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RHEUMATOID ARTHRITIS
Newer Treatment Modalities*

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SYNOPSIS-ABSTRACT

With the introduction of the newer nonsteroidal anti-inflammatory drugs (NSAIDs) and penicillamine, our therapeutic armamentarium for the rheumatoid disease group had been significantly broadened. In addition, there has been a renewed interest in anti-malarials, the use of some immunosuppressive agents, and plasmapheresis. The purpose of this article is to offer a helpful therapeutic scheme in the selection of these newer anti-rheumatoid agents. Furthermore, we have attempted to incorporate the clincial and laboratory profiles of rheumatoid patients into the treatment scheme. Rheumatoid arthritis can be divided into three subgroups: sero-negative rheumatoid arthritis, sero-positive rheumatoid arthritis, and hybrid rheumatoid arthritis. Such classification offers a guideline in selecting the most suitable anti-arthritic agents.

Key Words:
Treatment of rheumatoid arthritis
Nonsteroidal anti-inflammatory drugs
Penicillamine
Hybrid rheumatoid arthritis

INTRODUCTION

To date, there are about fifteen NSAIDs available in the United States. More anti-rheumatoid agents of this type are waiting to get into the marketplace. There might be as many as seventy new drug applications to the United States Food and Drug Administration (FDA). With the relatively fast introduction of these fifteen NSAIDs, there appears to be some confusion as to their place in the treatment of rheumatoid disorders. This confusion may turn into a chaos if even a portion of the seventy newer NSAIDs are to be approved by the FDA. In this article, we will try to provide a relatively simple guideline which will aid clinicians in selecting suitable NSAIDs and also incorporating them into their treatment protocols with other anti-rheumatoid agents.

Reprint requests to the above address to the attention of Dr. Gokcen.

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Rheumatoid arthritis is a clinical diagnosis; and perhaps, it is even more appropriate to consider it as a clinical syndrome. Rheumatoid arthritis associated with viral disease, such as viral hepatitis, is a self-limited disease that poses no therapeutic challenge. However, rheumatoid arthritis as a manifestation of internal malignancies is, as a rule, notoriuosly resistant to even the most potent anti-rheumatoid treatment. These cases also exemplify the importance of making an accurate diagnosis and of the alertness of the attending physician during the course of treatment.

Among the laboratory findings, we pay special attention to the presence of rheumatoid factors (RF) and anti-nuclear antibodies (ANA). (Table I). The term sero-negative rheumatoid arthritis refers to the negative test for RF, and sero-positive for the presence of circulating RF in rheumatoid arthritis patients. In cases of so-called hybrid rheumatoid arthritis, the immune profile is usually that of a positive test for RF and a positive ANA. (Table II). Drug therapy for rheumatoid arthritis can be guided by the aforementioned classification. Tables III, IV, and V give a summary of the treatment schedule which we follow for each type of rheumatoid arthritis.

SERO-NEGATIVE RHEUMATOID ARTHRITIS

As a rule, sero-negative rheumatoid arthritis cases appear to be clinically milder forms of rheumatoid arthritis and respond more readily to any drug therapy. These clinically mild cases may be managed by administration of salicylates or one of the NSAIDs as a single agent. Clinically severe or therapy-resistant cases may be candidates for gold or penicillamine. However, it is important to stress the fact that the sero-negative state might actually be an early stage of sero-positive rheumatoid arthritis, since it usually takes about two to five years for rheumatoid factors to appear in the circulation after the first clinical signs of rheumatoid arthritis. Another group of sero-negative rheumatoid arthritis

Table I

RHEUMATOID ARTHRITIS

Tests	% Positive
Rheumatoid Factors	75
Anti-Nuclear Antibodies	35
Positive L.E. Cells*	10

*L.E. Factor responsible for positive L.E. cell test is an anti-DNP type and included in anti-nuclear antibodies.

Table II

CLASSIFICATION OF RHEUMATOID ARTHRITIS

Sero - Negative Rheumatoid Arthritis
Sero - Positive Rheumatoid Arthritis
Hybrid Rheumatoid Arthritis

Table III

TREATMENT OF SERO-NEGATIVE RHEUMATOID ARTHRITIS

Salicylates
Aspirin, Sodium Salicylate, Trilisate, Disalcid, Dolobid.

NSAIDs
Motrin, Nalfon, Naprosyn, Indocin, Tolectin, Clinoril, Feldene, Meclomen.

Phenylbutazone
Butazolidine, Azolid.

