

## REVIEW ARTICLE

## DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

## Therapeutic Strategies for Rheumatoid Arthritis

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**R**HEUMATOID ARTHRITIS, A CHRONIC, SYSTEMIC, INFLAMMATORY autoimmune disease, has as its primary target the synovial tissues. When the disease is unchecked, it leads to substantial disability and premature death.<sup>1</sup> It affects approximately 0.8 percent of adults worldwide,<sup>2</sup> is more common in women (by a ratio of 3 to 1), and has an earlier onset in women, frequently beginning in the childbearing years.<sup>3</sup> Recent advances in understanding the cytokine networks that are responsible for the ongoing inflammatory response in rheumatoid arthritis<sup>4</sup> have led to the successful use of therapies that target tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin-1.<sup>5</sup> (These therapies were discussed in a recent review in the *Journal*.<sup>6</sup>)

During the past 10 years, improved understanding of the pathophysiology of rheumatoid arthritis has led to several key changes in the approach to therapy. First, early diagnosis and treatment are important. Second, the use of disease-modifying anti-rheumatic drugs (DMARDs) in combination is highly effective. Third, the use of agents that target cytokines, such as TNF- $\alpha$  and interleukin-1, is an effective strategy. And fourth, recognition is growing that the assessment of treatment outcomes should include an analysis of important coexisting illnesses (particularly cardiovascular disease and osteoporosis). In this article, I will discuss the clinical application of these principles, which has resulted in a marked improvement in clinical outcomes.<sup>7,8</sup>

## EARLY DIAGNOSIS AND TREATMENT

Joint damage occurs early in the course of rheumatoid arthritis; 30 percent of patients have radiographic evidence of bony erosions at the time of diagnosis, and this proportion increases to 60 percent by two years.<sup>9</sup> Unfortunately, bony erosions and deformities are largely irreversible. Initiation of therapy with DMARDs within three months after the diagnosis of rheumatoid arthritis is crucial; a delay of as little as three months in the introduction of these medications results in substantially more radiographic damage at five years.<sup>10-12</sup> Therefore, early diagnosis, although challenging,<sup>13</sup> is critical.<sup>14,15</sup>

The diagnosis cannot be established by a single laboratory test or procedure but is aided by the use of seven diagnostic criteria<sup>16</sup> that favor clinical factors and, therefore, depend on the clinician's asking insightful questions and recognizing the often-subtle early physical findings. The diagnostic criteria are the presence of morning stiffness, arthritis of three or more joint areas, arthritis of the hand joints, symmetric arthritis, rheumatoid nodules, elevated levels of serum rheumatoid factor, and radiographic changes. Many other syndromes, including self-limiting viral conditions lasting several weeks, mimic rheumatoid arthritis. Therefore, the first four criteria must be present for a minimum of six weeks before a diagnosis of rheumatoid arthritis can be made. This approach, however, leads to diagnostic uncertainty that may delay appropriate therapy for months or years. Serum antibodies have been detected that may help define

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subgroups of patients.<sup>17</sup> Antibodies to cyclic citrullinated peptides (CCPs) appear to have a high specificity (90 to 98 percent) and thus may prove useful in early diagnosis, even though the sensitivity of the test for them is approximately 50 to 65 percent at presentation.<sup>18,19</sup> Interestingly, these antibodies may appear in the serum years before the onset of clinical disease.<sup>20</sup> In any event, many patients present initially to primary care physicians, so these providers need to recognize patients with potential inflammatory arthritis and be aware of the importance of referral to a specialist within the first three months after the appearance of symptoms.

#### GENERAL THERAPEUTIC PRINCIPLES

Guidelines concerning therapy for rheumatoid arthritis have been published recently by the American College of Rheumatology (Fig. 1).<sup>21</sup> No treatment cures rheumatoid arthritis; therefore, the therapeutic goals are a remission of symptoms involving the joints, a return of full function, and the maintenance of remission with DMARD therapy. A useful intermediate goal is to have all patients evaluated by a rheumatologist within three months after the onset of symptoms, so that essentially all patients will be receiving DMARDs by the time they have had symptoms for three months.

To evaluate the success of interventions, investigators have used a number of clinical measures. They include the number of joints that are tender and swollen, markers of inflammation (including the erythrocyte sedimentation rate and C-reactive protein level), and patients' responses to questions about their pain, their global assessment of disease activity, and their physical function. The American College of Rheumatology criteria for improvement can be used by clinicians to quantify patients' improvement after treatment (Table 1).<sup>22</sup> Most clinical studies have required a benchmark of 20 percent improvement in these criteria, a result that is known as ACR 20; now that better treatments are being initiated earlier in the course of the disease, 50 percent improvement (ACR 50) is becoming a more frequent target.

#### MEDICATIONS

Medications that are used to treat rheumatoid arthritis are divided into three main classes: nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, and DMARDs (both synthetic and biologic).

#### NSAIDs

NSAIDs are particularly helpful during the first few weeks in which a patient has symptoms, because the drugs provide partial relief of pain and stiffness until a definitive diagnosis of rheumatoid arthritis can be established. NSAIDs have not been shown to slow the progression of the disease; therefore, in long-term care, NSAIDs should be used together with DMARDs.<sup>21</sup> Although both these classes of medications are well tolerated for short periods, long-term administration may result in gastrointestinal ulcer, perforation, and hemorrhage. Every year 1.5 percent of patients with rheumatoid arthritis are hospitalized with gastrointestinal problems.<sup>23</sup> The risk of these complications increases with older age, corticosteroid use, and a history of peptic ulcer disease.

