Abstract

Pulmonary arterial hypertension (PAH) is a progressive and often fatal disease. Currently available pharmacotherapies are often suboptimal when used singly, due to either a poor clinical response or a complication from the therapy. As a consequence, transitioning patients from one therapy to another or adding a therapy is a frequently encountered clinical conundrum. This chapter examines the rationale and limited data surrounding transitioning patients from one pharmacotherapy to another and combining individual therapies to produce an improvement in clinical outcomes. Much of the research discussed deals with animal models used to test combination therapies, as there are few clinical trials in human subjects, but this is rapidly changing, as a number of controlled trials are currently either in the planning stages or in progress. Transitions clearly have a role in enhancing the convenience and safety of pulmonary hypertension therapy for some patients. Combination therapy looks promising and may well represent the future of PAH pharmacotherapy.
1. INTRODUCTION

Prior chapters in this volume have detailed advances in the pharmacotherapy of pulmonary arterial hypertension (PAH), focusing on individual classes of agents. Although these therapies have significantly improved the functional status, quality of life, and, in the case of epoprostenol, survival of PAH patients, responses are usually partial and less than desired. On average, patients with severe pulmonary hypertension experience improvement in pulmonary hemodynamics, but pulmonary arterial pressures remain severely elevated. These agents also have potential adverse side effects and risks, and loss of efficacy may occur after an initial favorable response. This has led investigators to consider switching to an alternative safer or potentially more effective therapy or to ask whether combinations of agents may lead to greater and more durable therapeutic responses than individual agents. An emerging literature in both experimental models and clinical settings is examining these questions. This chapter first discusses the rationale for and information on the transition from one agent to another and then weighs the evidence supporting various combinations of agents. Presently, evidence on many of the possible transitions and combinations is lacking, and our discussion highlights areas where additional study is needed.

2. TRANSITIONS

2.1. Rationale

The presently approved therapies for PAH in the United States have significant limitations. The best established and probably most effective agent, epoprostenol, necessitates intravenous administration and has a half-life of minutes, posing the risks of intravenous catheter-related sepsis and sudden hemodynamic deterioration in the event of abrupt discontinuation. The subcutaneous prostacyclin treprostinil is also effective but causes infusion site pain in virtually all patients, reaching intolerable levels in a minority. The only endothelin-receptor antagonist thus far approved by the Food and Drug Administration, bosentan, causes at least threefold elevations in liver transaminases in approximately 10% of patients (1) When these complications occur,