Gold

Penicillamine

Table IV

TREATMENT OF SERO-POSITIVE RHEUMATOID ARTHRITIS

Salicylates
NSAIDs
Phenylbutazone
Gold
Penicillamine
Anti-Malarials: Plaquenil
Combinations:
- Salicylates - Gold
- NSAIDs - Gold
- Plaquenil - Gold - NSAIDs
- Salicylates - Penicillamine
- NSAIDs - Penicillamine
- Plaquenil - Penicillamine
- Plaquenil - Penicillamine - NSAIDs

Table V

TREATMENT OF HYBRID RHEUMATOID ARTHRITIS

Corticosteroids
Anti-Malarials: Plaquenil
Anti-Inflammatory Agents: Salicylates, NSAIDs, Gold, Phenylbutazone, Penicillamine.
Cytotoxic Agents: Cytoxan, Imuran, Methotrexate.
Plasmapheresis
Combinations:
- Steroids - Plaquenil
- Steroids - Plaquenil - Cytotoxic
- Steroids - Plaquenil - Anti-Inflammatory Agents
- Plaquenil - Anti-Inflammatory Agents

patients is that group with positive anti-nuclear antibodies (ANA). The most common pattern for ANA staining is the so-called "homogenous" pattern which usually occurs at low titers, i.e., 1:20 to 1:80 by the peripheral blood FANA method. (1) Some of these cases may remain sero-negative and ANA positive for years, although the ANA titer may decline with remissions. Some may progress, albeit rarely, into the hybrid rheumatoid arthritis state, i.e.,

positive RF, positive ANA. If the ANA pattern is that of "peripheral" staining, i.e., either the anti-DNP or anti-DNA antibody pattern, we follow these cases more closely since these patients may be progressing into hybrid rheumatoid arthritis or SLE. Although it takes years for RF to appear in the blood, anti-nuclear antibodies seem to be present at the onset of rheumatoid diseases. From the treatment standpoint, we do not hesitate to treat those patients with positive anti-DNA or anti-DNP as hybrid rheumatoid arthritis, especially if there is any evidence of extra-articular involvement. The rheumatoid arthritis of SLE usually presents itself as a mild rheumatoid state. These subgroups of sero-negative rheumatoid arthritis are summarized in Table VI.

Table VI
SUBGROUPS OR PROGRESSION OF SERO-NEGATIVE RHEUMATOID ARTHRITIS CASES

Initial Stage	Advanced Stage
Sero-Negative	Sero-Negative
Sero-Negative	Sero-Positive
Sero-Negative, ANA Positive	Sero-Negative, ANA Positive
Sero-Negative, ANA Positive	Hybrid RA
Sero-Negative, ANA Positive	SLE, MCTD

SERO-POSITIVE RHEUMATOID ARTHRITIS

Sero-positive rheumatoid arthritis cases make up the majority of cases since about 75% of rheumatoid arthritis patients exhibit a positive test for rheumatoid factors. However, about 25% to 40 % of these cases may probably be classified as hybrid rheumatoid arthritis. The drug therapy for sero-positive rheumatoid arthritis is summarized in Table IV. The selection of these agents is made on the basis of clinical stage. Mild cases may respond to a single agent of either salicylates, NSAIDs, or phenylbutazone. If there is poor response to these agents, then the clinician would best consider any of the three so-called "remission-inducing agents:" gold, penicillamine, or anti-malarials. In our experience, most patients in this group would require more than one agent to produce a remission. These agent "combinations" are listed in Table IV. The most familiar combinations might be salicylates — gold, NSAIDs-gold, Plaquenil-gold, Plaquenil-gold-NSAIDs, or Plaquenil-gold-salicylates. Phenylbutazones (Butazolidin, Azolid) should be used for acute flare-ups confined to short-term duration because of bone marrow toxicity, although this complication appears to be extremely rare. It is, however, common to observe a significant sodium retention with the administration of the phenylbutazone group and therefore we almost always add a small dose of a diuretic to phenylbutazone therapy. Remission-inducing agents (gold, penicillamine, anti-malarials) may take two to four months to exhibit significant clinical improvement. During this period, phenylbutazones or NSAIDs may be necessary to provide adequate comfort to the patient. If there is sufficient evidence for extra-articular involvement, with or without positive ANA, then the use of corticosteroids is indicated.