Recently, cyclooxygenase-2 (COX-2) inhibitors, which decrease the incidence of gastric and duodenal ulcers by approximately 50 percent as compared with traditional NSAIDs, have been introduced.<sup>24-26</sup> To a similar degree, the addition of proton-pump inhibitors to therapy with NSAIDs also decreases the incidence of bleeding ulcers associated with traditional NSAIDs.<sup>27</sup> The efficacy of the COX-2 inhibitors is no better than that of the older and less expensive NSAIDs.<sup>24</sup> Both traditional NSAIDs and COX-2 inhibitors have been associated with increased fluid retention, exacerbation of hypertension, and impairment of renal function in susceptible patients.<sup>24,28</sup> Thrombotic events have been reported in patients who are taking COX-2 inhibitors<sup>29-31</sup> and may occur more frequently than with traditional NSAIDs.<sup>29,30</sup>

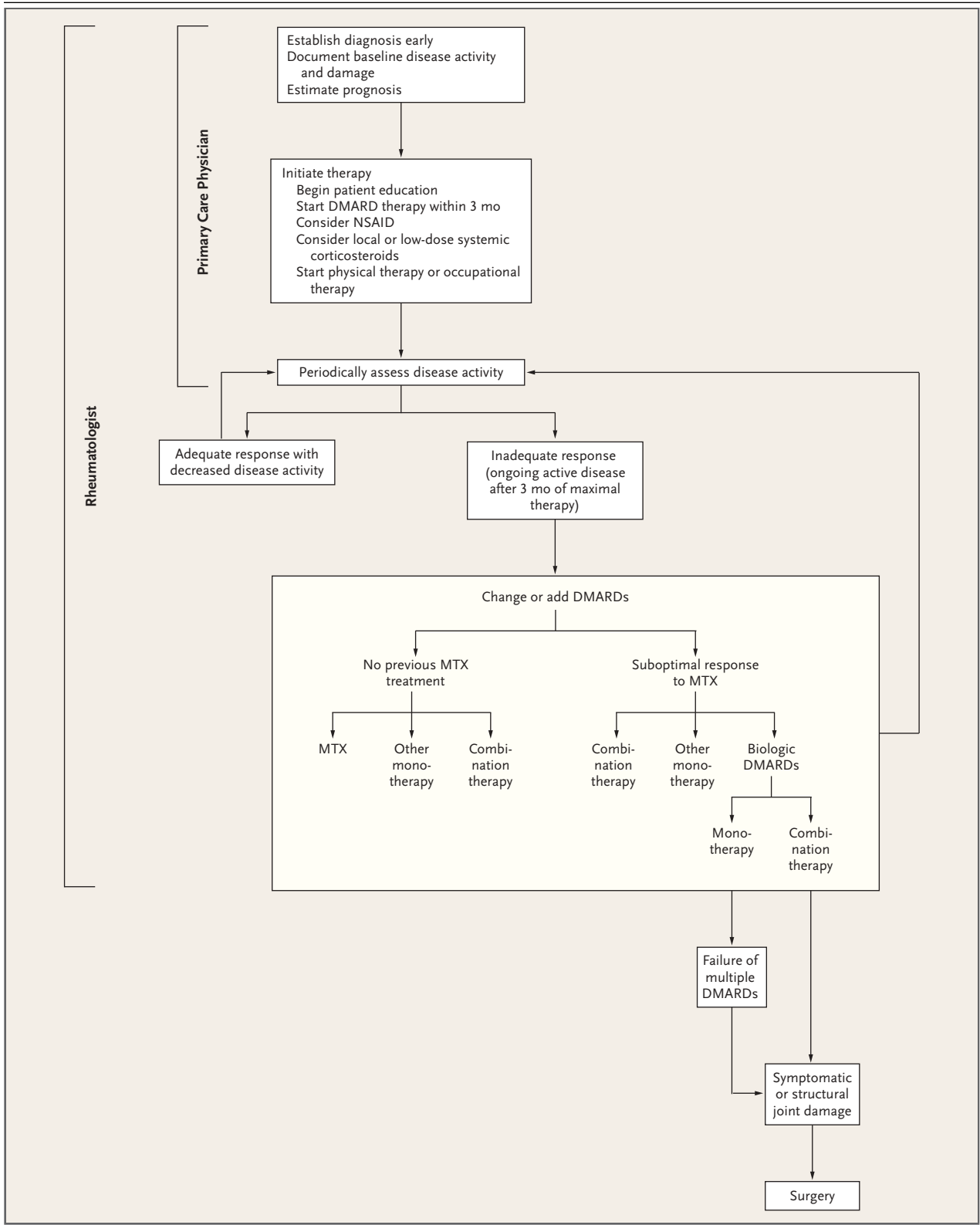
#### CORTICOSTEROIDS

Corticosteroids are potent suppressors of the inflammatory response in rheumatoid arthritis and in many other diseases; unfortunately, their dose-dependent side effects are familiar to all clinicians.

#### Figure 1. Management of Rheumatoid Arthritis.

Since many patients with rheumatoid arthritis present initially to primary care physicians, these providers need to suspect this diagnosis early and promptly refer the patient to a rheumatologist. Optimal care of patients with rheumatoid arthritis requires close collaboration between rheumatologists and primary care physicians. DMARD denotes disease-modifying antirheumatic drug, NSAID nonsteroidal antiinflammatory drug, and MTX methotrexate. Adapted from American College of Rheumatology guidelines.<sup>21</sup>

DRUG THERAPY



**Table 1. American College of Rheumatology Preliminary Definition of 20 Percent Improvement in Rheumatoid Arthritis (ACR 20).**

Measure of Disease Activity	Requirement
Tender-joint count	≥20% Improvement
Swollen-joint count	≥20% Improvement
Patient's assessment of pain	} ≥20% Improvement in three of the five measures
Patient's global assessment of disease activity	
Physician's global assessment of disease activity	
Patient's assessment of physical function	
Markers of inflammation	

Controversy continues about when, if, and how these compounds should be used to treat rheumatoid arthritis.<sup>32,33</sup> Studies conducted more recently<sup>34-36</sup> have corroborated findings from older trials<sup>37,38</sup> by clearly establishing that corticosteroids decrease the progression of rheumatoid arthritis as detected radiographically. Corticosteroids in low doses (e.g., ≤10 mg of prednisone per day) are used to treat 30 to 60 percent of patients.<sup>21,32</sup> The majority of patients who were enrolled in recent pivotal clinical trials were receiving corticosteroids at baseline.<sup>39-44</sup> Table 2 presents some useful guidelines for corticosteroid use in patients with rheumatoid arthritis.

