

Rational Use of New and Existing Disease-Modifying Agents in Rheumatoid Arthritis

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Because of radiographic evidence of progressive bone loss and the inability to eliminate synovial proliferation with methotrexate, it became apparent that therapy for rheumatoid arthritis needed further advancement. Methotrexate is not a remission-inducing drug and may have dose-limiting toxicity. In the past 2 years, three new disease-modifying antirheumatic drugs (DMARDs) have been approved: leflunomide, etanercept, and infliximab. Each of these agents has demonstrated efficacy compared with placebo in randomized, controlled studies. Because methotrexate had a dominant therapeutic role, the new drugs were also studied in combination with it. Other established DMARDs, such as sulfasalazine and hydroxychloroquine, have also demonstrated efficacy when used together with methotrexate. The results of these combination studies clearly demonstrate that clinical responses can be meaningfully improved when new and existing DMARDs are added to methotrexate. Although toxicity remains a serious concern when powerful immune modulators and antimetabolites are used in

combination, relatively few serious adverse events have been reported during 2-year treatment periods. It has also become apparent that combinations of new DMARDs and methotrexate virtually halt radiographic progression over 2 years. The new agents are expensive, but annual costs must be weighed against the personal and societal expense of joint arthroplasty, hospitalizations, disability, and diminished quality of life that accompanies poorly controlled rheumatoid arthritis. The ultimate value of combination DMARD therapy with methotrexate will be determined by long-term data on safety, efficacy, and effects on radiographic deterioration of bone. Additional long-term observational data on the incidence of joint arthroplasty and disability will help to place the issue of societal costs in a better perspective. This will allow the value of aggressive treatment to be established with certainty.

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Rheumatoid arthritis is a disease with considerable individual and societal costs (1–5). Disability is common (6, 7) and often occurs quickly (4, 5). Radiographic progression can also be rapid (8–10) and may be inexorable over the course of decades (11). Mortality rates increase in patients with severe continuing disease (7, 12). However, it is becoming increasingly clear that deformity, disability, and death may be avoided when newly approved and existing disease-modifying antirheumatic drugs (DMARDs) are combined.

The treatment of patients with rheumatoid arthritis has changed dramatically in the past 2 years. Three new agents, leflunomide, etanercept, and infliximab, have been approved by the U.S. Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis. Two of these agents, infliximab and etanercept, are biological interventions. Infliximab had been previously approved for use in patients with refractory inflammatory bowel disease. Its expanded use, which accompanied FDA approval of long-term dosing in patients with rheumatoid arthritis, represents a departure from its previous limited approval for Crohn disease. Several other new agents are also on the horizon. Indeed, after a period of more than a decade in which virtually no new DMARDs to treat patients with rheumatoid arthritis

were introduced, the present environment represents an unprecedented and extraordinary expansion of therapeutic possibilities from which to choose.

We should not entirely ignore the standard DMARDs, such as hydroxychloroquine, sulfasalazine, cyclosporine, azathioprine, D-penicillamine, auranofin, and intramuscular gold. For many years, these drugs were the only choices for DMARD treatment. Weekly methotrexate assumed a dominant role in the 1980s and 1990s because its efficacy and safety were demonstrated in both short-term trials (13, 14) and long-term observational studies (15, 16).

Methotrexate can cause serious liver and lung toxicity (17, 18), but both can be prevented by careful monitoring and by avoiding methotrexate use in patients at particular risk for harm (19, 20). In addition, other methotrexate-associated toxicities can be avoided with the use of supplemental folate (21, 22). While cases of spontaneous regression of non-Hodgkin B-cell lymphoma have been reported in patients with rheumatoid arthritis after stopping methotrexate, the overall incidence of malignancies with the use of this agent is still surprisingly low (23).

Methotrexate is not, however, an ideal agent for other reasons. True remissions of disease in patients tak-

ing the drug are rare. It cannot be used in patients with preexisting liver, kidney, or lung disease or in patients who wish to continue even the social use of alcohol (24, 25). Many patients are unable to tolerate a high enough dose of methotrexate to achieve an optimal therapeutic benefit, even with the simultaneous use of folate supplements (26, 27). Nevertheless, there may still be a great deal of potential to further improve the efficacy of methotrexate through a better understanding of its bioavailability (28) and metabolism. This understanding can be gained by studying genetically heterogeneous isoforms of certain folate-dependent enzymes (29, 30). In addition, substantial potential remains for advances in the understanding of the effects of methotrexate on a variety of intracellular pathways (31).

THE THERAPEUTIC PYRAMID

The therapeutic model that prevailed for at least two decades was depicted as a pyramid. The pyramid began with a base of nonsteroidal anti-inflammatory drugs and included sequential addition of slow-acting DMARDs in subsequent tiers. Disease-modifying antirheumatic drugs were not routinely combined. A single agent, such as hydroxychloroquine or gold salts, was prescribed for periods of up to 6 months before clinicians could determine that a patient had failed to respond.

Several problems with this approach became evident with time. The duration of treatment with traditional DMARDs was often limited to intervals of less than 2 years (32). Patients discontinued using these agents because of toxicity or lack of efficacy (33). Because of these disappointing outcomes, along with the radiographic progression of bony erosions (8–10) and early disability discussed elsewhere (2–7), it became clear that it made little sense to wait the many months or years that were needed to judge whether a DMARD from the pyramid was effective before changing to another. Data on long-term efficacy and tolerability of methotrexate emerged at the same time as the recognition of the disappointing clinical outcomes from traditional DMARDs used in sequential monotherapy (34, 35). The pyramid was abandoned and replaced by a concept of treating earlier with a more aggressive therapeutic approach, which always featured the earlier use of methotrexate (36–40).