HYBRID RHEUMATOID ARTHRITIS

Under the term of hybrid rheumatoid arthritis, we include most of the rheumatoid arthritis cases with extra-articular involvement. The immune profile of such cases usually shows a positive test for rheumatoid factors and a test for anti-nuclear antibodies. The extra-articular manifestation may vary from a mild form of Sjogren's syndrome to a severe systemic vasculitis. The most frequently involved organs are muscles, salivary and lacrimal glands, lungs, bone marrow, spleen and lymph nodes, peripheral nerves, serous membranes, heart, kidneys, intestines, and skin. Many terms and names, old and new, have been given to this group of rheumatoid conditions. We have tried to gather them in Table VII. The titer of rheumatoid factors tends to be higher in this group. The titer and pattern of ANA may vary. The most common pattern is that of so-called "homogenous" staining with mild to moderate elevation in titers. In rare cases, one sees very high rheumatoid factor titers reaching into the millions, and anti-nuclear anti-body titers as high as 1:10,000 with a pattern of anti-DNA, anti-DNP, "speckled," anti-RNP, etc.

Table VII

SYNONYM OR VARIANTS OF HYBRID RHEUMATOID ARTHRITIS

Rheumatoid Arthritis with Positive L.E. cells
Felty's syndrome
Sjogrens syndrome
Malignant Rheumatoid Arthritis
Rheumatoid Arthritis with Systemic Vasculitis
Rheumatoid Arthritis with Amyloidosis
Mixed Connected Tissue Disease
Lupoid Arthritis
Dysproteinemic Rheumatoid Arthritis
Rheumatoid Arthritis with Immune Complex Disease
M proteins and Rheumatoid Arthritis
Overlapping Syndromes in Connective Tissue Diseases
Systemic Rheumatoid Disease
Wegener's Granulomatosis

The treatment of hybrid rheumatoid arthritis is outlined in Table V. The use of a single anti-arthritic agent is not sufficient to induce a remission. Among the combinations which we have been using, a combined Plaquenil-steroid therapy seems preferable. There may be a synergistic effect in such a combination. In addition, anti-malarials have been known to have corticosteroid-sparing properties. We usually begin with 400 mg. of Plaquenil and 10-20 mg. of Prednisone or a Prednisone-equivalent daily. As soon as the patient shows adequate signs of remission, which may take four to eight weeks, the Prednisone dose is lowered by 50%. Plaquenil is continued at 400 mg. a day for four to eight months or longer; then it may be lowered to 200 mg. a day. Plaquenil appears to be safer with regard to eye complications if limited to a dosage of 200-400 mg. daily. In that dosage, it still acts as an effective anti-inflammatory agent. The patients who are on this combination are required to have an ophthalmology exam at least once every six months. If this combination is used as a maintenance therapy, the lowest possible steroid dose of 2-5 mg. of Prednisone and 200 mg. of Plaquenil daily may be considered. The alternate-day steroid therapy is not effective in rheumatology. Except for the advanced-state osteoporosis, other side effects of steroids are usually reversible. Of course, skeletal complications are related to dosage and treatment duration. In cases of steroid complications or fear of complications, one may choose the combination of Plaquenil and one of the anti-inflammatory agents. In the presence of peptic ulcer disease, Plaquenil and gold may be the safer and better-tolerated combination.

Among the cytotoxic agents, Imuran is the only one approved by the FDA for rheumatoid arthritis treatment. In our experience, it is very rarely indicated. If used, however, one of these agents may be added to the Plaquenil-Prednisone combination. Imuran appears to be the weakest immunosuppressive agent in the group. For effective immunosuppression, Cytotoxan is preferred. We have been using Cytotoxan along with the Plaquenil-Prednisone combination almost exclusively in cases of Wegener's Granulomatosis or systemic vasculitis. Methotrexate is reserved for severe psoriatic arthritis cases.

Plasmapheresis is another experimental treatment modality which may be restricted to certain acute severe cases of circulating immune complex conditions. Preferably, newer techniques which may try to filter out the harmful macromolecules should be sought out.(2)

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

The structural classification of these agents is given in Table VIII. All of these agents possess peripheral analgesic activity, as well as antipyretic and anti-inflammatory properties. They are also called prostaglandin inhibitors since they block the enzyme, cyclo-oxygenase, which converts arachidonic acid to prostaglandin. The anti-inflammatory effect can be observed within a few days after initiating the drug therapy.

The most common side effects peculiar to all of these agents are gastrointestinal in type: hyperacidity, gastritis, peptic ulceration, bleeding, diarrhea, etc. The central nervous system effects such as headaches, confusion, tinnitus and dizziness, may be more common with the indole group (Indocin, Clinoril, Tolectin, Zomax). The effects on the kidneys might include sodium retention, hyperkalemia, and allergic interstitial nephritis. Toxic hepatitis seems to be a very rare complication. In contrast to aspirin, Trilisate and Disalsid do not exhibit any significant anti-platelet or clotting factor effects.