Predictable side effects of corticosteroid drugs include thinning of the skin, cataracts, osteoporosis, hypertension, and hyperlipidemia.<sup>45,46</sup> The latter three conditions may be preventable with aggressive management of osteoporosis and cardiovascular risk factors. Essentially, all patients taking corticosteroids should receive supplemental calcium (1 to 1.5 g per day) and vitamin D (800 IU per day).<sup>47</sup> Bisphosphonates appear to be very effective in reducing vertebral fractures in patients taking corticosteroids<sup>47</sup> (offering a reported 70 percent reduction in incidence) and should be prescribed for patients who have low bone density (e.g., a T score of -2 or lower). Recent evidence suggests that inflammation plays a major role in atherosclerosis<sup>48-51</sup>; the ability of corticosteroids to decrease inflammation rapidly may offset some of the potentially detrimental effects of the drugs on the vascular endothelium.<sup>51</sup>

**SYNTHETIC DMARDS**

Optimal management of rheumatoid arthritis requires rapid and sustained suppression of inflammation with DMARDs, which are defined as med-

**Table 2. Keys to Optimizing the Outcome of Treatment.\***

Make an early diagnosis
Start DMARD therapy as early as possible (within three months after onset of symptoms)
Strive for remission (no joint symptoms) in all patients
Use corticosteroids as a bridge to effective DMARD therapy
Prednisone at doses >10 mg/day is rarely indicated for joint disease
Avoid using corticosteroids without DMARDs
Minimize duration and dose by tapering to the lowest dose that controls the disease
Always consider prophylaxis to avert osteoporosis
Recognize and treat coexisting illnesses
Facilitate communication between primary care physician and rheumatologist

\* DMARD denotes disease-modifying antirheumatic drug.

ications that retard or halt the progression of disease. Disease modification is most convincingly demonstrated by the ability of the medications to decrease radiographic progression. A meta-analysis of blinded clinical trials has suggested that the relative efficacy of methotrexate, sulfasalazine, intramuscular gold, and penicillamine is similar.<sup>52</sup> Antimalarial drugs (e.g., chloroquine and hydroxychloroquine) are less effective. Penicillamine, because of concern about its toxicity, and oral gold, because of its marginal efficacy,<sup>52</sup> are rarely used today.<sup>53</sup>

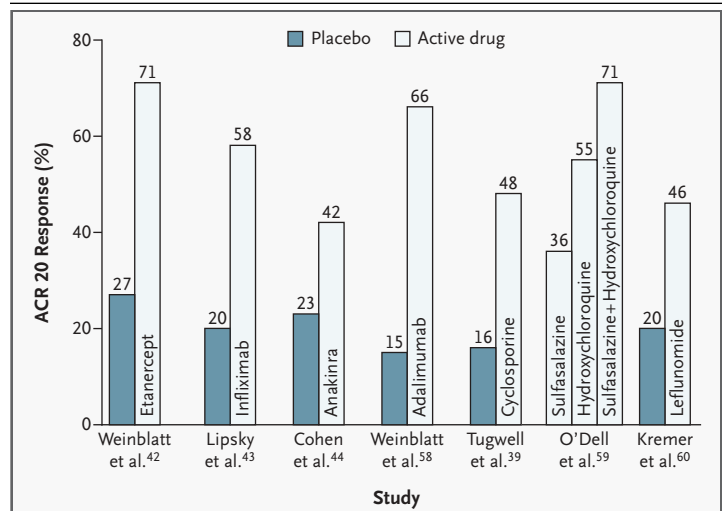
Since observational trials have clearly identified methotrexate as the synthetic DMARD that is most likely to induce a long-term response,<sup>54,55</sup> it is most often selected for initial therapy.<sup>53</sup> It has demonstrated efficacy and durability,<sup>56</sup> a long-term track record of acceptable toxicity, and low cost. An important observational study has shown that patients with rheumatoid arthritis who have been treated with methotrexate have significantly lower mortality (odds ratio for death, 0.4) than patients who have not been treated with methotrexate.<sup>57</sup> Methotrexate has become so much the standard of care that most of the recent pivotal trials of its use in patients with established disease (Fig. 2) have listed active disease despite methotrexate therapy as an inclusion criterion.<sup>39,42-44</sup> Concomitant administration of folic acid (1 to 3 mg per day) or folinic acid (2.5 to 5 mg given 12 to 24 hours after methotrexate) significantly decreases many toxic effects without a measurable decrease in efficacy and has improved the tol-

erability of methotrexate,<sup>61,62</sup> a finding that has permitted clinicians to administer 20 to 30 mg of methotrexate per week when necessary. Most data suggest that methotrexate is most effective at a dose of 17.5 to 30 mg per week<sup>63,64</sup> but that oral absorption may be highly variable.<sup>65,66</sup> Therefore, if oral methotrexate produces a suboptimal response, a trial of subcutaneous or intramuscular methotrexate is indicated.<sup>21</sup>

Leflunomide, a new synthetic DMARD, has an efficacy similar to that of sulfasalazine or moderate-dose methotrexate.<sup>67,68</sup> Hydroxychloroquine, considered the least potent but best tolerated of the DMARDs,<sup>52</sup> is the DMARD that is most commonly combined with methotrexate.<sup>53</sup> Sulfasalazine was the first DMARD that was developed specifically to treat rheumatoid arthritis<sup>69</sup> and has an efficacy similar to that of methotrexate.<sup>52</sup> Sulfasalazine is most commonly used in the United States as part of combination DMARD therapy.<sup>53</sup> Intramuscular gold is more likely both to produce a remission and to result in toxic effects as compared with methotrexate.<sup>70</sup> Its cumbersome administration and toxicity have limited its use.<sup>53</sup>

Historically, concern about the toxicity of DMARDs has delayed their use in treating rheumatoid arthritis. It is now accepted that the consequences of delaying therapy far outweigh the possible toxic effects for the majority of patients.<sup>21,71</sup> Safe administration of DMARDs requires critical and careful monitoring (Table 3).<sup>72</sup> Detailed monitoring guidelines have been published to help avert damage to the liver,<sup>73</sup> which was a major concern when use of the drug for rheumatoid arthritis became popular in the mid-1980s.<sup>74-77</sup> Since then only one case of cirrhosis has been reported in patients whose physicians were following the guidelines for monitoring.<sup>78</sup> These guidelines include measuring serum albumin and aminotransferase levels every four to eight weeks. Doses of methotrexate should be decreased when aminotransferase levels are elevated above the upper limit of normal, and treatment should be stopped if the elevation persists. Obtaining complete blood counts and measuring serum creatinine are also recommended,<sup>72</sup> since a decrease in renal function may precipitate toxic effects in a patient in previously stable condition who is taking methotrexate.<sup>79</sup>

Both methotrexate and leflunomide have a substantial potential for teratogenesis,<sup>80,81</sup> so women of childbearing potential who require these medications should be using reliable birth control. Sub-



