Approach to Initial Medical Treatment of Rheumatoid Arthritis

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In this article, we review the first line of therapy for rheumatoid arthritis. The components of first-line therapy include patient education, rest, physical therapy, occupational therapy, and nonsteroidal anti-inflammatory agents. We discuss each of these components in detail. Factors that might necessitate the addition of second-line agents (corticosteroids, antimalarials, gold salts, penicillamine, immunosuppressives, and surgery) are also outlined.

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Rheumatoid arthritis (RA) is a systemic disease involving the synovium of joints, tendon sheaths, and bursae in an intense inflammatory response resulting from a disordered immune system.[1] The classic approach to the treatment of RA has been conceptualized as a multilayered pyramid. Education, physical and occupational therapy, rest, and nonsteroidal anti-inflammatory drugs (NSAIDs) represent the base, or first-line, therapy. These therapies control inflammation but may not contain the destructive potential of RA. Subsequently, as the destructive manifestations of RA are discovered, treatment progresses to include additional (remittive) therapies such as hydroxychloroquine sulfate, gold salts, other disease-modifying agents, and cytotoxic drugs approaching the apex of the pyramid. These remittive agents have potential to halt the destructive properties of RA. Corticosteroid in its various forms (local injection, tablets, pulse therapy) may be used as an anti-inflammatory agent at different levels of the pyramid. The toxic effects associated with corticosteroids preclude their use as first-line agents. Several authors have challenged this approach, advocating early, aggressive use of disease-modifying agents alone or in combination[2-4] despite their having greater toxic effects than NSAIDs. With the knowledge of these toxic effects, however, many rheumatologists continue to believe that the appropriate initial therapy for most patients with RA is patient education, physical and occupational therapy, and NSAIDs. This article reviews these elements of therapy and discusses those factors that necessitate the addition of second-line agents in the treatment of RA.

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PATIENT EDUCATION

The importance of supplying information about the disease to the patient cannot be overemphasized. A multitude of misconceptions surround the pathogenesis, course, therapy, and potential disability associated with RA. Patients are frequently misinformed by the media, and may come to believe that the arthritic process cannot be controlled by the individual or physician because the cause of the illness is unknown. Patients may develop emotional or motivational difficulties in dealing with the illness. They may feel powerless, resulting in depression, anxiety, and a lackadaisical approach to activities of daily living. Educational materials and discussions should be geared to the med-

ical sophistication of the patient and should include all aspects of activities of daily living.[5-7] Educational materials discussing RA, its effects on daily functioning, and treatment options are available through local chapters of the Arthritis Foundation. Patients are encouraged to read the materials and ask questions about their illness or treatment during subsequent office visits.

Although patient education has not been shown to alter the ultimate outcome of the disease, several studies have demonstrated a positive effect of knowledge about the disease process, self-care behavior, and a decrease in perceived helplessness.[7,8] Knowledge about the underlying disease, its prognosis, and therapeutic options is important in allaying the patients' fears and allowing them to be an active participant in their treatment decisions.

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PHYSICAL MODALITIES

The goals of rehabilitation therapy for RA are the relief of pain, control of inflammation, maintenance of joint integrity, and maximization of function. Once prescribed, the program must continually be reassessed and adjusted to meet these goals and to avoid costly and ineffective treatment. The major components of rehabilitation therapy include rest, pain-relieving modalities, and exercise.

Rest

A prominent symptom in patients with active RA is generalized fatigue. Patients commonly experience fatigue in the middle to late part of the afternoon; however, in severe cases onset may be prior to the resolution of morning stiffness. Patients may require a full 8 hours of sleep in addition to 30 minutes or more of rest once or twice a day to combat fatigue and improve function.[9-11]

In the present circumstances of limited medical resources, hospitalization for bed rest for RA is not approved by insurance carriers. For a severe, generalized flare of disease in a patient who failed to respond to outpatient therapy, hospitalization for intensive medical therapy is an alternative that may diminish joint inflammation.[9,11] The potential benefits of bed rest must, however, be weighed against the possibility of deconditioning and the promotion of flexion contractures.

Rest may be prescribed for the whole body, or for individual joints. Restriction of motion of individual joints decreases stress on inflamed articulations, thereby decreasing swelling and pain.[12] A number of studies have demonstrated improved function using joint immobilization in patients with or without physical therapy. Current opinion favors adequate rest of the joints balanced with appropriate exercise and the maintenance of mobility.[13-15] Whether the use of splints is effective in preventing joint deformity remains to be determined. The difficulty in demonstrating the efficacy of splints is based on the slow progression of RA, which does not allow for determination of small differences in joint integrity over short periods.

