Management of Rheumatoid Arthritis: The Historical Context

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ABSTRACT. We review the historical highlights of the management of rheumatoid arthritis (RA). Studies of nonsteroidal antiinflammatory drugs, disease modifying antirheumatic drugs, and biological agents over 5 decades were evaluated and summarized. There is emphasis on drug therapy as it has developed and evolved from empirical relief of symptoms with salicylates to targeted intervention in the immunoinflammatory process with tumor necrosis factor inhibitors. A therapeutic paradigm has been proposed to rationalize the use of the available therapies. If one accepts the thesis that both the acute and chronic consequences of RA are due to persistent misdirected and inadequately controlled inflammation that causes tissue destruction and loss of function, then prolonged complete control of the abnormal inflammatory process is the fundamental first step in the management of all patients with RA. Unfortunately, even with the newest therapeutic options to treat RA, most patients achieve only partial suppression of inflammation and many lose therapeutic benefit after an initial good response. The management of persistent or recurrent rheumatoid inflammation and disability continues to be a challenge. It remains to be determined whether the future addition of more potent specific interventions in the immunoinflammatory process will be able to solve this problem without disarming host defenses against infections and tumors. (J Rheumatol 2001;28:1431–52)

Key Indexing Terms:
RHEUMATOID ARTHRITIS NONSTEROIDAL ANTIINFLAMMATORY DRUGS
TREATMENT BIOLOGICAL AGENTS DISEASE MODIFYING ANTIRHEUMATIC DRUGS

The ultimate goal of rheumatoid arthritis (RA) management is to restore the patient to normal non-RA status, asymptomatic, with normal physical, social, and emotional function and capacity to work, and with structurally and anatomically normal joints. Once achieved, this normalcy should be sustained without further medical intervention, i.e., the patient should have been "cured."

Even with the most optimistic scenarios, this goal could be attained only at the onset of RA before any irreversible joint or cartilage damage had occurred, or in those few fortunate patients whose arthritis does not cause structural damage. For the vast majority of patients who already exhibit evidence of joint erosions or cartilage damage, less perfect goals must be accepted. Since RA is a chronic disease that may begin any time between childhood and old age and usually persists for the entire remaining lifetime of the patient, it is evident that the specific aims of its management will vary among individual patients, depending on the aggressiveness of their disease, their age and life status at its onset, and their current life status as it is affected by the signs and symptoms of inflammation, decreased physical function, work disability, destruction of specific joints, and social and emotional coping capacity. A 25-year-old with recent onset RA who is incapacitated by the pain, stiffness, and exhaustion associated with uncontrolled inflammatory polyarthritis is very different from a 65-year-old with a 25 year history of RA who has been treated with a long list of antirheumatic therapies and is incapacitated by severely damaged or destroyed small joints of the hands and feet and a totally eroded hip joint. Thus, physicians who treat RA must be sensitive to the widely varying needs of the prevalent population of persons with RA and must be careful not to impose constraints that impede their therapeutic approach.

Nevertheless, if one accepts the thesis that both the acute and chronic consequences of RA are due to persistent misdirected and inadequately controlled inflammation that causes tissue destruction and loss of function, then prolonged complete control of the abnormal inflammatory process is the fundamental first step in the management of all patients with RA. Although the manifestations of acute inflammation, e.g., heat, redness, pain, swelling and loss of function, may become less obvious with time and symptomatic treatment, the progressive decline in functional capacity and increasing joint destruction demonstrated in longterm observational studies confirms the continued presence of inadequately controlled chronic inflammation[1-4]. Fortunately, controlled clinical trials have demonstrated that measurable

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radiographic progression of joint damage can be moderated by leflunomide[5], methotrexate (MTX)[5], sulfasalazine[5], and infliximab[6] (compared to placebo in patients with well established RA of 5 to 15 years' duration), and with etanercept[7] and leflunomide[5] (compared to MTX in patients with relatively early RA of 1 to 5 years' duration). In all cases, improvement of signs, symptoms, and function also occurred.

Therefore, the universal basic goal in the treatment of all patients with RA is complete control of the abnormal inflammatory process. In the short term, this should be associated with major improvements in joint swelling, tenderness, stiffness, and mobility, and generalized improvement in energy and normalization of acute phase reactants. Longterm inflammation associated pain should improve, but pain (of a different character) related to structural damage may persist. The degree of feasible improvement in function will depend in a given patient on the relative contributions of reversible inflammation and irreversible structural damage to the dysfunction; where the latter is marked, the rate of progressive loss of function should slow and there may be some improvement, but substantial disability will persist. Similarly, progression of inflammatory damage to joints should stop, although in theory further damage may occur in joints that already have been distorted by prior structural damage. Intermediate goals of treatment may be similar to those expressed in the US Food and Drug Administration Guidance for Industry[8]: reduction of signs and symptoms, major clinical response, complete clinical response, remission, improvement in function/disability, prevention of structural damage.

We review historical highlights of the management of RA, emphasizing drug therapy as it has developed and evolved from empirical relief of symptoms with salicylates to specific intervention in the immunoinflammatory process with tumor necrosis factor (TNF) inhibitors, and discuss therapeutic paradigms that have been proposed to rationalize the use of the available therapies.

HISTORY OF RA TREATMENT

Nonsteroidal Antiinflammatory Drugs (NSAID)

NSAID reduce the signs and symptoms of established inflammation, but do not in themselves eliminate the underlying cause of the inflammation. Their effects on pain, swelling, heat, erythema, and loss of function begin promptly after their absorption into the blood and become fully evident within a few weeks. Drug withdrawal is quickly followed by exacerbation of signs and symptoms of inflammation. The drugs have no effect on the course of the basic disease process and do not protect against tissue or joint injury; thus, damage to joints continues to occur during the administration of nonsteroidal antiinflammatory agents to patients with chronic inflammatory arthritis.

Willow and poplar barks that contain salicin have been used since antiquity to treat pain, gout, and fever (Table 1). Soon after the isolation of salicylic acid from the bitter glycoside, salicin, in 1838, salicylic acid was noted to be an effective analgesic and antipyretic agent for the treatment of "acute and chronic rheumatism." Acetylsalicylic acid was first synthesized by Von Gerhardt, a French chemist, in 1853, but was not used therapeutically at the time. Sodium salicylate was introduced about 1860 in an effort to reduce the marked dyspepsia associated with salicylic acid. Its value in rheumatic fever was demonstrated in 1875. Aspirin was developed by Hoffman and Dresser in 1899 when a search for a salicylate preparation with reduced toxicity was undertaken[9,10]. An asymmetrical dose-response relationship with salicylates was recognized and very high doses were used to control the acute manifestations of rheumatic fever (6 g/day) and juvenile rheumatoid arthritis (JRA, 70 to 120 mg/kg/day)[11,12].

The term nonsteroidal antiinflammatory drug was first applied to phenylbutazone, which was introduced into clinical practice in 1949, three years after the dramatic demonstration of the antiinflammatory properties of the corticosteroids. Antipyrine, a forerunner of phenylbutazone, had been introduced in 1884, but fell into disuse when salicylates became more popular. A pharmacologic breakthrough occurred when indomethacin was selected by deliberate screening of numerous chemicals for activity against inflammation induced in rat paws by injection of carrageenan. Since the introduction of indomethacin in 1965, many other compounds have been found to suppress the acute development of rat paw edema following the injection of carrageenan or other irritating substances. Essentially all of the traditional NSAID were initially identified by their *in vivo* effects on this model of acute inflammation, and the model's ability to identify additional similar compounds seems limitless. Standard NSAID such as ibuprofen, fenoprofen, ketoprofen, flurbiprofen, naproxyn, diclofenac, tolmetin, piroxicam, and sulindac were selected by screening large numbers of chemicals with *in vivo* models of inflammation. Since these NSAID were selected because of their effect on induced acute inflammation in a whole animal model, it is apparent that they successfully moderate the general process of acute inflammation *in vivo*.

Various hypotheses have been advanced to explain the actions of NSAID. Under appropriate conditions, NSAID have been shown to uncouple oxidative phosphorylation, to displace an endogenous antiinflammatory peptide from plasma proteins, to inhibit lysosomal enzyme release, to inhibit complement activation, and to antagonize the generation or activity of kinins[13]. In 1971, Vane reported that aspirin and related compounds selectively inhibit the synthesis of prostaglandins[14] and proposed that the major toxic and therapeutic effects of NSAID might be accounted for by their ability to suppress the synthesis of prostaglandins by the enzyme cyclooxygenase. In 1990

Table 1. Historical highlights of NSAID therapy.