**Figure 2. Responses to Drug Therapy in Seven Studies Involving Patients Receiving Methotrexate.**

All the patients in these seven studies were already receiving methotrexate, to which the other medication was added. Responses were measured in terms of an improvement of at least 20 percent in symptoms, as defined by the American College of Rheumatology (ACR 20). Numbers above the bars are response rates.

acute pneumonitis is rare with methotrexate (51 cases have been reported worldwide) but may be life-threatening.<sup>82</sup> If pneumonitis is suspected on the basis of clinical findings or a chest radiograph, methotrexate should be promptly discontinued and not reintroduced. As the best tolerated of all the DMARDs, hydroxychloroquine<sup>83</sup> — if it is used at doses below 6.5 mg per kilogram of lean body mass per day — requires only yearly visits to the ophthalmologist to prevent the rare occurrence of retinal toxic effects.<sup>84</sup>

Four double-blind, controlled trials have now shown that minocycline is effective in treating rheumatoid arthritis.<sup>85-88</sup> In patients with long-standing disease, a small but statistically significant benefit was observed.<sup>85,86</sup> Minocycline that was used as initial therapy in patients who tested positive for rheumatoid factor was superior to placebo (response rate, 65 percent, as compared with 13 percent for placebo<sup>87</sup>) and superior to hydroxychloroquine (60 percent vs. 33 percent<sup>88</sup>) when measuring ACR 50. The mechanism by which minocycline works is incompletely understood but probably involves immunomodulation,<sup>89</sup> suppression of matrix metalloproteinases,<sup>90</sup> and suppression of nonspecific infections that would otherwise

**Table 3. Guidelines for Monitoring the Treatment of Rheumatoid Arthritis.\***

Drug	Potential Toxic Effects	Baseline Evaluation	System Review or Examination	Laboratory Tests	Comments
Hydroxychloroquine	Macular changes	None unless patient is >40 years old or has previous eye problems	Visual changes; check funduscopic and visual fields every year	None	Best tolerated DMARD
Sulfasalazine	Neutropenia, myelosuppression	CBC; consider G6PD and ALT assessment for patients at risk	Fever, bruising, pallor	CBC every 2–4 weeks for 3 months, then every 3 months	Enteric-coated tablets better tolerated
Methotrexate	Myelosuppression, hepatic fibrosis, pneumonitis	CBC, recent chest radiograph, ALT, creatinine, and albumin, hepatitis B and C serology	Mouth ulcers, shortness of breath, new-onset cough, nausea	CBC, ALT, albumin every 4–8 weeks	Pregnancy contraindicated; patients must avoid alcohol
Leflunomide	Myelosuppression, hepatic fibrosis	CBC, ALT, albumin, hepatitis B and C serology	Diarrhea, weight loss, elevated blood pressure	CBC, ALT, albumin every 4–8 weeks	Long half-life; pregnancy contraindicated; patients should limit alcohol intake
Gold (intra-muscular)	Myelosuppression, proteinuria	CBC, creatinine, urine dipstick for protein	Rash, mouth ulcers, fever, bruising, pallor	CBC and dipstick urinalysis every 2 weeks, then with each injection	Least well tolerated DMARD
Minocycline	Hyperpigmentation, nausea, dizziness	None	Hyperpigmentation	None	May interfere with efficacy of birth-control pills
Azathioprine	Myelosuppression	CBC, creatinine, ALT for patients at risk	Fever, bruising, pallor	CBC every 2 weeks until stable dose, then every 1–3 months	Works well in combinations
Cyclosporine	Renal insufficiency, anemia, hypertension	CBC, creatinine, blood pressure	Edema; check blood pressure monthly	Creatinine every 2 weeks until stable dose, then every month; CBC every 3 months	Poor long-term continuation rates
Etanercept	Infections	Screen for previous tuberculosis	Infections; symptoms of CHF or demyelinating disease	None unless patient also receiving other DMARDs	Discontinue during infections
Infliximab	Infections	Screen for previous tuberculosis	Infections; symptoms of CHF or demyelinating disease	None unless patient also receiving other DMARDs	Discontinue during infections
Adalimumab	Infections	Screen for previous tuberculosis	Infections; symptoms of CHF or demyelinating disease	None unless patient also receiving other DMARDs	Discontinue during infections
Anakinra	Pneumonia, neutropenia	Screen for asthma	Infections	CBC monthly for 3 months, then every 3 months	Discontinue during infections

\* DMARD denotes disease-modifying antirheumatic drug, CBC complete blood count, G6PD glucose-6-phosphate dehydrogenase, ALT alanine aminotransferase, and CHF congestive heart failure. The CBC includes a platelet count in all cases listed. Measurement of aspartate aminotransferase may be substituted for measurement of ALT.

stimulate inflammatory cytokine production.<sup>88</sup> Reversible hyperpigmentation is seen in up to 30 percent of patients who are receiving long-term minocycline therapy.

#### **BIOLOGIC DMARDS**

Three biologic products that inhibit the actions of TNF- $\alpha$  (infliximab, etanercept, and adalimumab)

and one that inhibits the action of interleukin-1 (anakinra) are now available to treat rheumatoid arthritis.<sup>6</sup> Other agents are being tested; some have targeted cytokines in ways that are similar to those previously mentioned. There is also renewed interest in products that target the activation of T cells or B cells,<sup>91,92</sup> including anti-CTLA4Ig<sup>93,94</sup> and anti-CD20 (rituximab).<sup>95</sup> (A report on a study of

rituximab appears elsewhere in this issue of the *Journal*.<sup>96</sup>)

#### COMBINATION THERAPY WITH DMARDS

Ten years ago, the use of combinations of DMARDs was rare; now at least one third of patients with rheumatoid arthritis who are treated by rheumatologists in the United States are receiving combination therapy.<sup>53</sup> Trials that have compared combinations of DMARDs head-to-head with methotrexate<sup>40,97</sup> and trials that have shown the additional benefit of adding drugs to methotrexate for patients who have active disease despite methotrexate<sup>39,42-44,58-60</sup> (Fig. 2) have fueled the rise of combination DMARD therapy.