Splints, or orthoses, are constructed for specific joints with material (plaster and thermoplastic materials) chosen based on the stresses it will be subjected to and the biomechanical function that the splint is to provide. Durability, ease of use, and patient acceptance are also important considerations in splint selection.[16,17] The wrist, metacarpophalangeal joints, proximal interphalangeal joints, knee, and ankle are most commonly benefited with the use of an orthosis. Splints may be constructed for a static, stabilizing purpose, or may be designed for dynamic effect to prevent deformity or correct contractures.

Rigid splinting of the hand and wrist may be used during intense activity of joint inflammation and pain during early stages of the disease. The orthosis extends from the forearm, past the wrist, to a variable point in the palm or fingertips, depending on the need to stabilize fingers. The splint is constructed to maintain the normal anatomical relationships of the wrist, fingers, and thumb. The ideal position is that of wrist extension of 25°, correction of any ulnar deviation, the metacarpophalangeal joints in slight flexion, and thumb in slight extension and opposition. The full wrist-hand resting splint is constructed of lightweight plastic and is worn day and night except for brief intervals of range of motion exercises. After the acute inflammatory stage of arthritis is controlled, working or static wrist extension splints may be manufactured that allow for use of the fingers in daily activities while limiting excessive motion of the wrist.

Splints for the thumb and fingers are constructed with the function of the appendage in mind. The thumb is involved with pinching, providing opposition, and grasping. The carpometacarpal joint is essential for normal function of the thumb. Thumb splints usually stabilize the carpometacarpal and metacarpophalangeal joint while allowing motion of the interphalangeal joint. This splint configuration offers stability to the painful joints of the thumb most frequently affected by RA while allowing modified pinch-and-grasp function of the hand.

The metacarpophalangeal joints of the fingers function as stabilizers of the hand. Ulnar drift and palmar subluxation are results of the mechanical forces of daily activities on inflamed joints. Attempts at preventing or slowing the progression

of ulnar drift with the use of dynamic splints are usually unsuccessful.[17] Dynamic splints are useful after hand surgery on the wrist and metacarpophalangeal joints.

Swan-neck and boutonniere deformities occur in the proximal interphalangeal joints with RA. Splints that apply pressure distal and proximal to the joint are necessary to modify joint configuration. A pressure point system is necessary to correct joint deformity. With swan-neck deformity, in addition to pressure points proximal and distal to the proximal interphalangeal joint, a third point is applied over the palmar surface of the joint. With boutonniere deformities, the splint is rotated 180°, with the third point of pressure over the dorsal side of the proximal interphalangeal joint. These splints are most effective before deformities become fixed.

Rheumatoid arthritis frequently affects the knee, resulting in varying degrees of flexion with contracture, subluxation, valgus deformity, and external rotation.[18] Knee splints for ambulation are frequently bulky, cumbersome, and ineffective. These splints offer relatively little benefit in ambulation compared with the cost and time of manufacture, difficulty in obtaining an appropriate fit, and restriction of mobility.[19]

Ankle-foot orthoses are made of lightweight plastic and fit into special shoes. These splints limit motion during ambulation and should be reserved for patients with instability in the foot or ankle.

Physical Therapy

An equally important component of therapy is the maintenance of joint motion, and muscle strength and function. Exercise, physical therapy modalities, and assistive devices are used to accomplish these goals.

Exercise helps to maintain range of motion for affected joints and increase muscle strength.[20] Aerobic exercise has been shown to increase cardiovascular endurance as well as improve muscle strength and joint motion in RA without exacerbation of joint disease.[21-25] Harkcom et al[24] reported an improvement in general fitness and decreased joint activity after a three-times-a-week, 35-minute, low-impact aerobic exercise program in women with RA. Minor et al[25] reported a significant benefit in aerobic capacity, walking time, depression, anxiety, and physical activity from a 12-week aquatic or walking exercise regimen in 120 patients with RA or osteoarthritis. No significant changes were noted in flexibility scores, number of active joints, duration of morning stiffness, or grip strength. Another study reported a decrease in number of active joints and an elevation of hemoglobin levels in patients with RA who participated in a physical training program.[26]

Swimming is an excellent exercise for patients with arthritis. The buoyancy of the water puts less physical stress on the joints while stressing the cardiovascular system. Danneskiold-Samsoe et al[27] reported that exercise therapy done in a pool during a 2-month period increased both median maximal isometric and isokinetic quadriceps strength and aerobic capacity.

