Remodeling the therapeutic pyramid:
evolving therapeutic strategies for rheumatoid arthritis

KENNETH R. WILSKE

Head, Section of Rheumatology and Clinical Immunology, Virginia Mason Medical Center and Clinical Professor of Medicine, University of Washington, School of Medicine, 1100 Ninth Avenue, Seattle, WA 98101, USA

Abstract—The approach to treatment of rheumatoid arthritis (RA) is undergoing dramatic change. With a prevalence of 1% of the general population, RA is the most common cause of disability that is potentially reversible if correct management of the disease is begun in the early phases. While the traditional therapeutic pyramid model has been in place for the past 25 years, evolving therapeutic strategies suggest that it is appropriate primarily for patients with benign synovitis, and an inverted pyramid is necessary to treat aggressive synovitis, control inflammation early and to prevent rapid joint destruction, disability and early death. Important principals underlying the remodeling of the therapeutic pyramid and evolving therapeutic strategies include: identifying patients with benign and aggressive synovitis; early control of inflammation to stabilize functional status at near normality; need for combination therapy in aggressive synovitis until a major breakthrough of 'magic' bullet becomes available; awareness that drugs that control inflammation in a more fundamental manner, such as disease-modifying anti-rheumatic drugs, are more effective in pain control and disability than non-steroidal anti-inflammatory drugs; and, most importantly, education of patients, primary and managing care physicians, health maintenance organizations, insurance companies, and government officials that two-thirds of the cost of RA lies in the complications of the disease and that providing resources for early aggressive therapy is a good investment for all. Successful treatment of rheumatoid arthritis is best accomplished by a coordinated team of a consultant rheumatologist and a managing primary care physician. Much like an early consultation with an oncologist when cancer is suspected, an early consultation with a rheumatologist can help separate benign and aggressive synovitis. If the latter, the rheumatologist can help identify important co-morbid conditions and recommend appropriate therapy. Follow-up programs can then be outlined to maintain control of inflammation at all times, utilize appropriate pharmacologic and non-pharmacologic physical and occupational therapy modalities for mechanical pain, and highlight potential toxicities to be monitored. This program, initiated early, will help prevent administration of toxic drugs to patients with benign synovitis. And, just as important for patients with aggressive synovitis, this strategy is designed to reduce the high incidence of morbidity and mortality and the costly episodes of hospitalizations and salvage surgery that can be so devastating to patients and their families.

Key words: Rheumatoid arthritis; therapeutic pyramid; therapeutic strategy.
INTRODUCTION

The approach to the treatment of rheumatoid arthritis (RA) is undergoing dramatic change. This is based on accumulating information which shows that patients with aggressive synovitis, usually rheumatoid factor and/or HLA DR ‘disease-epitope’ positivity (Caucasian 0401, 0404, 0101; Japanese 0405; Yakima Indians 1402; Israeli Jews 0101) [1, 2], have a poor prognosis with 50% of these patients becoming disabled in the first 5–10 years of disease, 90% by 20 years and life expectancy shortened by 5–10 years [3–5]. Joint damage leading to this disability occurs in an early and accelerated fashion with 90% of patients having joint damage in the first 2 years of disease, 50% in the first 6–12 months after diagnosis [6–8].

The financial impact on a society is significant. This disease has been estimated to occur in 1–2% of the general population and may be the most common cause of disability that is potentially reversible if correct management of the illness is begun early. Using conservative data from the Health Interview Survey, a national probability sample of the non-institutionalized population in the US, from 1989 through 1991, an average of 1.74 million persons met the criteria for RA. These individuals made 19.65 million physician visits at a cost of about $1.5 billion in 1994 terms, hospital admissions numbered 540,000 accounting for $3.2 billion, with wage losses amounting to $3.98 billion. Thus, the cost of complications of RA, i.e. hospitalizations, operations and lost wages, far exceed the cost of patient visits to physicians and emphasize that ‘an ounce of prevention is worth a pound of cure’ [9].

In considering these outcomes and looking at new therapeutic strategies for the treatment of disabling RA, it is important to keep in mind that aggressive RA is not benign or indolent, sustained remission is rare and joint damage occurs early; the inflammation reaction is complex and currently available drugs used singly have not controlled it satisfactorily for a sufficient time; the efficacy:toxicity ratio of second- and third-line drugs appears superior to the traditional first-line drugs, and, most importantly, patient outcomes appear best with early treatment and sustained control of inflammation.

TRADITIONAL THERAPY

The traditional pyramid approach (Fig. 1) [10], sequential use of single drugs, usually beginning with a salicylate or one of the many non-steroidal anti-inflammatory drugs (NSAIDs), then progressing up to second- and third-line disease-modifying anti-rheumatic drugs (DMARDs) such as gold preparations, chloroquine medications, penicillamine or sulfasalazine, has been based on a risk–benefit concept that the prognosis of RA is good and that the disease can be controlled with a program aimed at avoiding drug toxicity. This model has evolved from epidemiologic studies in which up to two-thirds of patients meeting the 1958 American Rheumatism Association (ARA) criteria for ‘definite or probable RA’ had no clinical evidence of disease when examined 3–5 years later [11, 12]. The resulting view of RA as...