One of the first randomized studies that directly compared combination DMARD therapy with methotrexate was a two-year, double-blind trial in which patients were assigned to three groups: those who took methotrexate alone (at 17.5 mg per week), those who took a combination of sulfasalazine (at 1 g per day) and hydroxychloroquine (at 400 mg per day), and those who took all three medications.<sup>40</sup> At two years, the end point of 50 percent improvement in composite symptoms of arthritis was reached by 77 percent of patients who were treated with all three drugs but by only 33 percent of patients who were treated with methotrexate alone. Patients who received combination therapy did not have more side effects than those who received methotrexate alone. In another study, the triple combination of methotrexate (at 17.5 mg per week), sulfasalazine (at 2 g per day), and hydroxychloroquine (at 400 mg per day) was superior to either the combination of methotrexate and sulfasalazine or the combination of methotrexate and hydroxychloroquine.<sup>59</sup>

In patients who have early disease, three critical trials have all shown that initial combination therapy is superior to therapy with a single DMARD.<sup>96,98,99</sup> The Combinatietherapie Bij Reumatoide Artritis (COBRA)<sup>98</sup> trial compared sulfasalazine alone with the combination of sulfasalazine, low-dose methotrexate (which was stopped at 40 weeks), and prednisolone (which was given initially at 60 mg per day but tapered off by 28 weeks). Patients in the combination group had a more rapid response to treatment, fewer withdrawals from the study because of toxicity, and most important, less radiographic evidence of progression at five years.<sup>100</sup> Other trials involving patients with early disease have demonstrated the superiority of

triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) over sulfasalazine alone,<sup>99</sup> double therapy (methotrexate and sulfasalazine or methotrexate and hydroxychloroquine), and monotherapy.<sup>96</sup> However, no trials have compared initial combination therapy with a rapid step-up to combinations only in patients with active disease despite monotherapy.

In the much-studied group of patients with active disease despite taking methotrexate, a number of trials with similar designs have been completed. In these trials, patients continue taking methotrexate plus either the active treatment or placebo. Figure 2 details the ACR 20 responses seen in seven trials involving patients with these characteristics. This summary of the data is not intended to imply that a specific level of response in one trial can be directly compared with that in another trial. These seven effective therapies have not yet been compared head to head.

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#### INITIAL TREATMENT

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Establishing a diagnosis as early as possible and then starting DMARD therapy is the foundation for successful treatment of patients with rheumatoid arthritis. Many questions remain, including the following: Which drug should be used first? Can drug toxicity or a patient's response be predicted by pharmacogenomics? Should drug combinations be used initially? Should we try to induce rapid disease suppression with corticosteroids or TNF inhibitors? Are there biologic markers that should be used to monitor outcome in place of or in addition to standard assessment?

Until these questions are answered, most rheumatologists select methotrexate as the initial therapy for most patients.<sup>53</sup> The characteristics and personal choices of patients influence this decision.<sup>21</sup> Methotrexate should not be used in patients who have underlying liver or renal disease, who consume alcohol, who plan to become pregnant in the near future, or who do not want to undergo regular laboratory monitoring. Whether to start a course of low-dose corticosteroids initially along with the chosen DMARD is controversial; many clinicians start treatment with prednisone at 5 to 7.5 mg per day as bridge therapy until the slower-acting DMARDs have a chance to work. Once the DMARD begins working, corticosteroids should be tapered (Table 2).

Methotrexate is started at a dose of 7.5 to 15 mg,

given orally once weekly. If patients continue to have active disease (as indicated by swollen and tender joints), as most do, the dose should be increased in 5-mg increments each month or two to 20 to 30 mg per week. If patients continue to have active disease, consideration should be given to switching to subcutaneous administration.<sup>21,65,66</sup> If active disease persists despite optimal methotrexate therapy, other DMARDs should be added.<sup>21</sup>

Compelling data from the COBRA trial<sup>98,100</sup> — in which patients with active early rheumatoid arthritis were given either sulfasalazine alone or the combination of sulfasalazine, methotrexate, and either a high or a low dose of oral prednisolone for 28 weeks — have raised the question of whether therapy to suppress the disease rapidly should be given immediately after the diagnosis. The rapid suppression of rheumatoid arthritis by corticosteroids has been recognized since the middle of the 20th century.<sup>101</sup> The Early Rheumatoid Arthritis (ERA) trial<sup>102</sup> is an important study that compared methotrexate (at a dose that escalated to 20 mg per week) with etanercept in patients with disease diagnosed within the preceding three years. Both treatments were very effective in controlling the disease at one year, but etanercept (administered at 25 mg subcutaneously twice a week) was more effective in rapidly suppressing disease activity. In both the ERA and COBRA trials, markers of inflammation (including the erythrocyte sedimentation rate and the C-reactive protein level) were dramatically reduced after two weeks of therapy. If, in fact, it is important to control disease in days, rather than in weeks or months, then corticosteroids and TNF inhibitors (both of which appear to be capable of stopping active disease) should be examined in trials to test the concept of induction therapy (i.e., medication that is administered initially and then withdrawn).

#### THERAPY FOR ESTABLISHED RHEUMATOID ARTHRITIS

If patients continue to have active disease after two to three months of methotrexate at a dose of 20 to 30 mg per week, or if they cannot tolerate higher doses of methotrexate despite folate replacement, the current standard practice is to add another DMARD to methotrexate<sup>21</sup>; all the trials included in Figure 2 address this patient population.

To date, clinically significant differences have not emerged with regard to toxicity for the treatments

shown in Figure 2, with the exception of poor long-term tolerability of combining methotrexate and cyclosporine.<sup>103</sup> Until there are studies that compare the relative efficacy of these effective therapies, the most economical initial choice<sup>104</sup> for the patient who has active disease despite taking methotrexate is the addition of sulfasalazine, hydroxychloroquine, or both. Data from the United Kingdom have shown that if conventional DMARDs are optimized and used in combination, control of the disease can be achieved in more than half of patients who would otherwise be candidates for TNF inhibitors.<sup>105</sup> If active disease (manifested by swollen and tender joints) persists after three months of these DMARD combinations, leflunomide or a TNF inhibitor should be added to methotrexate.

If DMARD therapy is started within three months after the onset of symptoms and escalated with the goal of achieving remission, the majority of patients will have their disease well controlled within a year while taking conventional single or combination DMARD therapy.<sup>106</sup> If inflammatory disease is inadequately controlled, therapy with TNF inhibitors should be started.

#### COEXISTING ILLNESSES

The long-term prognosis for patients with rheumatoid arthritis depends not only on how well their joint disease is treated but also on how well their coexisting illnesses are addressed.<sup>107,108</sup> The three coexisting conditions that have the greatest effect on morbidity and mortality in rheumatoid arthritis are infection (particularly pulmonary infection), osteoporosis, and cardiovascular disease.