Introduced	Drug	Dose Range mg/day	Half-life (h)	GI Adverse Effects		Lethal Side Effects	Comments
				Symptoms	Ulcers, Bleeds, Perforations, %/yr		
Antiquity	Willow bark (salicin)	?	?	+++	?	?	For pain, fever, gout
1838	Salicylic acid	?	4–15	+++	?	?	
1860	Sodium salicylate	1500–6000	4–15	+++	?	Overdoses lethal	Rheumatic fever 1875
1899	Aspirin	1000–6000	4–15	+++	2–4	Overdose lethal, GI bleeding or perforation lethal	Platelet anticoagulant
1949	Phenylbutazone	200–800	40–80	++		Blood dyscrasia (16–22 deaths/million), Stevens-Johnson syndrome } occ. deaths Granulomatous hepatitis }	
1965	Indomethacin	50–200	3–11	+++			
1960s	Non-acetylated salicylates, enteric released aspirin	1500–5000	4–15	+ to ++		Overdose lethal	Better tolerated
1970s, 1980s	1st Generation NSAID					Overdose not lethal	↑Liver toxicity with diclofenac
	Ibuprofen	1200–3000	2			Estimate 7600	Rare acute renal failure
	Ketoprofen	100–400	2		PUB occur in 2–4%	deaths per year	Rare anaphylaxis,
	Diclofenac	75–150	1–2	++ to +++	per patient-year	in US from	aseptic meningitis,
	Naproxen	250–1500	13		of exposure	NSAID induced GI	agranulocytosis,
	Sulindac	300–400	16			PUB	serious rashes
	Tolmetin	800–1600	1				
	Piroxicam	20	30–86				
1990 to 1995	2nd Generation NSAID					Probably lower	Somewhat better
	Etodolac	600–1200	7	+	2–4	risk than 1st	tolerated than 1st
	Oxaprozine	600–1200	49–60	++	2–4	generation	generation NSAID,
	Nabumetone	750–2000	24	+	0.5	NSAID	Nabumetone is a non-acidic prodrug with active acidic metabolite
1997 to 1998	COX-2 selective						Rofecoxib not approved
	Celecoxib	200–400	11	+	Probably < 1	Probably rare	for RA. Fluid retention
	Rofecoxib	12.5–25	17	+	Probably < 1	Probably rare	with high doses

PUB: perforation, ulcer and bleed.

Masferrer, *et al*[15] proposed that different pools of cyclooxygenase (COX) might be present, encoded by different genes. The complementary DNA (cDNA) of two isoenzymes, COX-1 and COX-2, and their respective messenger RNA (mRNA) were rapidly identified, cloned, and expressed in cultures of insect cell, making it possible to produce pure human COX-1 and COX-2[16]. These findings helped explain the linkage between the antiinflammatory benefits and the gastrointestinal (GI) adverse effects of the NSAID. Cyclooxygenase-1 (COX-1) is constitutively present in many tissues, and is responsible for the physiologic production of homeostatic and cytoprotective prostanoids in the gastric mucosa, endothelium, platelets, and kidney. Its inhibition is linked to many of the familiar adverse effects of NSAID. Cyclooxygenase-2 (COX-2) generally is not produced by unstimulated cells. Its production in leukocytes, vascular smooth muscle cells, human rheumatoid synoviocytes, and brain neurons is induced by stimuli such as mitogens, cytokines, and endotoxin, thus catalyzing the synthesis of proinflammatory prostaglandins. COX-2 is associated with carrageenan induced inflammation in experimental animals, certain aspects of inflammatory pain, and fever. In the brain, induction of COX-2 is associated with neurogenic pain and fever. COX-2 is induced during tissue repair and may be involved in healing of *Helicobacter pylori* associated peptic ulcers and mucosal damage in a rat model of colitis. COX-2 is physiologically involved in reproduction, i.e., the timing of ovulation and implantation of the blastocyst in the uterine wall. It is involved in bone remodeling and is induced in the renal macula densa and medullary interstitial cells during sodium restriction of rats[17]. COX-2 is also expressed in the podocytes of the

human glomerulus and the endothelial cells of renal arteries and veins, and is upregulated by inhibitors of angiotensin converting enzyme. Specific COX-2 inhibitors induce transient sodium retention without altering glomerular filtration rate[18].

To a considerable extent, the clinical properties and side effect profiles of NSAID are explained by their suppression of COX-1 and COX-2. Most NSAID inhibit COX-1 more efficiently than COX-2; COX-1 preferential NSAID include aspirin, indomethacin, ibuprofen, naproxyn, and piroxicam. Non-acetylated salicylates and diclofenac are about equal inhibitors of COX-1 and COX-2. Etodolac and meloxicam are COX-2 preferential by a ratio of about 10 to 1. Celecoxib and rofecoxib are COX-2 selective; the concentration required to inhibit COX-1 is about 1000 times greater than that required to inhibit COX-2[19].

Efficacy of NSAID. NSAID reduce the signs and symptoms of established inflammation. Amelioration of pain, swelling, heat, erythema, and loss of function begins promptly after their absorption into the blood and is rapidly reversible. Improvement of laboratory abnormalities, e.g., rheumatoid factor, acute phase reactants, serum albumin, hemoglobin, is not generally seen in clinical trials of NSAID therapy. Nevertheless, patients with RA who have symptoms of joint pain, tenderness, swelling, and stiffness during disease modifying antirheumatic drug (DMARD, e.g., MTX) therapy experience measurable benefit when adequate doses of an NSAID are added, and these symptoms promptly flare when the NSAID is withdrawn. This has been demonstrated in numerous NSAID clinical trials in which stable "background" treatment with a DMARD is continued, but the NSAID is shown to be more effective than control treatment with placebo.

NSAID clinical trials show more efficacy than is apparent in routine clinical practice because the baseline observations for the clinical trial are done during a required NSAID withdrawal flare of the signs and symptoms being measured. Patients who do not flare within a few days after stopping their pretrial NSAID are not admitted to the trial.

The maximum antiinflammatory potential of the various NSAID is about equal and is related to the duration of tissue exposure to effective concentrations of drug. Thus, higher doses and longer plasma half-life increase efficacy up to a point. For most NSAID, GI toxicity associated with COX-1 inhibition limits dosage. This is not the case with selective COX-2 inhibitors; nevertheless, with increasing doses, their efficacy reaches a plateau, and further increases in dose do not significantly increase antiinflammatory benefit. Thus, high doses of aspirin or indomethacin are as effective as the latest COX-2 selective drugs in the suppression of the symptoms of inflammation and fever.

In clinical use, the benefit of an NSAID is most evident during the post-withdrawal flare of joint pain, swelling, and stiffness that generally occurs within 5 or 6 half-lives after stopping an effective NSAID in an RA patient with active inflammatory disease. Resumption of the same or another NSAID rapidly reverses the flare, with statistically significant improvement within a few days to weeks. Patients adapt to the NSAID induced decrease in symptoms by increasing their physical activities as much as tolerated, until limited by increases in pain and stiffness. At this point, the benefit of the NSAID is no longer evident to the patient or physician, prompting a change to a different NSAID. Although clinical trials fail to document significant differences between NSAID if maximally effective doses are compared, individual patients frequently prefer one drug over others, perhaps due to better tolerability or efficacy in that individual at that time. Some NSAID, such as ketorolac, have been developed as analgesics, and others such as indomethacin and phenylbutazone are reputed to be more effective for spondyloarthropathies and gout. The scientific basis for these differences is not clear, but may relate to differences in drug metabolism or tissue penetration.

The efficacy of NSAID and DMARD should not be compared. Effective doses of an NSAID relieve many of the symptoms of inflammation without much effect on the underlying progression of the disease. An effective DMARD may completely suppress the disease progression, inducing a remission in some patients. Yet if a physician mistakenly stops an NSAID as soon as a slowly acting DMARD is started, the patient almost immediately notes increased pain, stiffness, swelling, and dysfunction, which is relieved by resumption of the NSAID. However, corticosteroid efficacy overlaps and surpasses that of NSAID. If one is willing to accept the adverse effect liability of corticosteroids, RA patients can and frequently are treated without NSAID.

Adverse effects. Toxicity has been a major problem with NSAID and since the 1800s development of new drugs has been driven by attempts to decrease their toxicity. Therapeutic or accidental overdoses of aspirin and salicylates (and acetaminophen) may be fatal, and frequently were encountered before the use of childproof caps and their displacement by safer NSAID. Phenylbutazone use was largely discontinued because of its association with aplastic anemia, agranulocytosis, and thrombocytopenia, with estimates of 16 to 22 deaths per million patients[13], and occasional deaths due to Stevens-Johnson syndrome or granulomatous hepatitis. Hepatic toxicity is fairly common; persistent abnormal transaminase values occurred in 5.4% of RA patients treated with aspirin and in 2.9% treated with other NSAID; it is more frequent with acetaminophen, diclofenac, sulindac, and phenylbutazone. COX-1 inhibition has been associated with decreased glomerular filtration rate and renal failure, especially in patients with marginal renal blood flow that is being supported by renal prostaglandins. The role of COX-2 in renal function is not as clear, but high doses of the specific COX-2 inhibitor rofecoxib have been

associated with edema and transient decrease in urinary sodium excretion[13].