Exercises must strengthen muscles and maintain joint mobility in a manner that minimizes joint inflammation and pain.[28] The provocation of joint pain with exercise results in an inhibition of forceful muscular contraction thus limiting the stimulus required for muscle strengthening. Isometric exercise (increasing muscle tension at one fiber length) increases strength with limited joint motion. These exercises strengthen specifically type II (glycolytic, anaerobic) muscle fibers capable of brief, forceful, resistive contractions, and improve the function of muscles used in activities of daily living (walking, dressing, eating). However, isometric exercises are not ideal. They create high intra-articular compression forces and do not take joints through a range of motion. After an initial course of isometric muscle-strengthening exercises, a course of isotonic exercises that include range of motion exercises to maximize joint mobility should be attempted. These exercises may be completed most effectively in a swimming pool if a patient experiences increased joint pain with motion. Mobilizing exercises may be done passively by the physical therapist if active joint motion is painful. A patient participates in the therapy program with increasingly active exercise as joint inflammation is diminished.

Table 1. Rehabilitation Therapy of Rheumatoid Arthritis

Disease Level	Therapy
Acute	Splinting (rest); energy conservation; range of motion exercises (passive); education in joint protection; isometric exercise
Subacute	Active assisted range of motion and stretching exercises; hydrotherapy; functional splints; assistive devices
Chronic	Isometric exercises; active range of motion exercises; serial splints; assistive devices (canes)

Rest may be prescribed for the whole body, or for individual joints

A physical therapist, in concert with the physician, can develop an exercise program tailored to fit the patient's joint involvement, physical capability, and life-style. At home, the timing and periodicity of the exercises are varied according to the state of activity of inflammation of the patient's joint (5 minutes twice a day with acute early disease or 15 minutes five to eight times a day with late inactive disease). If the exercises cause increased pain for more than

2 hours after the session, a decrease in the intensity or frequency of the exercises is warranted. Several arthritis education and exercise programs have been developed for the patient with RA and their efficacy continues to be evaluated.[29-31]

Temperature Modalities

The compliance of a patient with a physical therapy program can be improved with the proper use of heat and/or cold applications to the exercised joints.[32] Temperature modalities (heat and cold) share some physiologic effects on musculoskeletal structures. Both relieve pain and reduce muscle spasm. In contrast, joint stiffness is decreased by heat and increased by cold. Blood flow, bleeding, and edema formation are accel-

Table 2. Characteristics of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Based on Chemical Categories*

Drug/Chemical Class	Half-life (Dosing)	Usual Dosage for RA	Major Toxic Effects	Comments
Salicylates				
Acetylated	...	...	...	Therapeutic level 20-25 mg/dL
Acetylsalicylic acid (aspirin)	Low dose: 2-3 h; high dose: 16 h (three to four times a day)	3-6 g/d	GI, R	The first NSAID agent
Nonacetylated				
Salsalate	16 h (twice a day)	3 g/d	GI, R	Nonacetylated salicylates have fewer GI toxic effects than aspirin but are weaker anti-inflammatory agents
Choline magnesium trisalicylate	9-17 h (twice a day)	3 g/d	GI, R	...
Diflunisal	8-12 h (two to three times a day)	1000-1500 mg/d	GI, R	...
Propionic Acids				
Ibuprofen	2-3 h (four times a day)	2400-3200 mg/d	GI, R	...
Fenoprofren calcium	3 h (four times a day)	2400 mg/d		...
Naproxen	10-16 h (two to three times a day)	1000-1500 mg/d	GI, R	...
Ketoprofen	3 h (three to four times a day)	300 mg/d	GI, R	...
Flurbiprofen	6 h (two to four times a day)	200-300 mg/d	GI, R	...
Acetic Acids				
Indomethocin	3 h (two to three times a day)	100-200 mg/d	GI, R, CNS, BM	Most toxic of all NSAIDs to the CNS; drug of choice for spondyloarthropathies
Tolmetin sodium	2-4 h (four times a day)	1600 mg/d	GI, R	...
Sulindac	16-18 h (two times a day)	300-400 mg/d	GI	...
Phenylacetic Acids				
Diclofenac sodium	1-2 h (two to three times a day)	100-225 mg/d	GI, R	Inhibits both cyclooxygenase and lipoxygenase pathways suggesting possible superior anti-inflammatory effect; reports of hepatotoxic effects require monitoring LFTs
Pyranocarboxylic Acids				
Etodolac	7 h (two to three times a day)	800-1200 mg/d	R	Fewer GI toxic effects
Oxicams				
Piroxicam	38-45 h (once a day)	20 mg	GI, R	Long duration of action
Anthranilic Acids				
Meclofenamate sodium	2-4 h (four times a day)	400 mg/d	GI, R	Diarrhea in one third of patients
Pyrazoles				
Phenylbutazone	72 h (three times a day)	300 mg/d	GI, R	Potential but rare toxic effects in the bone marrow
Naphthylalkanone				
Nabumetone	22-29 h (twice a day)	1000-2000 mg/d	GI, R	Few GI toxic effects

