WILLIAM S. WILKE, MD, EDITOR

Highlights from medical grand rounds

COMBINATION THERAPY FOR RHEUMATOID ARTHRITIS: NEW PARADIGMS OF TREATMENT

The usefulness of the "therapeutic pyramid" as a model for traditional management of rheumatoid arthritis (RA) has been recently questioned. This paradigm is based on the disease model of a slowly progressive, relatively benign process that can be readily controlled with monotherapy. Recent evidence contradicts this perception. Long-term prospective observational studies have suggested that despite monotherapy, joint destruction and functional disability progress in nearly all patients. Indeed, this progression is most rapid during the first 2 years after diagnosis. In addition, not only does RA produce disability, it also affects longevity. RA at its worst results in a mortality rate similar to that of stage IV Hodgkin's disease.

MONOTHERAPY

Monotherapy has been shown to be of limited efficacy in the treatment of RA. The majority of patients who are prescribed a single agent are no longer taking the drug after 3 years.

COMBINATION THERAPY

On the other hand, a number of prospective and retrospective studies have suggested that combinations of disease-modifying drugs are well tolerated and more efficacious than higher doses of a single agent. This is especially true if combination therapy is introduced within the first year or two after diagnosis.

Of the various combinations tested, methotrexate (MTX) plus azathioprine (AZA) plus hydroxychloroquine (HCQ) was well tolerated and more effective than any one agent alone. Other studies suggest that MTX plus auranofin (AUR), MTX plus sulfasalazine (SSZ), SSZ plus d-penicillamine (DPN), and MTX plus parenteral gold are useful combinations. The combination of HCQ and DPN has not been shown to be useful and, in fact, may result in mutual drug antagonism. In general, however, the superiority of combination therapy over monotherapy has been difficult to prove in controlled trials.

MEASURING DISEASE ACTIVITY AND FUNCTIONAL IMPAIRMENT

It is now clear that acute disease activity in RA can be accurately measured using both subjective and objective parameters. Subjective parameters include the duration of morning stiffness, the onset from awakening to fatigue, and an estimation of joint pain using a visual analog scale. Semi-objective measures include the sum of swollen tender joints and the patient's global assessment. The most objective measures of active disease include acute-phase reactants (Westergren sedimentation rate, C-reactive protein), hemoglobin concentration, and platelet counts.

Function can also be measured by tests easily performed in the office. These include grip strength using a modified sphygmomanometer, the time to walk 50 feet, and the time to button a standard vest. Standardized questionnaires that further define function, such as the Health Assessment Questionnaire, are also useful. Preliminary data suggest that long-term control of the acute-phase reactants and joint count results in improvement in the grip strength and Health Assessment Questionnaire scores. Improvement in these "independent" variables that define the biologic activity of the disease then becomes a goal of therapy and should be achieved early in the course of the disease.

NEW PARADIGMS OF THERAPY

A number of untested paradigms have been suggested to replace the therapeutic pyramid. Wilske and Healey have proposed the "step-down bridge." In this paradigm, patients are given a medium dose of pred-

nisone (10 to 20 mg/day). Patients in whom disease is not suppressed or patients in whom prednisone can not be tapered to lower doses after 1 month are given a combination of agents including MTX, parenteral gold, AUR, and HCQ. As disease is controlled, the most dangerous drugs are withdrawn in the hope of achieving maintenance control with the less toxic medications, such as HCQ or AUR. At the present time, 54 patients have been entered into this paradigm, and those with disease duration of less than 2 years have generally fared very well. Unfortunately, reduction to monotherapy alone has not been possible.

We have proposed the "graduated-step" paradigm. In this model, immediately after diagnosis is established, patients are numerically staged as having mild, moderate, or severe disease. Staging is based on the presence of prognostic factors and the level of disease activity. Those with mild disease receive HCQ and nonsteroidal anti-inflammatory drugs. Patients with moderate disease receive those drugs and may also be given a second disease-modifying agent, such as AUR, SSZ, or MTX. These patients may also be given low doses of prednisone. Patients with severe disease may be given up to three disease-modifying agents, including the three previous agents and DPN, parenteral gold, or AZA, at their initial visit. Disease control is maintained by applying a disease activity index at subsequent visits designed to control acute-phase reactants and limit the number of swollen tender joints to four or less. At this time, 16 patients have been entered into the paradigm and analysis is underway.

AN ESTIMATE OF THE EFFECT OF THE GRADUATED-STEP PARADIGM

Because the graduated-step paradigm is based on the style of treatment for RA in the Department of Rheumatic and Immunologic Disease at The Cleveland Clinic Foundation over the past 10 years, an estimate of the effectiveness of the paradigm was possible. We retrospectively analyzed the medical records of 34 consecutive RA patients seen in the department. We then compared their long-term outcome with existing series in the literature that show declining grip strength and functional capacity over time. The Westergren sedimentation rate was maintained below 30 mm/hour for most of our patients, and the joint count hovered around five during the period of treatment. Rather than falling, the mean grip strength of our patients improved and nearly doubled from the initial visit to the final visit, with a mean observation period of 8.3 years. Grip-strength improvement, as in other studies, was accompanied by improvement in functional class.

Although these retrospective data are not conclusive, they suggest that there is at least a subset of patients with RA who tolerate aggressive combination therapy and whose outcome is considerably better than has been previously reported.

CONCLUSION

It is unlikely that one therapeutic strategy or a single treatment modality will prove best for all patients with RA. A variety of therapeutic approaches is necessary. These approaches should emphasize early control of the biologic activity of the disease, which should result in improved function. These attempts at treatment should be performed as part of prospective, long-term, carefully documented trials, designed so that future analysis can determine which regimens are most effective and least toxic.

WILLIAM S. WILKE, MD
Department of Rheumatic and Immunologic Disease
The Cleveland Clinic Foundation

SUGGESTED READING

Dawes PT, Fowler PD, Clarke S, Fisher J, Lawton A, Shadforth MF. Rheumatoid arthritis: treatment which controls the c-reactive protein and the erythrocyte sedimentation rate reduces radiologic progression. Br J Rheumatol 1986; **25**:44–49.

Paulus HE. Current controversies in rheumatology: the use of combinations of disease-modifying anti-rheumatic agents in rheumatoid arthritis. Arthritis Rheum 1990; **33**:113–120.

Pincus T. Rheumatoid arthritis: disappointing long-term outcomes despite successful short-term clinical trials. J Clin Epidemiol 1988; **41**:1037–1041.

Wilke WS, Clough JD. Therapy for rheumatoid arthritis: combinations of disease-modifying drugs and new paradigms of treatment. Semin Arthritis Rheum 1991; **21(Suppl)**:21–34.

Wolfe F, Hawley DJ, Cathey MA. Clinical and health status measures over time. Prognosis and outcome assessment in rheumatoid arthritis. J Rheumatol 1991; **18**:1290–1297.

CUSHING'S SYNDROME: EASY TO SEE, TRICKY TO DIAGNOSE

PATIENTS WITH CUSHING'S syndrome are usually easy to recognize. The round plethoric facies, supraclavicular and infrascapular fat pads, thinning of the skin, and truncal weight distribution are typical. Cushing's syndrome also is associated with proximal weakness, abnormal menses in women, impotence in men, and osteoporosis. The challenge is to determine whether the syndrome has a pituitary or nonpituitary cause.