By far the most important adverse effects of NSAID are related to the suppression of COX-1 mediated gastroprotective prostaglandins, which suppress excess gastric acid secretion and help to maintain the gastric mucosal barrier, leading to NSAID related dyspepsia, epigastric pain, indigestion, heartburn, nausea, and vomiting. Loss of gastroprotection results in mucosal hyperemia, diffuse gastritis, superficial ulcers, and penetrating ulcers that may be associated with GI bleeding or perforations and sometimes death. By life table analysis of prospectively collected data from multiple NSAID submissions, the US Food and Drug Administration (FDA) estimates that GI ulcers, bleeding, and perforation occur in about 1 to 2% of patients who use NSAID for 3 months and about 2 to 4% of those who use them for one year. Based on ARAMIS (Arthritis, Rheumatism and Aging Medical Information System) data, Fries estimates that NSAID induced gastropathy is responsible for 76,000 hospitalizations and 7600 deaths each year in the United States[20].

Over the years, various strategies were used to try to improve the gastric tolerability of aspirin and the NSAID. Administration was recommended with food to dilute the direct gastric irritation. Aspirin was prepared in rapidly disintegrating tablets, enteric coated tablets, and timed release dosage forms with some decrease in gastric distress. Nabumetone is an inactive prodrug in the stomach; after absorption, it is rapidly metabolized to the active NSAID 6 MNA (6-methoxy-2-napthyl acetic acid). At first antacids, then H2 blockers, and finally proton pump inhibitors were used to decrease gastric acid. Then the synthetic prostaglandin misoprostol was developed to prevent the toxicity associated with NSAID induced suppression of gastric prostaglandins by replacing them with an orally administered exogenous prostaglandin analog. The Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) trial was designed to prospectively evaluate serious upper GI clinical events in a double blind, randomized, placebo controlled 6 month study of 8843 older patients with RA (> 52 yrs of age; mean age 68) in a protocol designed to reflect normal clinical practice[21]. All patients were taking one or more of 10 specified NSAID. None had active peptic ulcer disease or were taking antiulcer medications. During the 6 month study, 67 events occurred that were defined as definite serious events (i.e., bleeding, perforation, or obstruction): 25 serious upper GI events (0.5 percentage rate of complication) occurred in the 4404 patients taking misoprostol, 200 g 4 times a day, and 42 (0.95% rate of complication) occurred in the 4439 patients receiving placebo, a statistically significant difference ($p = 0.049$ by Fisher's exact test). Thus, the misoprostol group showed a 40% reduction in the rate of serious complications compared with the placebo group. The 0.95% rate of serious upper GI events during 6 months of NSAID treatment in the control group confirms the earlier 2% to 4% per year estimates of the FDA. Risk factors for NSAID associated upper GI tract complications in this prospective randomized clinical trial are similar to those found in case control and cohort studies: older age, previous peptic ulcer disease (odds ratio twice that of comparison patients), previous GI bleeding (2.5 times more common than in the comparison group), and history of cardiovascular disease (rate with cardiovascular disease history 1.84 times higher than in the comparison group). The rate of occurrence of symptomatic GI adverse events over the course of the MUCOSA trial was relatively uniform in both groups. Other suspected risk factors include concomitant corticosteroid use, degree of disability, and presence of comorbidity.

The cumulative risk of these serious events increases with the duration of therapy and is greater in patients with previous peptic ulcer disease. Fatal outcomes are more likely in elderly or debilitated patients. Higher dosages of NSAID probably entail greater risk than lower dosages. The patient's disease, age, and degree of inflammation need to be considered in determining the optimal dosage for each patient, and every attempt should be made to use the lowest dose that adequately controls the patient's symptoms.

The incidence of endoscopically determined gastric erosions or ulcers in prospective double blind controlled clinical trials with selective COX-2 inhibitors is similar to that with placebo and much less than that with naproxen or ibuprofen. However, there was no significant reduction in the incidence of symptoms of nausea, dyspepsia, or abdominal pain[17]. Thus, specific COX-2 inhibitors appear likely to markedly decrease the serious and potentially lethal GI complications of NSAID therapy, but may only marginally improve their GI tolerability, and seem unlikely to increase their efficacy. In addition, because COX-1 inhibition is required for platelet anticoagulation, specific COX-2 inhibitors cannot replace low dose aspirin prophylaxis for myocardial infarction or strokes. COX-2 is upregulated by direct lipopolysaccharide stimulation of brain microglial cells and may be important in the brain response to infection. It also seems to be necessary for embryo implantation in the uterine myometrium[18]. However, the potential adverse effects in brain or reproductive functions are unlikely to be more severe with specific COX-2 inhibitors than they have been with standard NSAID, which also inhibit COX-2. Nevertheless, displacement of traditional nonselective COX-1/COX-2 inhibitors has important public health implications and should reduce the risks of symptomatic treatment of RA.

Future improvements in the efficacy of NSAID-like symptomatic therapy for RA will probably require new approaches to the control of inflammation, such as inhibition of inducible nitric oxide synthase, inhibition of nuclear factor-kappa B, inhibition of MAP kinase (mitogen activated protein kinase), or other mediators of inflammation.

Disease Modifying Antirheumatic Drugs (including Biologicals)

Historical highlights of drug treatment for RA with DMARD and biological therapies are presented in Table 2. The major toxicities known to be associated with these therapies and "estimated" efficacy are listed for each agent.

Gold salts. Based on the benefits of aurothioglucose in the management of articular symptoms in patients with rheumatic fever and endocarditis, in 1927 there was a hypothesis that rheumatoid joint inflammation might be a manifestation of infection with mycobacteria, which at that time was thought to be suppressed by gold. Gold salts were subsequently used for treatment of RA and shown to be beneficial[22]. The clinical experiences with gold compounds over several decades resulted in acceptance of the utility of gold in the management of RA.

Although gold compounds have shown efficacy in RA[22–31], the mechanism(s) underlying their clinical efficacy remains to be established. The efficacy of gold compounds in the treatment of RA was first reported by Forestier, who noted benefit in over two-thirds of 550 patients he treated with gold salts[22]. Double blind studies later confirmed the efficacy of gold sodium thiomalate in the treatment of RA[23]. Serum rheumatoid factor titer, erythrocyte sedimentation rate, C-reactive protein levels, fibrinogen levels, circulating immune complexes, and levels of gamma globulin all have been shown to decrease significantly during treatment with gold compounds[24-26]. Some clinical studies suggest that progression of joint space narrowing and erosions is diminished during treatment with gold sodium thiomalate[27,28].

Unfortunately, a large percentage of patients with RA either continue to have manifestations of active disease despite 4 to 6 months of weekly chrysotherapy or, after initially responding to gold therapy, develop recrudescence of disease activity despite continued treatment[32,33].

Due to many factors, including lack of initial response to or subsequent escape from the initial beneficial effects of chrysotherapy, and significant numbers of patients who must discontinue treatment because of toxicity, only a minority of patients remain on gold treatment beyond 3 to 5 years[32,33]. Some longterm (5 year) outcome assessments indicate that chrysotherapy does not significantly influence the natural course of RA with regard to functional status and overall symptoms[34].

During the course of treatment with parenteral gold compounds, about 33% of patients experience adverse reactions (Table 2). Although many of these reactions are relatively mild and may require only temporary withholding of, or adjustments in, the dose of gold, severe mucocutaneous, bone marrow, or renal toxicity may require cessation of therapy. Less than 50% of patients treated with parenteral gold compounds continue gold after 5 years, with about 60% of treatment terminations attributable to toxicity[33].

Antimalarials. The first published use of antimalarial compounds for treatment of rheumatic diseases was in the 1890s for lupus rash. Observations concerning the beneficial effects of quinacrine in individuals with RA were first reported in 1951[35].

The early controlled trials with antimalarials showed suppression of joint inflammation in patients with RA treated with chloroquine[36-39] or with hydroxychloroquine[39–41]. Recent controlled, multicenter studies in patients with early RA[42] have shown a decrease in joint inflammation and stiffness with a low level of significant side effects. Antimalarial drugs also have been shown to be effective in decreasing joint inflammation in children with JRA[43].

The initial efficacy and lack of reported toxicity associated with antimalarial therapy in RA patients during the 1950–1960 period led to escalation of daily doses up to 10 to 15 mg/kg/day. While hydroxychloroquine is effective in the treatment of RA, its onset of action is generally slow, requiring 3-6 months to become effective[41,44]. To investigate the usefulness of hydroxychloroquine dose loading to increase the percentage of responders or rate of response in treating RA, a recent study was performed where RA patients with mild disease were randomized to receive either 400, 800, or 1200 mg/day for 6 weeks[45]. The degree of clinical response was increased in those patients who received the highest doses. Short term ocular toxicity was not dose related, although GI toxicity was dose related.

Retinal changes occur in patients with chloroquine and hydroxychloroquine[46,47]. A recent review of the ophthalmology literature supports the safety of hydroxychloroquine at a dose of 6 to 7 mg/kg/day in patients without renal failure[48]. Retinopathy was initially reported after use of chloroquine[49] and several retinopathy cases were reported in chloroquine treated patients, particularly in patients with discoid lupus erythematosus, with daily doses exceeding chloroquine 500 mg/day[50]. The retinopathy may persist or progress even after chloroquine has been discontinued[51].