Rheumatoid arthritis is associated with approximately a doubling of the risk of infection, as compared with the risk in age-matched controls,<sup>109</sup> and the degree of increase in this risk correlates with the severity of the disease.<sup>110</sup> Although some studies suggest that corticosteroids may increase the risk of infection,<sup>111</sup> controversy exists about whether such an increase is due to the use of corticosteroids itself or to the fact that patients who are at higher risk are more likely to use corticosteroids. Whether the new TNF inhibitors increase the risk of infection is a matter for debate since the drugs have been associated with a change in the spectrum of infections<sup>112</sup> — specifically, increased tuberculosis, histoplasmosis, and listeria.<sup>6</sup>

The clinician who is caring for patients with

rheumatoid arthritis should be aware of the risk of infection. All patients should have yearly influenza vaccinations and should receive the pneumococcal vaccine at appropriate intervals. Since patients may have a better immunologic response to vaccination before taking methotrexate,<sup>113</sup> it seems prudent to vaccinate before starting DMARD treatment, when possible. Live vaccines should be avoided in patients who are receiving immunosuppressive medications. When considering TNF inhibitors, clinicians should recommend that all patients be tested for prior exposure to tuberculosis. Both clinicians and patients with rheumatoid arthritis should be vigilant with regard to avoiding infections and treating them early and aggressively. Stopping or withdrawing drug treatment during infections is critical.<sup>112</sup>

The advent of diagnostic tools that are accurate and easy to use and the availability of effective therapies for osteoporosis have been tremendous advances in the treatment of rheumatoid arthritis.<sup>114</sup> The incidence of osteoporosis is doubled in patients with rheumatoid arthritis,<sup>114,115</sup> and baseline bone-density studies should be performed in all patients, particularly those who will receive corticosteroids. If osteoporosis is present, bisphosphonate therapy, which is reported to decrease the risk of fracture by 70 percent despite the coadministration of corticosteroids,<sup>47</sup> should be used.

Cardiovascular disease accounts for most of the excess mortality associated with rheumatoid disease.<sup>49</sup> The newer concepts of the pathogenesis of atherosclerosis suggest that inflammation is a key factor in causing vascular endothelial damage.<sup>49,50,116</sup> It has been hypothesized that the systemic inflammation that characterizes rheumatoid arthritis may play a key role in the excess atherosclerosis seen in patients with this disease.<sup>49,50</sup> Risk factors for atherosclerosis should be aggressively sought and addressed. In particular, smoking cessation may be fruitful, since smoking has been associated with increased severity of arthritis.<sup>117</sup> Current trials of statin therapy in patients with rheumatoid arthritis may address the risk of cardiovascular disease, since statins should decrease both atherosclerosis and inflammation.<sup>118,119</sup>

Caring for patients with rheumatoid arthritis poses significant challenges. Three issues deserve special mention: the lack of an accurate method for making an early diagnosis, which permits early treatment; inadequate predictors of the differential response to available therapy, as well as too few studies comparing effective therapies; and the enormous cost of new therapies, which has made them unavailable to many patients. Since musculoskeletal disease accounts for one quarter of all visits to the offices of primary care physicians,<sup>120</sup> formal training in rheumatic disease needs to be included in the education of all primary care physicians. Preliminary studies suggest that genetics might be useful in predicting responses to DMARDs.<sup>121</sup> Until these research efforts come to fruition, studies that directly compare current therapies are urgently needed. Many of our new therapies are expensive, with initial costs that may exceed \$1,500 per month. However, these upfront costs may be justified in the long term by savings that result from an improved quality of life and enhanced productivity.

The treatment of rheumatoid arthritis has improved dramatically in the past decade,<sup>7,8</sup> thanks to early diagnosis and the availability of DMARDs. Physicians can now have the goal of eradicating active disease and aggressively intervening to address coexisting illnesses. Remission in patients who are receiving therapy is now a realistic goal. Recent reports that only a small minority of patients (i.e., 5 percent) who are being treated by rheumatologists have disease that is active enough to qualify them for current clinical trials are a testament to the success of these therapies.<sup>107</sup>

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## REFERENCES

1. Scott DL, Symmons DPM, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.
2. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;27:269-81.
3. Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. *Br J Rheumatol* 1994;33:735-9.
4. Choy EHS, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001;344:907-16.