RA indicates rheumatoid arthritis; GI, gastrointestinal; R, renal; CNS, central nervous system; BM, bone marrow; and LFTs, liver function tests.

erated by heat therapy and reduced by cooling. In theory, the activity of destructive enzymes present in the inflamed joint could be potentiated by alteration of joint temperature. However, the effect of temperature modalities on the activity of joint inflammation is not clear. In particular, heat does not always increase the inflammatory response in a joint.

Heat may be applied to joints through a number of different modalities. Ultrasound (acoustic vibration), shortwave diathermy (high-frequency current), and microwave diathermy (electromagnetic radiation) are forms of deep heating. Hydrocollator packs, paraffin wax application, whirlpool, and infrared lights are modalities of superficial heating. Cold may be applied with immersion, packs, or massage. The choice of modality depends on the depth of the affected site. In theory, superficial heating produces vigorous vasodilatation in the skin and subcutaneous tissues. The structures under the subcutaneous tissues may receive decreased blood flow. In contrast, deep heating increases the flow of blood to deeper tissues such as joint structures. Cold decreases inflammation by vasoconstriction that reduces hyperemia, heat, swelling, and enzymatic activity.[33] A recent study by Oosteveld et al[34] on 42 healthy volunteers demonstrated that paraffin application, which has been considered a superficial heating modality, also significantly elevated knee joint temperature. Thus, the classification of methods as *superficial* and *deep* may not be evident.

Swimming is an excellent exercise for patients with arthritis

Which is the most effective temperature modality for treating RA? In the presence of acute or subacute joint inflammation, deep heating is contraindicated. In patients with inactive RA with contracted periarticular structures, heating may help in increasing joint mobilization and decreasing stiffness. Superficial heat application has been felt to be useful in acute joint inflammation to decrease stiffness and muscle spasm, but further studies are needed to document benefit in patients with acute RA.[35] The role of cold therapy in RA is controversial. Although cold application to inflamed joints may relieve pain and decrease joint temperature and thus enzymatic activity, the increase in joint stiffness may outweigh the benefits.[34,36]

Temperature modalities are not indicated for all patients. They should not be used for patients with anesthetic areas, ischemic tissues, hemorrhagic diatheses, cold urticaria, cold hemolysins, or Raynaud's phenomenon. An additional factor to consider is that temperature modalities have only short-term effects on musculoskeletal structures. These modalities must be part of a comprehensive program to achieve maximum benefit.

Other pain-relieving modalities have been used in the care of patients with RA. Transcutaneous nerve stimulation relieves pain by hyperstimulation of large myelinated nerve fibers that tend to override input from unmyelinated C and small myelinated A delta fibers.[37] Mannheimer et al[38] reported reduced joint pain in 18 of 19 rheumatoid patients who received transcutaneous electrical nerve stimulation to their joints. However, Griffin and McClure[39] described patients with increased pain after transcutaneous electrical nerve stimulation. Until additional studies are completed, transcutaneous electrical nerve stimulation cannot be recommended as a therapy for rheumatoid patients.

Phonophoresis and iontophoresis are two methods for administering drugs (ie, lidocaine hydrochloride and corticosteroids) though the skin and into adjacent tissues. The former uses ultrasound, the latter, electrode stimulation. No studies have demonstrated a role for these modalities in treating RA. In theory, these techniques offer a noninvasive way of delivering medications to superficially placed joints, tendon sheaths, and bursae.[40] These methods offer a means to transport therapeutic agents to structures near the skin in individuals with a contraindication to injection (anticoagulants).