Ocular toxicity with hydroxychloroquine was first reported in 1967[46]. From 1960 to 1989 a total of 18 cases of retinopathy in patients receiving hydroxychloroquine were reported either in the literature or to the FDA[48]; in 16 of 18 of these cases, the dose of hydroxychloroquine was greater than 7 mg/kg/day. The issue of cumulative dose toxicity with hydroxychloroquine remains controversial, but several reports indicate the risks are low[52]. Other ocular effects include corneal deposits that may cause haloes to appear around lights. These superficial corneal deposits are often linear-appearing streaks and are located below the pupil; they are reversible when the drug is discontinued, and do not progress to visual damage[53]. The corneal deposits are relatively infrequent in hydroxychloroquine treated patients. In high doses, antimalarial drugs can impair visual accommodation due to dysfunction of the ciliary body, a problem experienced as blurred vision[46].

Maculopapular rash may occur in 3 to 5% of patients

Table 2. Historical highlights of DMARD therapy.

Introduced	Drug/Biological	Toxicity Frequency	Toxicity Severity	Drug Related Mortality	Efficacy (1+ to 4+)
1935	Gold salts Gold sodium thiomalate Aurothioglucose	Mucocutaneous Renal (proteinuria) Myelosuppression Pneumonitis Polyneuropathy Nitritoid reactions Ocular or cutaneous chrysiases	Mild to severe	Yes	2+
1951	Antimalarials	Retinopathy (rare) Maculopapular rash (3–5%) Myopathy/cardiomyopathy Neuropathy (rare)	Mild to moderate	None	1+ to 2+
1960s	D-penicillamine	Mucocutaneous Renal Bone marrow suppression Hepatitis Pneumonitis Autoimmune disorder	Mild to severe	Yes	2+
1970s	Sulfasalazine	Mucocutaneous Hematologic Pneumonitis Drug induced SLE	Mild to moderate	Rare	1+ to 2+
1970s	Azathioprine and Cyclophosphamide	Myelosuppression Gastrointestinal Hepatotoxicity Pneumonitis Rash Congenital deformities Malignancy Infections	Mild to severe	Uncommon	2+
1980s	Auranofin	Same as injectable but less frequent	Mild to severe	Rare	1+
1980s	Methotrexate	Stomatitis Hepatotoxicity Lung-fibrosis, pneumonitis Lung-pneumonitis Hematopoietic-cytopenia Abortifacient, teratogenic Infections-opportunistic (rare) CNS toxicity Alopecia, rash Neoplasia-?	Mild to severe	Uncommon	3+
1990s	Cyclosporine	Nephrotoxicity Hypertension Hirsutism	Mild to severe	Uncommon	2+
1998	Leflunomide	Diarrhea Rash Alopecia Elevated liver enzymes Teratogenic	Mild to severe	Rare	3+
1998	Etanercept	Injection site reactions (37%), infections	Mild	Rare	4+
1999	Infliximab	Antibody responses to murine protein, infections	Mild	Rare	4+

receiving antimalarial medications. Patients taking longterm chloroquine and hydroxychloroquine may develop areas of hyperpigmentation in photo exposed regions. Muscle weakness and vacuolization of muscle cells on biopsy have been reported in patients receiving chloroquine[54]. A few cases of cardiomyopathy have been reported in chloroquine treated

patients[55-57]. Leukopenia and aplastic anemia have developed during antimalarial treatment with both chloroquine and hydrochloroquine, but the relationship to drug treatment remains unclear[58-60].

Many mechanisms have been proposed for modulation of the immune response by antimalarial drugs. One attractive mechanism is that antimalarials interfere with the "presentation of antigen" by macrophages to T cells[61]. Additional mechanisms of action for antimalarials have been proposed including inhibition of DNA polymerase[62] and interference with phospholipase A1[63], interference with neutrophil superoxide release[64], and inhibition of cytokine release [including interleukin 1 (IL-1), tumor necrosis factor (TNF), interferon–γ] has been reported with chloroquine and hydroxychloroquine[65-67]. These activities would be expected to result in a rapid onset of antiinflammatory activity (i.e., similar to corticosteroids or NSAID), but the clinical onset of benefit with antimalarial drugs takes several months after starting medication.

D-Penicillamine. Penicillamine was first identified in acid hydrolysates of penicillin[68]. The potential effectiveness of penicillamine in disrupting disulfide bonds in IgM rheumatoid factors provided the initial rationale for its use in rheumatoid arthritis[69]. Improvement in synovitis and other disease manifestations was documented during clinical trials with the drug in the 1960s and early 1970s.

In controlled clinical trials, penicillamine has been found to be as effective as gold and azathioprine in the treatment of RA[70-72]. Since the dose must be increased gradually, clinical responses may not become apparent for several months after institution of therapy.

Treatment with penicillamine is usually initiated with an oral daily dose of 250 mg. The daily dose is gradually increased in 125 to 250 mg increments every 8 to 10 weeks. If the desired clinical effect has not been achieved after 6 months of treatment with this dose, gradual increases in the dose up to 1000 mg daily may benefit some patients[73,74].

Side effects observed in patients treated with D-penicillamine include mucocutaneous, hematologic, and renal toxicity and are often a limiting factor when using penicillamine in the treatment of RA (Table 2). Cutaneous reactions are the most common side effects experienced during treatment with penicillamine. In patients with RA, therapy with penicillamine is associated with a greater than expected occurrence of a variety of autoimmune syndromes. These include polymyositis, myasthenia gravis, pemphigus, and systemic lupus erythematosus.

Cytotoxic drugs (azathioprine and cyclophosphamide). Although commonly referred to as a cytotoxic drug, azathioprine also exerts antiproliferative, immunoregulatory, and antiinflammatory actions that may play as important roles as the cytotoxic effects in treating RA.

Controlled trials have documented the effectiveness of azathioprine in RA[75-77], and longterm followup studies confirmed continued clinical benefit[78-81]. Comparisons of azathioprine and MTX in patients with RA have produced conflicting results[82-86]. A retrospective study and one prospective controlled trial comparing azathioprine and MTX suggested that MTX was superior to azathioprine[83]. Three other prospective randomized trials, however, have not revealed a difference in efficacy between the two drugs[84-86].

Several adverse effects have been associated with azathioprine (Table 2). Adverse drug effects caused discontinuation of azathioprine in 19 to 32% of patients[87-90].

Nitrogen mustard was the first alkylating agent used in the treatment of refractory RA in 1951[91]. Cyclophosphamide has since become the principal alkylating agent used to treat rheumatic diseases. Although efficacious, the alkylating agents exhibit serious longterm toxicity, especially the induction of malignancies, which is a major concern. Cyclophosphamide and chlorambucil are not approved by the FDA for the treatment of RA. Several uncontrolled[92-96] and controlled trials have evaluated cyclophosphamide therapy in patients with RA. The daily dose of cyclophosphamide used in RA is generally 1 to 2 mg/kg. In view of their carcinogenicity, alkylating agents are now rarely used to treat RA.

Alkylating agents exhibit significant associated toxicities that must be considered in the risk-benefit assessment and reviewed with each patient before treatment is considered (Table 2). Monitoring is essential to minimize adverse effects in patients receiving these drugs.

Sulfasalazine. Sulfasalazine was initially developed specifically for the treatment of RA. In the late 1930s, Svartz designed a compound that contained both a salicylate and a sulfa component, and, in early 1942, reported positive therapeutic benefits of salazopyrin (sulfasalazine) in rheumatic polyarthritis and ulcerative colitis. In 1949, Sinclair and Duthie[97] published an uncontrolled trial comparing gold, sulfasalazine, and placebo. However, no significant differences were reported in any group. The results of this study were widely accepted for the next 30 years, and investigation into the efficacy of sulfasalazine in RA did not progress until the reports from McConkey, *et al* suggested beneficial effects with sulfasalazine in RA[98,99]. Since then several controlled clinical trials have also suggested efficacy in RA[100-103]. Although sulfasalazine has been used as therapy for RA for almost 50 years, its mechanism of action remains undefined.

About 30% of patients treated longterm with sulfasalazine discontinue the drug because of adverse effects. The adverse reactions associated with sulfasalazine are usually benign and readily reversible with discontinuation of the medication. The adverse effects associated with sulfasalazine can be divided into two major categories. The first is dose related and acetylator phenotype dependent. These effects include nausea, vomiting, headache, malaise,

hemolytic anemia, reticulocytosis, and methemoglobinemia[101]. The second group of adverse events appears as a hypersensitivity reaction and includes rash, aplastic anemia, and autoimmune hemolysis (Table 2).

Methotrexate. Aminopterin, a folic acid analog and precursor of MTX, was first reported as being used for the treatment of RA by Gubner in 1951[104]. Over the next few years dermatologists investigated the use of MTX and demonstrated its efficacy for manifestations of psoriasis[105]. In the 1980s randomized clinical trials for RA were conducted[106-109] and MTX was approved by the FDA as a DMARD for the treatment of this disease in 1987[110].

The exact mechanism of action of MTX in improving the clinical manifestations of RA is not completely understood. MTX is capable of inhibition of folic acid-dependent pathways. In addition, MTX affects several mediators of inflammation, which likely explains the rapid clinical response observed in patients treated with this agent. These include IL-1[111,112], IL-6[113], leukotriene B4[114,115], and phospholipase A_2 activity[116]. MTX also has been shown to have immunosuppressive effects[117-119].