Since the efficacy of these drugs is comparable, with the exception of the pyrazolomes, therapy selection by the treating physician is based on convenience factors and patient tolerance. In the convenience or compliance factors, the drug half-life, i.e., the frequency of administration, is a factor. Drugs such as Motrin, Indocin, Nalfon, Tolectin, and Meclomen have half-lives of two to five hours thus requiring three or four times a day dosage regimens. Drugs with half-lives of fourteen to eighteen hours, such as Maprosyn, Clinoril, Butazolidin, and Azolid, require twice a day administration. Feldene, with the longest half-life of fifty hours, is a once a day agent.

If an analgesic is needed in addition to a NSAIDs, the use of acetaminophen (Tylenol) or a member of the codeine group is advised, rather than aspirin, Dolobid, Zomax, or Anaprox, because of the competitive action on cyclo-oxygenase caused by the latter group of drugs.

For more information on NSAIDs, the reader may wish to refer to one of the latest review articles. (3, 4)

PENICILLAMINE (PCM)

In the United States, penicillamine was approved for the treatment of "severe" rheumatoid arthritis in 1978. However, clinicians have been gaining experience in the use of PCM for about thirty years with the treatment of Wilson's disease, heavy metal poisoning, cystinuria, and Waldenstrom's macroglobulinemia. This long history has provided us with a valuable background on the drug in terms

of its toxicities and the skills of its successful use. There is no lab test such as HLA-typing to identify a good responder to PCM therapy. The only way, then, is to try this therapy once the indications for its use are met. Unfortunately, it might take two to four months to observe the true effectiveness of this drug provided that the patient's tolerance and the side effects are no problem. Penicillamine therapy is usually continued for several years. Most of the toxic reactions are observed during the first eighteen months of therapy. The responders exhibit a good clinical remission, as well as laboratory and roentgenographic improvement. Therefore, penicillamine has been termed a "disease-modifying agent." Its efficacy is similar to gold, with a 70-80% remission rate. The failure of gold therapy is probably another indication for PCM therapy. Such failure does not seem to influence the chance of benefit from PCM. We have summarized the most helpful information on the administration and monitoring of PCM therapy in Table IX.

Penicillin allergy is not a contraindication in the use of PCM. For minor side effects of PCM, such as nausea, vomiting, +1 proteinuria, and mild skin rash, the treatment may be temporarily stopped or the dosage reduced. More serious side effects, such as a platelet count of less than 80,000/mm^3, a leukocyte count of 3,000/mm^3 or less, drug fever, persistent proteinuria of +2 or greater, persistent gastrointestinal toxicity, and autoimmune syndromes, may require the patient to permanently discontinue the use of PCM. (5)

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Abbreviations:

ANA: Anti-Nuclear Antibodies
RA: Rheumatoid Arthritis
SLE: Systemic Lupus Erythematosus
MCTD: Mixed Connective Tissue Disease

Table VIII

CLASSIFICATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Salicylates:
Aspirin (acetylsalicylic acid)
Sodium Salicylate
Trilisate (choline magnesium salicylate)
Disalcid (salicysalicylate)
Dolobid (diflunisal)

Indoles:
Indocin, Indocin-SR (indomethacin)
Clinoril (sulindac)
Tolectin (tolmetin)
Zomax (zomepirac)

Propionic Acids:
Motrin (ibuprofen)
Nalfon (fenoprofen)
Naprosyn (naproxen)
Anaprox (naproxen sodium)
Oraflex (benoxaprofen)

Fenamates:
Meclomen (meclofenamate)

Oxicams:
Feldene (piroxicam)

Pyrazolones:
Butazolidin, Azolid (phenylbutazones)

Table IX

PENICILLAMINE THERAPY

Available:
Cuprimine 125 mg., 250 mg. capsules.
Depen 250 mg. scored tablets.

Treatment program:
Initiate at 250 mg. a day for 4 weeks. Increase by 125 mg. every 4 weeks to a maximum dose of 750 mg. daily. It should be taken on an empty stomach. Maintenance dose is determined by reducing from 750 mg. level slowly with decrements of 125 mg. to 250 mg. every 4 weeks.

Laboratory testing:
Initial: Complete chemistry profile, CBC, platelet count, urinalysis, and rheumatoid profile (ELP,

RF, ANA...).
Follow-up: CBC, platelet count, urinalysis: Every weeks x 4.
CBC, platelet count, urinalysis: Every 2 weeks x 4.
CBC, platelet count, urinalysis: Every month.

Side effects:

Fever, rash, pruritis, bullous dermatosis, stomatitis, protein-uria, nausea, vomiting, leukopenia, aplastic anemia, thrombo-cytopenia, loss of or impaired taste, auto-immune syndromes (SLE, Goodpasture's syndrome, myasthenia gravis, polymyositis...).