Occupational Therapy

The purpose of occupational therapy is to identify impairments and accommodate them to allow maximal functional capacity both at home and at work. Occupational therapists are particularly helpful in developing assistive devices and with joint protection education. Devices may improve function in mobility, eating, dressing, hygiene, communication, and recreation. Joints are protected by maintenance of muscle strength, avoidance of positions of joint deformity, and use of the strongest joints to complete a task in its most functional position. Avoiding overuse of muscle groups and conserving energy are also important goals of therapy.[41] Using proximal body parts in lieu of the more distal ones involves using the stronger part while protecting the weaker. For example, handles for bags can be placed over the forearm as opposed to being carried in the hand.

In summary, physical and occupational therapy plays a role in the treatment of patients with RA at each stage of their illness (**Table 1**). These therapies by themselves are not capable of controlling the symptoms and activity of RA. However, in conjunction with other components of a basic therapeutic program (patient education, NSAIDs), physical therapy helps control the discomfort and loss of function associated with this disease.

Nonsteroidal Anti-inflammatory Drugs

The final component of first-line therapy for RA includes NSAIDs. These drugs do not alter the progressive

course of RA, but provide control of the symptoms and signs of local and systemic inflammation. They provide analgesia at low doses and have an anti-inflammatory effect at higher doses. These NSAIDs act rapidly and their clinical effects diminish rapidly after cessation of therapy. They are effective at all stages of disease, although efficacy is most prominent at the onset.

Nonsteroidal anti-inflammatory drugs as a class share some common characteristics. They all have the same basic mechanism of action, namely inhibition of prostaglandin production. All are weak organic acids that are highly bound to plasma proteins, particularly albumin.

Absorption is usually through the small intestine with a smaller component absorbed in the stomach. Although concomitant food, other drugs, and diseases that alter intestinal motility may affect drug absorption, the clinical effect of altered absorption with long-term administration is minimal.

The distribution of the NSAIDs corresponds with the distribution of albumin. Protein binding of NSAIDs is unimpaired in RA.[42] The majority of NSAIDs are metabolized by the liver, with metabolites and remaining parent drug being excreted by the kidney.

Nonsteroidal anti-inflammatory drugs may be divided into chemical categories for classification, including salicylates (acetylated and nonacetylated), propionic acids, acetic acids (indoles), phenylacetic acids, pyranocarboxylic acids, anthranilic acids, oxicams, naphthylalkanones, and pyrazoles. The characteristics of the drugs in each of these groups are listed in **Table 2**. The separation of the NSAIDs into specific groups has not been helpful in selecting a specific agent for particular rheumatic diseases; nor has any great difference in efficacy among the available agents been noted. The responses of patients to the drugs cannot be ascribed to the pharmacokinetics or plasma concentration of the drugs. For example, drugs with short half-lives can have beneficial effects hours after the serum concentration had returned to zero. Explanations for this extended effect may be related to accumulation of the drug in joint spaces, persistent enzyme inhibition, or metabolic by-products with prolonged activity.[43]

Some clinicians suggest that if a patient does not respond to treatment with a drug in a chemical class or displays toxic effects, an agent from a different chemical class should be used. Other physicians do not believe that choosing another chemical class of drug is necessary. Gall et al[44] reported the results of a crossover comparison study of five NSAIDs in the treatment of RA. No specific drug class was preferred by the patients and no specific pattern of disease response was detected with intragroup or intergroup drug selections. The choice of a specific NSAID for an individual must be based on the characteristics of the drug and patient. The characteristics of the drug that are considered in the selection process include frequency of dose, dose forms, variability of dose amounts, cost, and potential toxic effects. Patient characteristics that need to be considered are those that potentiate the toxic effects of the drugs, ie, renal, gastrointestinal, and hepatic dysfunction. A review of the characteristics of each agent and its associated toxic effects should help the physician in his or her choice of a specific agent for a patient with RA.

Early progression to other agents should be considered in patients with progressive, active disease despite first-line therapy. Patients who are hypersensitive or display toxic reactions to treatment with NSAIDs should be considered for treatment with a second-line agent. In addition, second-line therapy should be considered early in patients with poor prognostic factors even in the face of a good symptomatic response to NSAIDs. Prognostic factors associated with a high risk of rapidly progressive disease and increased mortality rates include an insidious onset of disease in women, rheumatoid nodules, high-titer rheumatoid factor, and the presence of periarticular osteopenia without bony erosions. The physician must keep these factors in mind as he or she follows up and reevaluates the patient with RA. A patient's disease may go into remission or become rapidly progressive; and a patient may show an excellent clinical response to a medication or a severe adverse reaction. Only constant vigilance by the clinician can determine the point at which the probability of disease progression is great and more aggressive therapy is necessary.

Occupational therapists are particularly helpful in developing assistive devices and with joint protection education

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