New Directions in Pulmonary Hypertension Therapy

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Abstract

Great progress in the understanding of the pathogenesis of as well as the therapy for pulmonary hypertension has been made in the last 20 years, but many challenges remain. Combinations of prostanoids, endothelin antagonists, and phosphodiesterase inhibitors are seeing increasing use, and clinical trials currently underway should identify which combinations work best. Nebulized treprostinil, selective endothelin-A antagonists, and newer phosphodiesterase inhibitors may offer advantages and expand our therapeutic armamentarium in the near future. Clinical trials of statins, SSRIs, VIP, potassium channel activators, or antiplatelets are also ongoing or are likely to commence in the near future. Agents that interrupt signaling pathways such as Rho kinases and tyrosine kinases also show promise. The biological plausibility, availability,
and relative safety of these newer agents make it tempting to prescribe them now, particularly when faced with gravely ill patients. However, these and all future therapies require proof of efficacy and safety from properly conducted clinical trials before widespread use can be advocated. Too many patients are still severely limited by and dying of pulmonary arterial hypertension to warrant therapeutic complacency at this time. While we await proof of safety and efficacy, we must continue to enroll patients in clinical trials.

Key Words: future directions of pulmonary hypertension; Rho kinase inhibitors; tyrosine kinase inhibitors; potassium channels; growth factors; serotonin; serotonin transporter; apoptosis.

1. INTRODUCTION

This is an exciting time for the pulmonary hypertension community. The “holy grails” in the management of pulmonary arterial hypertension—early recognition, side effect-free targeted treatment, robust tools for noninvasive follow-up—are being actively and successfully pursued. Preceding chapters have reviewed the progress made in our understanding of the pathobiology of pulmonary arterial hypertension (PAH) and the targeted therapeutic options that are currently available. Progress in the management of lung transplantation, the role of atrial septostomy, and also the intriguing promise shown by statin drugs and nitric oxide donors has also been outlined. Here we propose to outline the progress that we anticipate will continue to improve clinical outcomes for patients with PAH.

Progress in our understanding of the abnormal pathophysiological processes that lead to pulmonary arterial hypertension, and the mechanisms by which we may influence these, has led to the recognition and application of the currently available targeted therapies for PAH. Pursuing this further by completely dissecting the abnormal cellular and molecular pathways at the heart of PAH, recognizing therapeutic targets within these, and exploring these therapies in model systems is an obvious direction for pursuing new therapies. Recent developments have identified a number of possible targets. It seems timely to review these and suggest the ones we consider most promising. Progress in the development of novel therapeutic modalities (e.g., gene transfer, cardiac pacing strategies) and new drugs for other diseases that may be applicable to the management of PAH are also discussed.

Impediments to the exploration of new PAH therapies are inevitable. The worldwide patient pool is limited and has been extensively utilized