MTX is currently the most commonly used therapeutic agent for RA. Several randomized, placebo controlled clinical trials were conducted in the 1980s demonstrating its short term clinical benefits[106-109]. The longterm efficacy of MTX in RA has been established by several investigators[120–130]. After 5 years, MTX treated patients with RA exhibited about a 50% probability of still receiving MTX, compared to 15 to 20% for other DMARD such as gold salts or D-penicillamine[129]. It has been noted that the drug survival curves suggested that patients who began taking MTX early in the 1980s had a lower probability of continuing MTX than those patients who had started it in the late 1980s, possibly related to the growing experience of both patients and physicians with its use[129,131].

Until recently prevention of disease progression by MTX had not been definitely determined radiographically[132-134]. The recently published placebo-controlled trial comparing MTX to leflunomide showed that both these drugs were superior to placebo in slowing radiographic progression of disease in a relatively early onset RA patient population[5,135].

Adverse events reported with MTX therapy in RA vary in severity from minor to severe (Table 2). GI manifestations have been reported to occur in as many as 60% of MTX treated RA patients[136]. Many GI manifestations can be alleviated by the concomitant administration of folic acid, or a change in route of administration (from oral to parenteral). The occurrence of liver damage after prolonged administration of MTX for RA was a matter of serious concern in the 1980s based on previous experience with the drug in the treatment of psoriasis[137-144]. It has now become evident that clinically significant liver disease is less frequent than previously predicted. The potential toxicities of MTX in the treatment of RA patients has resulted in the American College of Rheumatology (ACR) developing guidelines for monitoring for some of these events[145].

An acute pulmonary syndrome or allergic pneumonitis, although uncommon, is a potentially severe and fatal adverse event[146-153]. Infectious processes need to be ruled out in this clinical setting.

Longterm observational studies with the use of MTX in RA patients have revealed an acceptable toxicity profile as well as sustained clinical benefit. However, few data are available regarding the effect of MTX on mortality in RA. Recent data suggest that MTX therapy may improve life expectancy even in patients with advanced RA[154].

Leflunomide. Leflunomide was recently approved (1998) for the treatment of RA. Three pivotal clinical trials have been performed within the past few years. A phase III study conducted in the United States and Canada included 482 MTX naïve adults with active RA[135]. Patients received either leflunomide (20 mg/day), MTX (7.0-15.0 mg/wk), or placebo for 52 weeks. Leflunomide was statistically equivalent to MTX in relieving the signs and symptoms of active RA.

Another study was conducted in 358 sulfasalazine naïve adults with active RA comparing leflunomide (20 mg/day), sulfasalazine (2 g/day), or placebo[155]. Leflunomide was equivalent to sulfasalazine in improving signs and symptoms of RA. A third study was conducted in Europe, Australia, and New Zealand, where 999 MTX naïve adults with active RA were randomized to receive leflunomide (10 mg/day) or MTX (7.5–15.0 mg/wk) for 52 weeks[156]. In this study MTX was superior to leflunomide in improving RA signs and symptoms.

In these 3 studies, leflunomide, MTX, and sulfasalazine were all statistically better than placebo in slowing disease progression measured radiographically. Leflunomide, MTX, and sulfasalazine were not statistically different from each other in mean changes in total scores[5].

In an open label trial of leflunomide and MTX combination treatment, 30 patients with RA were treated for 52 weeks[157]. Sixteen (53%) of the patients met the ACR criteria for a 20% improvement in symptoms. Of concern, a 10% incidence of transaminase elevations was observed. A randomized, placebo-controlled combination trial is currently in progress to better define the tolerability of this combination.

Adverse events considered related to leflunomide in the controlled trials included diarrhea, rash, reversible alopecia, and liver transaminase elevations (Table 2). Pregnancy is contraindicated with leflunomide and MTX because both are teratogenic. Additional clinical studies are needed to determine if extended treatment with leflunomide causes liver damage.

Cyclosporine. Cyclosporine has been the most extensively investigated of the immunomodulatory agents. Cyclosporine has variable antifungal properties, but was devel-

oped primarily because of its potent immunosuppressive properties[158,159]. Most of its effects on immune responses are secondary to relatively selective inhibition of T cell activation[160,161]. Cyclosporine forms complexes with cytoplasmic binding proteins, called immunophilins, which appear to be essential in exerting the immunosuppressive effects.

The first study of cyclosporine as a treatment for RA was reported by Herrmann and Mueller in 1979[162]. This initial open label evaluation of what would now be considered very high doses of cyclosporine was performed in 7 patients with RA. Elevations of serum creatinine and the development of herpes zoster in 2 patients slowed the development of this agent for treating RA. Other open label trials in RA were initiated in the early to mid-1980s[163-168]. While clinical efficacy was noted, again elevations of serum creatinine levels were of major concern. Multiple controlled trials evaluating cyclosporine in RA have now been performed[169–176]. A majority of patients with RA treated with cyclosporine in clinical trials had average disease durations of over 10 years and had previously received 3 or more slow acting antirheumatic drugs.

The toxicities of cyclosporine include reversible and irreversible renal disease, hypertension, and hirsutism.

Combination DMARD. Only a few years ago combination DMARD therapy was regarded as an unusual approach to patients with RA, and was generally a treatment for patients with the most severe disease[177-179]. However, in 2000 almost all rheumatologists use combination DMARD therapy in some patients[180,181]. This shift in the treatment paradigm for RA may be explained in part by a more accurate description of the natural history of RA, availability of improved DMARD (i.e., MTX), and recognition that partial control of inflammation likely does not prevent joint damage.

DMARD were once referred to as "remission-inducing," a term that should no longer be used, as sustained remission is seen in fewer than 2% of patients treated with traditional DMARD monotherapy[182]. However, continuous treatment with DMARD does ameliorate the course of RA[183-186], including retardation of radiographic progression[187-189]. Over the past 10 years several new DMARD have become available, including cyclosporin A, leflunomide, etanercept, and infliximab, all of which have been studied as monotherapy and in combination with MTX. MTX emerged as a major advance during the 1990s, with longterm effectiveness. Although MTX is continued for over 5 years by more than 50% of patients[190,191], few patients with RA are in complete remission, and many, if not most, may be candidates for combination therapy.

MTX is the most commonly used "anchor drug" in combination therapy. Evidence from randomized, controlled clinical trials and observational studies has indicated increased efficacy and acceptable (and often lower) toxicity for combinations of MTX plus cyclosporine, hydroxychloroquine, sulfasalazine, leflunomide, etanercept, and/or infliximab. Further studies lasting 5 years or more are needed to determine the longterm effectiveness, toxicities, and optimal clinical use of disease modifying antirheumatic drug combinations.

Early uncontrolled clinical studies suggested that combination therapy with DMARD was efficacious[178,192]. However, initial randomized controlled clinical trials yielded varying results, with some suggesting no advantages to combination therapy[194-198]. The conflicting conclusions of these early studies may partly reflect design issues in clinical trials, such as patient selection, short time frame, and use of surrogate markers, all of which may limit recognition of differences between various regimens despite inclusion of control groups. Over the past 5 years, several randomized, controlled clinical trials with more complex designs have indicated that combinations of MTX with other DMARD are more effective than single agents, with acceptable toxicities (Table 3).

It seems unlikely that one particular combination of DMARD will be best for all patients, and some patients will respond sufficiently to monotherapy and will not require combination therapy. Although more patients respond to MTX than to any other drug, certain patients cannot tolerate MTX and other patients may respond more to other available drugs.

Anti-TNF agents. An important advance in treatment of RA is the advancement of therapies targeted at specific inflammatory processes involved in the disease. Etanercept, a TNF inhibitor, was the first biological agent approved for the treatment of RA (November 1998). Infliximab, a chimeric (mouse/human) anti-TNF monoclonal antibody (Mab), was also approved by the FDA for use in the treatment of RA in November 1999.

The TNF precursor is found in a variety of cells throughout the body. Macrophages appear to be the primary site of TNF production in RA with the active form of TNF, via TNF-α converting enzyme (TACE) mediated cleavage of the precursor molecule. After being shed from the cell surface, these soluble TNF molecules aggregate into trimolecular complexes that subsequently bind receptors found on a variety of cells, including fibroblasts, leukocytes, and endothelial cells. Two TNF receptors have been described, the p55 (also called p60) receptor and the p75 (also called p80) receptor.

TACE also cleaves the extracellular domain of the cell bound TNF receptors, forming soluble TNF receptors (sTNFR). These circulating sTNFR are then free to bind the trimolecular TNF complexes, rendering them biologically inactive; thus, the sTNFR function as natural inhibitors of TNF mediated inflammation.

A variety of physiological functions have been ascribed to TNF-TNF receptor interactions. TNF blocks the action of lipoprotein lipase, causing severe cachexia in experimental models of chronic infection. Additionally, TNF induces

Table 3. Recent clinical trials of combination therapy with 2 or more disease modifying antirheumatic drugs in RA that indicate greater efficacy of combination therapy*.