5. McInnes IB. Rheumatoid arthritis: from bench to bedside. *Rheum Dis Clin North Am* 2001;27:373-87.
6. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. *N Engl J Med* 2004;350:2167-79.
7. Krishnan E, Fries JF. Reduction in long-term functional disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. *Am J Med* 2003;115:371-6.
8. da Silva E, Doran MF, Crowson CS, O'Fallon WM, Matteson EL. Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. *Arthritis Rheum* 2003;49:216-20.
9. van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol* 1995;34:Suppl 2:74-8.
10. Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001;111:446-51.
11. Egmose C, Lund B, Borg G, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5-year followup of a prospective double blind placebo controlled study. *J Rheumatol* 1995;22:2208-13.
12. Tsakonas E, Fitzgerald AA, Fitzcharles MA, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the Hydroxychloroquine in Early Rheumatoid Arthritis (HERA) study. *J Rheumatol* 2000;27:623-9.
13. Koopman WJ, ed. *Arthritis and allied conditions: a textbook of rheumatology*. 14th ed. Vol. 1. Philadelphia: Lippincott Williams & Wilkins, 2001:1153-74.
14. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? *Rheumatology (Oxford)* 2001;40:1211-20.
15. O'Dell JR. Treating rheumatoid arthritis early: a window of opportunity. *Arthritis Rheum* 2002;46:283-5.
16. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
17. Goldbach-Mansky R, Lee J, McCoy A, et al. Rheumatoid arthritis associated autoantibodies in patients with synovitis of recent onset. *Arthritis Res* 2000;2:236-43.
18. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 1998;101:273-81.
19. Jansen ALMA, van der Horst-Bruinsma IE, van Schaardenburg D, van de Stadt RJ, de Koning MHMT, Bijkmans BAC. Rheumatoid factor and antibodies to cyclic citrullinated peptide differentiate rheumatoid arthritis from undifferentiated polyarthritis in patients with early arthritis. *J Rheumatol* 2002;29:2074-6.
20. Nielen MM, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 2004;50:380-6.
21. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002;46:328-46.
22. Felson DT, Anderson JJ, Boers M, et al. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.
23. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998;105:Suppl 1B:31S-38S.
24. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-42.
25. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
26. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA* 2000;284:1247-55.
27. Chan FKL, Hung LCT, Suen BY, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 2002;347:2104-10.
28. Whelton A, Maurath CJ, Verburg KM, Geis GS. Renal safety and tolerability of celecoxib, a novel cyclooxygenase-2 inhibitor. *Am J Ther* 2000;7:159-75. [Erratum, *Am J Ther* 2000;7:341.]
29. Food and Drug Administration. Arthritis Advisory Committee open panel meeting 2/8/2001: review of VIGOR, cardiovascular safety review of rofecoxib. (Accessed May 5, 2004, at [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2\\_03\\_med.pdf](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.pdf).)
30. Strand V, Hochberg MC. The risk of cardiovascular thrombotic events with selective cyclooxygenase-2 inhibitors. *Arthritis Rheum* 2002;47:349-55.
31. Crofford LJ, Oates JC, McCune WJ, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase-2 inhibitors: a report of four cases. *Arthritis Rheum* 2000;43:1891-6.
32. Moreland LW, O'Dell JR. Glucocorticoids and rheumatoid arthritis: back to the future? *Arthritis Rheum* 2002;46:2553-63.
33. Saag KG, Criswell LA, Sems KM, Nettlemann MD, Kolluri S. Low-dose corticosteroids in rheumatoid arthritis: a meta-analysis of their moderate-term effectiveness. *Arthritis Rheum* 1996;39:1818-25.
34. Kirwan JR, Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;333:142-6.
35. Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. *Br J Rheumatol* 1998;37:930-6.
36. van Everdingen AA, Jacobs JWJ, Sievertsz van Reesema DR, Bijlsma WJ. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002;136:1-12.
37. A comparison of prednisolone with aspirin or other analgesics in the treatment of rheumatoid arthritis. *Ann Rheum Dis* 1959;18:173-88.
38. A comparison of prednisolone with aspirin or other analgesics in the treatment of rheumatoid arthritis: a second report by the joint committee of the Medical Research Council and Nuffield Foundation on clinical trials of cortisone, ACTH, and other therapeutic measures in chronic rheumatic diseases. *Ann Rheum Dis* 1960;19:331-7.
39. Tugwell P, Pincus T, Yocum D, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995;333:137-41.
40. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334:1287-91.
41. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552-63.
42. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253-9.
43. Lipsky PE, van der Heijde DMFM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;343:1594-602.
44. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46:614-24.
45. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994;96:115-23.
46. McDougall R, Sibley J, Haga M, Russell A. Outcome in patients with rheumatoid arthritis receiving prednisone compared to

- matched controls. *J Rheumatol* 1994;21:1207-13.
47. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. *Arthritis Rheum* 2001;44:1496-503.
48. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135-43.
49. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum* 2002;46:862-73.
50. Del Rincon I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. *Arthritis Rheum* 2003;48:1833-40.
51. Hallgren R, Berne C. Glucose intolerance in patients with chronic inflammatory diseases is normalized by glucocorticoids. *Acta Med Scand* 1983;213:351-5.
52. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two metaanalyses. *Arthritis Rheum* 1990;33:1449-61.
53. Mikuls TR, O'Dell J. The changing face of rheumatoid arthritis therapy: results of serial surveys. *Arthritis Rheum* 2000;43:464-5.
54. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices. II. Second line drugs and prednisone. *J Rheumatol* 1992;19:1885-94.
55. Wolfe F, Hawley DJ, Cathey MA. Termination of a slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990;17:994-1002.
56. Ortendahl M, Holmes T, Schettler JD, Fries JF. The methotrexate therapeutic response in rheumatoid arthritis. *J Rheumatol* 2002;29:2084-91.
57. Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173-7.
58. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48:35-45. [Erratum, *Arthritis Rheum* 2003;48:855.]
59. O'Dell JR, LefR, Paulsen G, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46:1164-70.
60. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:726-33.
61. Morgan SL, Baggott JE, Vaughn WH, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis: a double-blind, placebo-controlled trial. *Ann Intern Med* 1994;121:833-41.
62. Van Ede AE, Laan RF, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001;44:1515-24.
63. Furst DE, Koehnke R, Burmeister LE, Kohler J, Cargill I. Increasing methotrexate effect with increasing dose in the treatment of resistant rheumatoid arthritis. *J Rheumatol* 1989;16:313-20.
64. Genovese M, Keystone EC, Tesser JRP, Finck BK, Spencer-Green GT. High dose oral methotrexate (MTX) in early RA is needed for maximum efficacy. *Arthritis Rheum* 2000;43:Suppl:S382. abstract.
65. Herman RA, Veng-Pedersen P, Hoffman J, Koehnke R, Furst DE. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. *J Pharm Sci* 1989;78:165-71.
66. Brooks PJ, Spruill WJ, Parish RC, Birchmore DA. Pharmacokinetics of methotrexate administered by intramuscular and subcutaneous injections in patients with rheumatoid arthritis. *Arthritis Rheum* 1990;33:91-4.
67. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomized, multicentre trial. *Lancet* 1999;353:259-66.
68. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999;159:2542-50.
69. Svartz N. Salazopyrin, a new sulfanilamide preparation. *Acta Med Scand* 1942;110:577-98.
70. Rau R, Herborn G, Menninger H, Blechschmidt J. Comparison of intramuscular methotrexate and gold sodium thiomalate in the treatment of early erosive rheumatoid arthritis: 12 month data of a double-blind parallel study of 174 patients. *Br J Rheumatol* 1997;36:345-52.
71. Pincus T, Callahan LF. The 'side effects' of rheumatoid arthritis: joint destruction, disability and early mortality. *Br J Rheumatol* 1993;32:Suppl 1:28-37.
72. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. *Arthritis Rheum* 1996;39:723-31.
73. Kremer JM, Alarcon GS, Lightfoot RW Jr, et al. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994;37:316-28.
74. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985;312:818-22.
75. Thompson RN, Watts C, Edelman J, Esdaile J, Russell AS. A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. *J Rheumatol* 1984;11:760-3.
76. Williams HJ, Willkens RF, Samuelson CO Jr, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. *Arthritis Rheum* 1985;28:721-30.
77. Andersen PA, West SG, O'Dell JR, Via CS, Claypool RG, Kotzin BL. Weekly pulse methotrexate in rheumatoid arthritis: clinical and immunologic effects in a randomized, double-blind study. *Ann Intern Med* 1985;103:489-96.
78. Kremer JM. Not yet time to change the guidelines for monitoring methotrexate liver toxicity: they have served us well. *J Rheumatol* 2002;29:1590-2.
79. O'Dell JR. Methotrexate use in rheumatoid arthritis. *Rheum Dis Clin North Am* 1997;23:779-96.
80. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med* 2000;160:610-9.
81. Nelson JL, Ostensen M. Pregnancy and rheumatoid arthritis. *Rheum Dis Clin North Am* 1997;23:195-212.
82. Kremer JM, Alarcon GS, Weinblatt ME, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. *Arthritis Rheum* 1997;40:1829-37.
83. Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis: a metaanalysis of published clinical trials. *Arthritis Rheum* 1992;35:1117-25.
84. Marmor ME, Carr RE, Easterbrook M, Farjo AA, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology* 2002;109:1377-82.
85. Kloppenburg M, Breedveld FC, Terwiel JP, Mallee C, Dijkmans BA. Minocycline in active rheumatoid arthritis: a double-blind, placebo-controlled trial. *Arthritis Rheum* 1994;37:629-36.
86. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;122:81-9.
87. O'Dell JR, Haire CE, Palmer W, et al. Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 1997;40:842-8.

