peak systolic pulmonary pressure (80 mm Hg). Accordingly, doses of intravenous diuretics were progressively decreased and were administered orally. The patient was discharged and referred to outpatient care. After 6 months of tadalafil treatment, the patient's functional status improved (New York Heart Association class II to III). Physical examination showed stable normotension, further reduction of heart rate and respiratory frequency, and disappearance of leg edema. Arterial PO2 during oxygen therapy (fraction of inspired oxygen, 0.24%) remained stably above 70 mm Hg. Doppler echocardiography showed progressive reduction of estimated peak pulmonary systolic pressure (up to 65 mm Hg). Accordingly, we reduced oral doses of diuretics and prescribed oxygen therapy only during physical activity. Table. Overall Effects of Low-Dose Steroids Based on Corticotropin Stimulation Testing Results Outcome Nonresponders (Events/Total Patients) Responders (Events/Total Patients) Control Group, % (n/n) Steroid Group, % (n/n) P Value Control Group, % (n/n) Steroid Group, % (n/n) P Value Death 63 (83/132) 51 (63/123) 0.05 57 (32/56) 49 (34/69) 0.2 Shock reversal 39 (48/123) 53 (63/118) 0.03 44 (20/45) 56 (30/54) 0.2 Letters www.annals.org 2 November 2004 Annals of Internal Medicine Volume 141 • Number 9 743 Discussion: By stabilizing guanosine 3,5-cyclic monophosphate in vascular smooth-muscle cells of the pulmonary artery, sildenafil prolongs the effect of endogenous vasodilators. Through this mechanism, it reduces mean pulmonary artery pressure and the pulmonary- to-systemic vascular resistance ratio and improves the overall ventilation–perfusion mismatch, arterial oxygenation, and functional capacity (3– 8). However, because it has a half-life of about 4 hours (1), sildenafil requires many daily administrations, which in the long term may compromise treatment adherence and may be costly. In our patient with end-stage primary pulmonary arterial hypertension, we observed that long-term treatment with tadalafil, which has a half-life of about 18 hours, was safe and greatly improved pulmonary hemodynamics and arterial oxygenation (Figure). These improvements were paralleled by a striking improvement in clinical and functional status. Besides confirming the efficacy of phosphodiesterase- 5 inhibitors in treatment of

primary pulmonary arterial hypertension, this finding may alert physicians to the possibility that tadalafil may be mo