Study, Year	Patients	Therapy Compared
Tugwell, 1995[230]	148	MTX plus cyclosporine**; MTX only
O'Dell, 1996[233,238]	102	MTX plus sulfasalazine plus hydroxychloroquine; sulfasalazine plus hydroxychloroquine, MTX only
Boers, 1997[236]	155	Sulfasalazine plus MTX plus prednisolone; sulfasalazine only (may be replaced by MTX after 6 months)
Maini, 1999[231]	428	Infliximab** plus MTX; MTX plus placebo
Maini, 1998[209]	101	Infliximab plus MTX; infliximab only; MTX only
Weinblatt, 1999[203]	89	MTX plus etanercept**; MTX plus placebo
Mottonen, 1999[232]	199	MTX plus sulfasalazine plus hydroxychloroquine plus prednisolone; sulfasalazine

*Modified from reference[237].
**Added in patients who tolerated MTX but had inadequate benefit.
MTX: methotrexate.

programmed cell death (apoptosis) and stimulates the release of several proinflammatory cytokines, including IL-6, IL-8, and IL-1. TNF also induces the release of matrix metalloproteinases from fibroblasts, chondrocytes, and neutrophils, and upregulates the expression of endothelial adhesion molecules, leading to the migration of leukocytes into extravascular tissues.

Etanercept. Etanercept is a recombinant, soluble TNF receptor (p75) fused to the Fc portion of a human IgG1 molecule. Fusion to an Fc fragment gives the agent several advantages over unconjugated soluble receptors. The dimeric construct results in significantly longer serum half-life, increasing the binding affinity for the trimolecular TNF aggregate. Etanercept's mode of action relies on its ability to bind TNF in serum, rendering the cytokine biologically inactive. The serum half-life of etanercept is 3–4 days.

Etanercept has proven to be a potent DMARD with a favorable toxicity profile[7,199-205]. A phase II, double blind, placebo controlled 3 month trial[201] randomized 180 patients with active, longstanding RA to 1 or 3 doses of etanercept (0.25, 2, or 16 mg/m^2) or placebo, all given by subcutaneous (sc) injection twice weekly. High dose (15 mg/m^2) etanercept was superior to both the low doses and placebo. Using standard ACR criteria[206] to evaluate the treatment response, 75% of patients receiving etanercept 16 mg/m^2 experienced 20% improvement at trial end, the majority showing substantial benefit as early as 1 month into the study. Etanercept injections were associated with minimal toxicity; minor injection site reactions were the only observed adverse effect seen more commonly in the etanercept groups versus placebo.

The phase III trial[202] differed from the phase II trial both in terms of dosing and duration of the investigation. In this 6 month, double blind, placebo controlled trial, investigators compared fixed doses (10 mg and 25 mg sc twice a week) with placebo. Again, the high dose regimen resulted in substantial clinical benefit with little associated toxicity. Patients receiving etanercept experienced sustained rapid benefit, often within the first month of therapy. Fifty-nine percent of patients met ACR criteria for 20% improvement (ACR 20). Forty percent met similar criteria for 50% improvement. Functional activity, measured by the Health Assessment Questionnaire (HAQ), showed significant improvement over the course of the study. In terms of the disability index, patients receiving placebo had a mean change from baseline of 2%, compared with 39% for those in the etanercept 25 mg group. Again, transient injection site reactions remained the most commonly observed adverse event in the etanercept groups compared with placebo. In all of the controlled trials, injection site reactions were seen in 37% of those receiving etanercept versus 10% of those receiving placebo ($p < 0.05$).

Data on the longterm use of etanercept has been presented at the ACR national meetings[205]. A large cohort of patients (N = 713) receiving etanercept with a cumulative exposure to drug of 1152 patient-years was followed longitudinally. The clinical benefit seen in previous short term clinical trials was maintained in longterm followup. There was no increase in serious toxicity over the course of the study. Minor injection site reactions, resulting in study withdrawal by less than 0.5% of patients, were the most common adverse event.

Data from this longterm study begins to address some of the concerns about the general effects of blocking TNF activity. Specifically, there was no increase in infections requiring intravenous antibiotics. Longterm followup

revealed no increase in the incidence of any infection compared with placebo controlled studies. There were 9 reported cases of incident neoplasia, less than the expected number (10.7) calculated from the NCI SEER (National Cancer Institute Surveillance, Epidemiology and End Results) database. No patients have developed drug induced lupus or anticardiolipin antibody syndrome while receiving etanercept.

The use of etanercept in combination with MTX for the treatment of longstanding refractory RA has been studied[203]. Patients with active disease despite an average of 18.3 mg/wk of MTX were randomized to receive either etanercept (25 mg sc twice a week) or placebo. The addition of etanercept to MTX resulted in substantial benefit. At the end of the 24 week trial, 71% of those receiving combination therapy met ACR 20 criteria, compared with 27% of those receiving placebo plus MTX. The combination resulted in significantly greater improvement in all individual measures of disease activity used to define improvement by the ACR method. Minor injection site reactions were the only adverse event reported more often in the MTX-etanercept group.

Currently, etanercept is approved for use in RA patients who have not improved with 1 or more DMARD. While the majority of studies have been in patients with longstanding DMARD refractory disease, there is accumulating evidence that etanercept will slow disease progression when given earlier in the disease course. Results from the ERA (the Use of Etanercept in Early RA) trial were published[7].

The ERA trial included 632 patients with early RA (disease duration < 3 years) assigned to 1 of 3 treatment arms: (1) etanercept 25 mg twice a week and placebo oral tablets once a week, (2) etanercept 10 mg and placebo tablets, or (3) MTX 7.5 initially, rapidly increased to 20 mg and placebo injections. All patients received 1 mg folic acid daily, to reduce the dose limiting toxicity of MTX. The trial duration was 1 year, and the data was assessed using intent-to-treat analysis. The MTX dose was rapidly escalated in the first 8 weeks of the trial in order to optimize its effect, and an average dose of 18.3 mg/wk was achieved. Baseline characteristics of the study groups, including measures of disease activity, were similar.

Radiographic evidence of joint damage was measured by a modified Sharp score, including components for both joint space narrowing and erosions. At the end of the trial, there were no statistically significant differences in radiographic progression between Sharp total scores for etanercept and MTX. However, when examining the results by individual component scores, etanercept (25 mg) was more effective than either low dose etanercept or MTX at reducing the progression of joint erosions. This difference was statistically significant. Seventy-five (75%) of the patients in the etanercept 25 mg group had no erosions, versus 57% of the MTX group ($p < 0.001$).

In the ERA trial clinical efficacy was assessed by the area under the curve (AUC) calculated from a numeric ACR (ACR-N) response. The ACR-N represents the actual percentage of improvement in ACR criteria for an individual patient. The AUC for etanercept was significantly superior to that for MTX at both 6 months and 12 months ($p = 0.002$ and $p = 0.009$, respectively).

Study withdrawals related to toxicity were more common among those receiving MTX, while infection rates were lower in those receiving etanercept. Of patients receiving MTX (n = 217), 10 withdrew secondary to adverse events, compared with 5 of 207 receiving etanercept 25 mg. Laboratory abnormalities were similar among the 3 cohorts, with the exception of elevated liver function tests and lymphopenia, which were more frequent in the MTX group. About twice as many patients taking MTX as patients taking etanercept (both dose groups) had elevations of SGOT (32% vs 16%) or SGPT (44% vs 23%). Minor injection site reactions were the most commonly observed adverse event for patients receiving etanercept (37% of those receiving 25 mg of etanercept experienced these reactions, vs 7% of those receiving MTX).

Infliximab. Infliximab is a chimeric (murine/human construct) anti-TNF Mab composed of a constant region from human immunoglobulin and a variable region from murine immunoglobulin. Previously approved for the treatment of Crohn's disease, infliximab received FDA approval for the treatment of RA in November 1999. Clinical trials summarized below have confirmed both the efficacy and tolerability of the agent when used in patients with DMARD refractory RA, both alone and in combination with MTX[6,207-210].

In the initial phase I, open label trial, Elliott and colleagues[210] studied the use of infliximab in 20 patients with active, longstanding RA. Patients had a median disease duration of 10.5 years and had failed a median of 4 previous DMARD. Patients received a total of 20 mg/kg of intravenous infliximab given in divided doses over the course of 12–14 days. Clinical response to the treatment was substantial. Morning stiffness decreased from a median of 180 minutes at study entry to a median of 5 minutes at week 6. Pain scores decreased from 7.1 to 1.9 (range 0–10) over the same time period, representing an improvement of 73%. Swollen joint count dropped from 18 to 5, while serum C-reactive protein (CRP) levels fell from a median 39.5 mg/dl at study entry to 8 mg/dl at week 6. Functional capacity, as measured by HAQ score, improved significantly from a median of 2.0 at study entry to 1.1 by 6 weeks. Patients showed sustained benefit following the last dose of infliximab, with response duration ranging from 8 to 25 weeks (median of 14).

A phase II placebo controlled trial[207] included 73 patients who, similar to those in the phase I trial, had longstanding DMARD refractory RA. Results in this trial were similar. Patients in the active treatment groups received only a single

intravenous infusion of infliximab, either 1 mg/kg or 10 mg/kg. At the 4 week assessment, 79% of patients receiving 10 mg/kg reported at least 20% improvement in symptoms and half had at least 50% improvement in disease activity.