88. O'Dell JR, Blakely KW, Mallek JA, et al. Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001;44:2235-41.
89. Ritchlin CT, Haas-Smith SA, Schwarz EM, Greenwald RA. Minocycline but not doxycycline upregulates IL-10 production in human synoviocytes, mononuclear cells and synovial explants. *Arthritis Rheum* 2000;43:Suppl:S345. abstract.
90. Golub LM, Evans RT, McNamara TF, Lee HM, Ramamurthy NS. A non-antimicrobial tetracycline inhibits gingival matrix metalloproteinases and bone loss in *Porphyromonas gingivalis*-induced periodontitis in rats. *Ann N Y Acad Sci* 1994;732:96-111.
91. Panayi GS, Corrigan VM, Pitzalis C. Pathogenesis of rheumatoid arthritis: the role of T cells and other beasts. *Rheum Dis Clin North Am* 2001;27:317-34.
92. Zhang Z, Bridges SL Jr. Pathogenesis of rheumatoid arthritis: role of B lymphocytes. *Rheum Dis Clin North Am* 2001;27:335-53.
93. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349:1907-15.
94. Weinblatt M, Schiff M, Goldman M, Kremer J, Breazna A, Becker J-C. A pilot, multi-center, randomized, double-blind, placebo controlled study of a co-stimulation blocker CTLA4Ig (2 mg/kg) given monthly in combination with etanercept in active rheumatoid arthritis. *Arthritis Rheum* 2002;46:Suppl:S204. abstract.
95. Edwards JCW, Szczepanski L, Szechinski J, et al. Efficacy and safety of rituximab, a B-cell targeted chimeric monoclonal antibody: a randomized, placebo-controlled trial in patients with rheumatoid arthritis. *Arthritis Rheum* 2002;46:Suppl:S197. abstract.
96. Edwards JCW, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572-81.
97. Calgüneri M, Pay S, Caliskaner Z, et al. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 1999;17:699-704.
98. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;350:309-18. [Erratum, *Lancet* 1998;351:220.]
99. Möttönen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. *Lancet* 1999;353:1568-73.
100. Landewe RBM, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002;46:347-56.
101. Hench PS, Kendall EC, Slocumb CH, Polley HE. The effect of a hormone on the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis: preliminary report. *Proc Staff Meet Mayo Clin* 1949;24:181-97.
102. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586-93. [Errata, *N Engl J Med* 2001;344:76, 240.]
103. Yocum DE, Stein M, Pincus T. Long-term safety of cyclosporin/Sandimmune (CsA/SIM) alone and in combination with methotrexate (MTX) in the treatment of active rheumatoid arthritis (RA): analysis of open label extension studies. *Arthritis Rheum* 1998;41:Suppl:S364. abstract.
104. Choi HK, Seeger JD, Kuntz KM. A cost effectiveness analysis of treatment options for methotrexate-naïve rheumatoid arthritis. *J Rheumatol* 2002;29:1156-65.
105. Bingham SJ, Buch MH, Lindsay S, Tennant A, Emery P. The impact of escalating therapy in rheumatoid arthritis patients referred for anti-tumour necrosis factor-alpha therapy. *Rheumatology (Oxford)* 2004;43:364-8.
106. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. *Arthritis Rheum* 2003;48:313-8.
107. Mikuls TR, Saag KG. Comorbidity in rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;27:283-303.
108. Gabriel SE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: have we made an impact in 4 decades? *J Rheumatol* 1999;26:2529-33.
109. Doran ME, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;46:2287-93.
110. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;37:481-94.
111. Doran ME, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002;46:2294-300.
112. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor  $\alpha$  therapy. *Arthritis Rheum* 2003;48:3013-22.
113. O'Dell JR, Gilg J, Palmer W, Haire C, Klassen L, Moore G. Pneumococcal vaccine in rheumatoid arthritis: decreased response while taking methotrexate. *J Clin Rheumatol* 1996;2:59-63.
114. Haugeberg G, Orstavik RE, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. *Arthritis Rheum* 2002;46:1720-8.
115. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557-65.
116. Michel BA, Bloch DA, Fries JF. Predictors of fractures in early rheumatoid arthritis. *J Rheumatol* 1991;18:804-8.
117. Mathey DL, Hutchinson D, Dawes PT, et al. Smoking and disease severity in rheumatoid arthritis: association with polymorphism at the glutathione S-transferase M1 locus. *Arthritis Rheum* 2002;46:640-6.
118. Blake GJ, Ridker PM. Are statins anti-inflammatory? *Curr Control Trials Cardiovasc Med* 2000;1:161-5.
119. Leung BP, Sattar N, Crilly A, et al. A novel anti-inflammatory role for simvastatin in inflammatory arthritis. *J Immunol* 2003;170:1524-30.
120. Spitzer WO, Harth M, Goldsmith CH, et al. The arthritic complaint in primary care: prevalence, related disability, and costs. *J Rheumatol* 1976;3:88-99.
121. O'Dell JR, Nepom BS, Haire C, et al. HLA-DRB1 typing in rheumatoid arthritis: predicting response to specific treatments. *Ann Rheum Dis* 1998;57:209-13.

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