

## EDITORIALS



### Introduction to Clinical Therapeutics

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Five years ago, the *Journal* introduced Clinical Practice, a series of review articles intended to provide practical guidance in the diagnosis, evaluation, and management of clinical problems at the interface of primary and specialty care. Our goal was to combine in a concise format a critical review of the literature with practical advice about management. Authors are chosen for their established expertise in a subject area and asked to provide clinical recommendations, specifying whether these are supported by rigorous data.

In this issue of the *Journal*, we introduce a related series of review articles entitled Clinical Therapeutics. Like Clinical Practice articles, Clinical Therapeutics articles will be authored by established experts in the field and are intended to be concise, practical, and directed primarily to a clinical audience. Rather than focusing on a clinical problem and the various approaches to management, each Clinical Therapeutics article will focus on a specific therapy for a given clinical problem; topics covered will include not only medications, but also devices and procedures.

The format of Clinical Therapeutics will be modeled on that of Clinical Practice. Each article will begin with a clinical vignette, followed by a brief description of the general clinical problem and of the particular therapy to be discussed. Subsequent sections will discuss the effects of the therapy, evidence from the medical literature (in particular, data from clinical trials when available) that supports or fails to support its use, a detailed description of how the therapy is used, adverse effects, and areas of uncertainty. As in the Clinical Practice series, a section on guidelines from major professional societies (if any) will be included, and each article will end with the author's own recommendations.

Clinical Therapeutics articles will complement the related Drug Therapy series. Drug Therapy articles, which are considerably longer and more detailed than those planned for Clinical Therapeutics, are intended to provide a comprehensive discussion of the pharmacology of an agent, or class of agents, including details of the basic science underlying the therapeutic effects. The Clinical Therapeutics series will provide a much briefer overview that will focus primarily on providing the practical information most relevant to patient care.

The need for practical guidance in the use of therapies has steadily been increasing. Rapid growth in the fields of genetics, immunology, molecular biology, and other basic sciences has expanded the range of potential therapeutic targets; advances in biotechnology, bioengineering, and technology transfer have accelerated the development of new therapeutic approaches and ideas; and decreases in the duration of regulatory review by the Food and Drug Administration have facilitated the more rapid approval of new therapies and their introduction into the clinical arena. Acknowledging the challenges inherent in keeping abreast of these rapid advances, we will keep the focus of the Clinical Therapeutics series on relatively new drugs, devices, and procedures. We will also include reviews of established therapies that remain fundamental to the clinician's armamentarium, however, especially when new data are available or controversy exists regarding clinical use.

We hope that readers of the *Journal*, particularly those who are active clinicians, will find the articles in the Clinical Therapeutics series to be practical and reliable guides for the use of therapeutic agents in patient care. We encour-

age readers to recommend topics of interest and have established a separate e-mail address (clinicaltherapeutics@nejm.org) for readers to

submit their ideas or comments regarding the new series.

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## Cyclophosphamide for Scleroderma Lung Disease

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Clinically significant interstitial lung disease affects patients with systemic sclerosis (scleroderma) and is a cause of morbidity and mortality in approximately 40 percent of these patients.<sup>1</sup> Management of this condition remains difficult and controversial.<sup>2,3</sup> In this issue of the *Journal*, Tashkin and colleagues<sup>4</sup> report the results of a multicenter, placebo-controlled trial of oral cyclophosphamide in patients with well-defined, symptomatic scleroderma-related interstitial lung disease and alveolitis. They document small but statistically significant improvements in lung function and symptoms with cyclophosphamide administered over the course of one year — the first positive results of a placebo-controlled trial in this field.

How should these results be translated into clinical care? In this trial, a change in the expected annual decline in the forced vital capacity (FVC, expressed as a percentage of the predicted value) was the primary end point. Although the dropout rate was higher than anticipated (approximately 33 percent of the patients did not complete one year of cyclophosphamide therapy), the statistical analysis allowed the calculation of longitudinal changes in the FVC in the majority of the patients. This analysis showed an adjusted difference of 2.53 percent in the FVC favoring cyclophosphamide ( $P=0.03$ ). This modest difference was less than that anticipated by the investigators — a 9 percent annual decline in the FVC, as derived from published case series. In the majority of the patients in the two study groups, the change in the predicted value of the FVC was less than 5 percent, which is close to the expected natural variability in the percentage of the predicted FVC.<sup>5</sup> In contrast, no significant treatment-related difference was noted in the diffusing capacity for carbon monoxide, a measure that is considered by some to be a better longitudinal marker of disease progression than the change in the FVC.<sup>2,6</sup> The explanation of this modest effect remains conjectural, but the size of the effect may reflect the patient population studied.

Previous investigators have suggested that progressive scleroderma-related interstitial lung disease is more likely to develop in patients with low pulmonary function at presentation or rapid disease progression during the first five years after the onset of the first scleroderma-related symptom.<sup>7</sup> In the patients in the current trial, the duration of the symptoms was longer and the physiological deficits fewer than in patients included in a previous case series that showed a more robust physiological effect of cyclophosphamide therapy.<sup>8</sup> In this trial, greater improvement with cyclophosphamide was observed in patients with more fibrotic abnormalities at baseline on high-resolution computed tomography than among those with fewer fibrotic abnormalities. These data provide a hint regarding which patients with scleroderma-related interstitial lung disease may be good candidates for treatment with cyclophosphamide.

A beneficial effect of cyclophosphamide therapy was also supported by several statistically significant differences in the secondary end points, even though these differences were also small. Changes in scores for skin thickness favored cyclophosphamide, although the magnitude of the change in the scores was limited, as compared with the inherent variability of this outcome measure.<sup>9</sup> In addition, changes in the severity of dyspnea, as assessed according to the transitional dyspnea index, favored cyclophosphamide. Given that the transitional dyspnea index was administered by nurse coordinators with access to other information, which could introduce a bias, and the limited validation of this index in interstitial lung disease, the results regarding dyspnea should be interpreted with caution.

An important consideration when interpreting these limited therapeutic benefits of treatment with cyclophosphamide is the need for a thorough assessment of the risks of the drug, arguably the most toxic immunosuppressive agent currently used to treat autoimmune diseases. The duration