In both the phase I and phase II trials, infliximab was well tolerated without reports of any clinically significant adverse events. No patients had evidence of human anti-chimeric antibodies (HACA) subsequent to infliximab administration when assessed at the 4 week examination[210].

In a continuation of this phase II trial[208], 8 of the original 20 patients from the phase I open label trial returned after a 4 week interval and were retreated with up to 3 additional doses of infliximab. The timing of the additional doses was determined by disease relapse. Repeat administration again resulted in significant clinical improvement with minimal adverse effects. The improvement interval between doses, however, became progressively shorter during the course of the study. Additionally, 4 of the 8 patients developed HACA; antibody development may well account for the decreasing response duration observed during the course of the study.

In a double blind, placebo controlled trial, 101 patients were given intravenous infliximab (1, 3, or 10 mg/kg) with or without MTX (7.5 mg/week) or MTX plus intravenous placebo[209]. Sixty percent of patients receiving infliximab, with or without MTX, experienced at least 20% improvement in disease activity. Importantly, coadministration of low dose MTX significantly prolonged the duration of response seen with low dose (1 mg/kg) infliximab. Coadministration of MTX with higher doses of infliximab (3 and 10 mg/kg) also prolonged response duration, although not statistically significantly. All treatment arms were associated with minimal toxicity; headache was the most commonly observed adverse effect in patients receiving combination therapy. The overall incidence of HACA was 17% for patients receiving infliximab (with and without MTX), with the incidence inversely proportional to the dose of infliximab. Half the patients receiving low dose infliximab (1 mg/kg) without MTX developed HACA, compared with 7% of those receiving 10 mg/kg. Concurrent administration of low dose MTX greatly diminished development of HACA (by about 3-fold), suggesting that MTX induces an immunologic tolerance to infliximab.

Results from a 54 week, double blind, placebo controlled trial of infliximab in combination with MTX were reported[6]. Infliximab (3 mg/kg or 10 mg/kg intravenously) or placebo was given at 4 to 8 week intervals to patients with active RA who were also receiving MTX. Fifty-nine percent of patients receiving 10 mg/kg and 42% of those receiving 3 mg/kg at 4 to 8 week intervals experienced 20% improvement by ACR criteria. There were no statistically significant differences in percentage of responders among the infliximab groups. When compared to placebo, there was no increase in the incidence of adverse effects. The combination resulted in a statistically significant reduction in radiographic progression (measured by Sharp score) compared with MTX treatment alone.

PYRAMIDS, INVERTED PYRAMIDS, AND THERAPEUTIC PARADIGMS

Historical Evolution of the Current Approach

The therapeutic pyramid was the principle paradigm on which discussions of rheumatoid therapy were based for the last quarter century. It took time to develop as the different layers became available and/or accepted, but it took much less time to "self-destruct" once it was clear that its use was inappropriate and outmoded.

The beginnings of rheumatoid therapy in the 1930s were associated with better delineation of the disease, but apart from prescriptions of rest and casts, included a wide variety of what would now be regarded as "alternative" approaches, e.g., vaccine therapy, treatment of focal infections, bee stings, high dose vitamins, etc. Acetylsalicylic acid (ASA) was available and was used, often to tolerance; gold had been introduced, but was not widely used and did not reach North America until its introduction by Adams and Cecil in 1950 in the USA, and by Robinson in the spa town of Banff, Alberta, Canada.

The base of the pyramid. This was, in the 1940s and 1950s, the standard approach involving "physical medicine and rehabilitation." Splints were *de rigeur*, and were designed for a wide variety of uses including the prevention of ulnar deviation. Bed rest, correct posture in bed, and a bed exercise program were incorporated into most rheumatoid programs through the 1970s. As recently as 1971 Boyle and Buchanan's textbook[211] makes the point that "there is no agent which will significantly alter the course of this disease over a number of years." This may have been true, but part of the problem was that there remained in the 1950s and beyond a significant optimism about the outcome of RA in at least some academic circles. Thus, in 1955 both Duthie in Scotland and Ropes from Massachusetts agreed with "the findings that suggest a good prognosis..." in rheumatoid patients[212]. This is clearly a reflection of the quality and quantity of available outcome measures at that time. The wide variety of available physical therapies, including moist and dry heat, waxes, the proper use of cold, massage, and even heliotherapy and fever therapy, were generally accepted by most without any sense of a requirement to assess outcomes or effectiveness. However, as the period of clinical trials came into its infancy there was a controlled study in 1963 demonstrating the benefits of complete immobilization of a rheumatoid joint using splints for a 3 week period[213].

The next layers. ASA was traditionally included in "the base," but the evidence for a developing pyramidal approach was present in the 1960s. The Empire Rheumatism Council had had a successful trial of gold so

that its acceptance became wider, but Copeman's (UK) textbook in 1965 included the statement that "gold should never be the treatment of first choice in early cases, many of whom do remarkably well on simple conservative measures."[214] Thus, "second line" treatment began. Svartz had developed salazopyrine in 1939 with some seeming initial success. In this newly developing scientific approach a clinical study was designed to assess it, but the drug showed no benefit and was rejected[97]. This was because of faulty study design, including poor statistical methods, but also — a recurrent theme for many decades — poor outcome measures. However, the drug was not restudied and reintroduced as a "second line" agent until the mid-1970s.

NSAID. At this period, the first of the new (post-ASA) NSAID were introduced. They gradually gained acceptance as (short term) clinical studies showed they reduced pain and stiffness. These then became the second tier. As new ones arrived they were added, and some, like butazolidin, and to some degree indomethacin and fenamates, were virtually discarded, chiefly because of toxicity issues. The NSAID overall were considered very safe, again longer term outcome studies had not been carried out.

2nd line drugs. Antimalarials were recognized, but again fear of toxicity, in this case ocular, restricted their use. As dosages were standardized over the years this issue has now virtually disappeared. Penicillamine was added to this list and remains accepted, levamisole was also included in some countries, and while efficacious in short term studies, was rejected because of toxicity concerns, specifically agranulocytosis.

The apex. Azathioprine and cyclophosphamide — or other alkylating agents — occupied this position. They represented "last resort" options, and although azathioprine gained acceptance in the UK particularly, it was especially as a "steroid sparing" agent, i.e., allowing a reduction in the dose of systemic steroids used. This did not have a strong appeal.

In Copeman's 5th edition (1978), Carson Dick described 1st line, 2nd line, and 3rd line drugs with progression from one class to the next[215]. In 1985, prior to its immediate demise, the pyramid was published as a formal structure in McCarty's 10th edition[216].

Over the same period two other major areas of therapy were evolving — steroids and surgery.

Systemic corticosteroids. Systemic corticosteroids, initially cortisone and ACTH, but subsequently prednisone and prednisolone, were introduced after the dramatic demonstration of their efficacy in individual patients. It did not take long to recognize that there were definite risks attached to their use, and the "steroid honeymoon" did not last long. First, controlled trials of cortisone and later prednisone by the Empire Rheumatism Council were not able to show a disease modifying effect of cortisone, and while the data from the prednisone study could be interpreted as showing a decrease in radiologic progression, the side effects and death rate in this 2 year study can only be described as awesome[217]. Textbooks in the 1960s and 1970s devote almost as much space to describing steroids and their side effects as they did to the rest of the therapeutic armamentarium combined. In 1964, Copeman, who had been a pioneer in the use of steroid therapy in the UK, said in his textbook, "it is clear that corticosteroids have a distinctly limited role in the treatment of rheumatoid arthritis."[214] Lightfoot, in the 1985 edition of McCarty's textbook, puts systemic steroids at the apex of the pyramid, above cytotoxic drugs[216]. Ward, however, pointed out even in 1990 that while "it is traditional teaching that systemic corticosteroids should not be used in the early treatment of rheumatoid arthritis, it is common practice to use them so."[218] This is borne out by tables in most therapeutic studies in RA from the US and elsewhere showing 50% of subjects receiving systemic steroids[1,2]. Pincus and others, including Corbett[3], have shown that those receiving steroids have an increased mortality. The data from Fries supported this, but were not consistent with the idea that it was merely a reflection of increased disease severity in those receiving steroids, in that he was not able to show an association for azathioprine and increased mortality[4]. Two recent controlled, prospective studies have shown a decrease in erosion progression in patients receiving low dose, 7.5 mg and 5 mg, of prednisone[219,220]. One of them curiously was not able to confirm symptomatic improvement, which was the usual reason for their use. This evidence is still not widely accepted, and remains controversial[221].

Some would argue that even if systemic corticosteroids do slow progression to some extent, the demonstrated negatives (not least an increase in mortality) markedly outweigh this advantage, and this is supported by cross sectional studies, but as yet there are no truly longterm trials available. If new therapies arrive that will allow the avoidance of systemic use of this potentially dangerous agent, many rheumatologists would be delighted. It is important to emphasize that the above discussion reflects chronic systemic use and not the use of local steroids.

Surgery. The other — much more positive — development that occurred alongside the sequential pyramidal approach to rheumatoid therapy is the surgical approach. Synovectomies, usually of the knees, were carried out in the 1930s, but the results then and subsequently were assessed only in the short term, and clearly recurrences were frequent. The procedure is much less frequent now as we recognize that the establishment of overall disease control is more important.

Arthrodesis was, and still remains, a "salvage" procedure. Many of these, e.g., knee and hip, provided major difficulties and had been largely abandoned. Some, e.g., fusion of joints in the wrist and mid-tarsals, can be very

effective in relieving pain and thereby improving function, and are still in use.

Arthroplasty. The old procedure of excision arthroplasty is largely confined to the metatarsophalangeal joints, and occasionally the radial head, but it is the advent of joint replacement, and especially total joint replacement, that has relieved so much suffering. This began with the development of vitallium, initially used as a cup and then as a prosthesis (Austin-Moore). The introduction of cement by Charnley, associated with positive pressure laminar air flow and antibiotics to reduce infection, as well as better implant materials and engineering, has transformed these procedures. They remain an indication of the failure of medical treatment, but replacement of hips and knees is in regular, routine use; those for shoulders, ankles, and other small joints may also have a role to play but are less standard. Given the clear improvement in health related quality of life and function as a result, for example, of total hip replacement, it is tempting to hope that the increased mortality seen with poor function in RA may also be improved[222,223].

Methotrexate. Folic acid antagonists — initially aminopterin, and later the safer amethopterin — were first used at the time of steroid introduction, and perhaps for that reason were not pursued. Hoffmeister (1983) published a large series of patients treated with MTX whom he had followed for a mean of 15 years with safety and good outcomes[127]. Controlled trials followed and it was included into the pyramid. As the initial concerns regarding the potential for marrow failure and liver damage eased, its use became popular and in many cases it became the slow acting drug of choice, especially in North America, although in Europe sulfasalazine retained this role.

The fate of the pyramid. Despite its "fame" or notoriety, the pyramid was not in universal or even widespread use. The structure of the pyramid, and even the principle involved, were not widely agreed to or known by general physicians in North America. Thus, in many longitudinal series, e.g., Pincus[224] and Wolfe[225], patients were first seen in the specialized units after almost a decade, and often had not previously received DMARD therapy. This situation seems to persist, for in a recent publication on leflunomide the mean duration of disease at trial entry was 7 years, and 40% had had no previous DMARD therapy[135]. Furthermore, as Ward[218] pointed out, steroid use in most of these studies was between 50% and 70%, even in recently published studies — sometimes more often than the use of DMARD. Thus, even in its heyday, the pyramid was not being adhered to. Even the ACR guidelines suggest that DMARD are not always required, and that the introduction of steroids may precede or supplant their use.

Well prior to this, newer patient centered measurement techniques, e.g., HAQ, Arthritis Impact Measurement Scale[218], etc., had entered first into clinical trials and subsequently to patient care and longterm studies. Using such techniques, Pincus reviewed the poor outcomes of the then current treatment paradigms, and demonstrated the increased mortality associated with severe disease, and the validity of questionnaires, including self-care, as predictors of mortality; others have confirmed this in different clinical settings[1,224].

It was shortly after this that Wilske and Healy, reacting in part to Pincus's report of poor outcomes of conventional rheumatoid treatment, described a reevaluation of the therapeutic pyramid[226,227]. Their approach was more, rather than less, aggressive, initiating therapy with a combination of drugs with the aim of inducing remission and then gradually stepping down some of the therapeutic agents involved. This was based on an analogy with cancer chemotherapy, where a remission is the aimed for result, and frequently several drugs are used in combination to achieve this. McCarty in part agreed with their philosophy of intervening more aggressively and emphasized that, "there was no point in waiting to assess the effectiveness of NSAID ..." and agreed that the pyramid should be demolished[228].

Fries put forward an alternative approach, a saw-tooth strategy[229]. He reviewed the ARAMIS and subsequently other data that NSAID were probably as toxic as the so-called 2nd line drugs, if not more so, and he emphasized therefore the importance of early DMARD use, and continued DMARD use, with changes sequentially as various drugs failed. However, his innovation was that he recommended setting a ceiling of progression using the HAQ score, and that the treatment should be changed whenever progression occurred. NSAID were used as adjunctive therapy and not basal.

Combination chemotherapy has now become widely accepted, although the evidence base for much of it remains marginal in the extreme. Most physicians, however, seem to arrive at a combination by virtue of adding sequential DMARD to partial failures (or partial successes!). This was clearly not the concept provided by Wilske. Nevertheless, when this adding approach has been studied in appropriate trials, it has not been shown to be effective, with the exception of a MTX/cyclosporine study[230], and more impressively with the recent anti-TNF agents, and here, as with the etanercept/MTX combination, it is not clear that it is truly additive, i.e., that the same result could not have been achieved if the MTX had been discontinued[203]. On the other hand, the use of MTX with infliximab, while not demonstrably enhancing the efficacy of the antiserum, does seem to prolong its efficacy, perhaps by decreasing antichimeric antibody formation[209,231]. In addition, there are now two studies showing that the initiation of combination therapy is not associated with any increase in side effects, and appears to have induced a marked degree of improvement, sometimes with the much sought after remission[232,233]. The combination studied specifically has been MTX, sulfasalazine, and hydroxychloroquine. Rather like the period of the 1960s, many physicians remain concerned that

patients will have difficulty accepting this triple therapy approach, and perhaps some even remain unconvinced that RA can be a devastating disease.

McCarty described triple therapy with cyclophosphamide, azathioprine, and hydroxychloroquine in 1982. A followup in 1986[192] also showed patients who had achieved remission, and one of his measures of success was a decrease or discontinuation in the dose of prednisone. However, this combination was nevertheless not recommended by him because of the oncogenic effects of cyclophosphamide. Overall, while the combination and step down approach is not widely accepted, the patterns of DMARD utilization clearly show that initiation of DMARD therapy is now much earlier in the disease than before[234]. Many rheumatologists will introduce DMARD as soon as a firm diagnosis is established. Thus, early, as well as more aggressive combinations of therapy are current themes.

Biologics. The development of biologic therapies was widely heralded as a breakthrough in rheumatoid disease therapy. The initial short term, uncontrolled pilot studies, for example of anti-CD4 antisera, were so successful that it was even suggested that it would be unethical to carry out placebo controlled studies. Fortunately, science prevailed, for those therapies were in fact not found to be useful, and the principle of controlled studies has been retained as part of the initial assessment of the biologics, as for more traditional agents. It has also become clear that the role of controlled clinical studies, while crucial, is limited, partly because of multiple exclusions to study entry, but also because longterm clinical followup studies, including measures of function, structure, and if possible behavior, are needed to assess effectiveness.

In 1991 a number of groups came together in a WHO/ILAR sponsored meeting, and a minimal core set for DMARD studies was adopted, including a measure of function. At this time new terminology was agreed upon. The terminology was changed: thus the term 2nd line agents became inappropriate as the introduction was advised early in the course of the disease. Slow acting was less valid as MTX, for example, began to work in some weeks. Disease modifying — DMARD — remains in vogue, although whether MTX always modifies the disease process any more than NSAID do is still unclear. Edmonds, *et al*[235] suggested the term DC-ART (disease controlling antirheumatic therapy) for those drugs of whatever type that had been shown to control radiologic progression of disease in studies of one year or longer. Thus, at least one of the currently approved biologic agents would be the first of the new biologics to fit under the heading of a one year DC-ART, although the demonstrated efficacy was in combination with low dose MTX, which might therefore complicate this designation. This approach recognizes the key role of joint protection — as assessed primarily radiologically — in the longterm management of RA.

Current and Future Issues

There is general agreement that rheumatoid inflammation should be controlled as completely as possible, as soon as possible, and that this control should be maintained for as long as possible, consistent with patient safety. The risk of RA management has decreased as rheumatologists have gained more experience using combinations of DMARD and as increasingly specific and less toxic agents (e.g., TNF inhibitors, COX-2 inhibitors) have become available to modify inflammation. Potential benefit has increased with the documentation of DC-ART properties for a number of interventions, and prevention of structural damage will be emphasized in the development of new treatments. This improved therapeutic risk/benefit and the progressive, irreversible nature of RA joint damage justify immediate initiation of DMARD treatment of newly diagnosed RA, and this is rapidly becoming the expected standard of care.

Unfortunately, most patients achieve only partial suppression of rheumatoid inflammation and many lose therapeutic benefit after an initial good response. Additive combination therapy is the usual response to this, but also may produce only temporary benefit. The management of persistent or recurrent rheumatoid inflammation and disability continues to be a challenge, and it is not clear whether the future addition of more potent specific interventions in the immunoinflammatory process will be able to solve this problem without disarming host defenses against infections and tumors.

Another problem is the temporary benefit of current treatments. Even in patients with a complete response, RA manifestations almost always recur after the treatment is stopped, confirming the non-curative nature of the treatments. The etiology of RA remains as obscure as ever, and a search for curative treatments is not likely to be fruitful without more knowledge about a cause.

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