A NEW TREATMENT PARADIGM

A patient who experiences a decrease from 30 tender and swollen joints to 10 or 15 while receiving methotrexate is initially pleased and grateful. However, in the absence of remission and with the passage of months or years, the disease will once again inevitably become physically and psychologically burdensome. Patients and physicians then question whether methotrexate is still efficacious, only to find that dramatic flares of disease activity occur when therapy with the drug is discontinued (41). That is, methotrexate is efficacious but does not eliminate disease. Although methotrexate therapy represents a significant therapeutic advance, we need to do substantially better. Results of earlier trials of combination DMARD therapy have most often been disappointing (42). Despite the relative success of methotrexate therapy and the previous efforts to combine DMARDs, it became apparent that further therapeutic advances would require a better understanding of disease, the development of new agents, or both.

CYCLOSPORINE–METHOTREXATE

The first reported success of combination therapy was achieved by adding cyclosporine to methotrexate (43). Patients with rheumatoid arthritis who did not respond to a maximum dose of methotrexate (15 mg/wk) were treated with the addition of cyclosporine at a mean dosage of 2.97 mg/kg of body weight per day. Clinically meaningful improvements were observed (Table 1). Transient increases in serum creatinine concentration were frequently reported in patients taking cyclosporine, but these values returned to the normal range when the dose of the drug was adjusted. However, an increase in serum creatinine concentration that is sustained longer than 3 months can be associated with permanent residual loss of renal function (44). Daily doses of cyclosporine that exceed 4 mg/kg are associated with biopsy-proven cyclosporine nephropathy. Even patients who initially tolerate cyclosporine without loss of renal function may experience an increase in serum creatinine concentration over a period of a few years (45). It has recently been reported that when used with methotrexate, cyclosporine may increase the area under the curve of methotrexate by 29% (46).

Table 1. Trials of New and Existing Disease-Modifying Antirheumatic Drugs Used with Methotrexate*

Variable	Methotrexate–Sulfasalazine–Hydroxychloroquine (47)†	Methotrexate–Cyclosporine (43)	Methotrexate–Leflunomide (54)	Methotrexate–Etanercept (55)	Methotrexate–Infliximab (59)‡
Study type	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Open	Double-blind, placebo-controlled	Double-blind, placebo-controlled
Study duration, wk	39	26	52	24	30
Mean patient age, y	50	55.4	52.4	50	56
Mean duration of rheumatoid arthritis, y	10	11.2	13.6	13	8.4
Previous DMARDs used, n	1.5	NP	2.9	NP	2.8
Mean tender/swollen joints at baseline, n/n	29/27	NP	16.9/16.3	33/25	32/19
Maximum weekly dose of methotrexate, mg	17.5	15	25	25	17.5
Mean weekly dose of methotrexate, mg	NP	NP	17.2	19	15
Positive results on test for rheumatoid factor, %	84	NP	NP	84	84
Corticosteroid use, %	52	80	NP	53	63
Clinical response§	70.3% decrease in swollen joints	25% decrease in swollen joints	56% response (ACR 20)	71% response (ACR 20)	52% decrease in swollen joints
	65.5% decrease in tender joints	25% decrease in tender joints	36% response (ACR 50)	39% response (ACR 50)	59% decrease in tender joints
	50% decrease in patient evaluation of global arthritis activity	19% decrease in physician evaluation of global arthritis activity			33% decrease in pain 53% decrease in patient evaluation of global arthritis activity
	50% decrease in physician evaluation of global arthritis activity	23% decrease in joint pain		15% response (ACR 70)	23% decrease in physician evaluation of global arthritis activity
Toxicity	Higher serum creatinine concentration at 39 wk, not seen at 104 wk; no other differences from methotrexate monotherapy	Increase in serum creatinine concentration at 24 wk ($P = 0.02$) Hypertrichosis (13.3%) Tremors (5.3%) Paresthesia (10.6%) Nausea (28%)	Elevated AST or ALT levels (63%) Hypertension (13%) Nausea (23%) Alopecia (23%) Diarrhea (33%)	Injection site reaction (71.2%)	Upper respiratory tract infection (33%) Headache (25%) Sinusitis (11%) Fatigue (17%)

* ACR = American College of Rheumatology; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DMARD = disease-modifying antirheumatic drug; NP = not provided. Parenthetical numbers in column headings are reference numbers.

† Double-blind through 39 weeks; thereafter, only patients with 50% improvement were allowed to continue through week 104. Results through 9 months are presented here.

‡ Dose-ranging study of 3 mg/kg of body weight and 10 mg/kg given at 4- and 8-week intervals. Only results of the 3-mg/kg dose given at 8-week intervals, the dosage approved by the U.S. Food and Drug Administration, are reported here.

§ ACR 20 indicates ACR criteria for a composite 20% improvement in the following: number of tender joints on examination, number of swollen joints on examination, patient evaluation of pain on a 10-cm visual analogue scale, patient evaluation of global arthritis activity on a 5-point scale, physician evaluation of global arthritis activity on a 5-point scale, results of an independently validated health assessment questionnaire, and an acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein level). ACR 50 and 70 represent a 50% and 70% improvement, respectively, in these criteria.

SULFASALAZINE–HYDROXYCHLOROQUINE–METHOTREXATE

Patients with rheumatoid arthritis receiving a maximum dose of methotrexate (17.5 mg/wk) were prescribed both sulfasalazine and hydroxychloroquine to determine whether the addition of these DMARDs would be associated with improved outcomes. The combination of these agents is unique for several reasons.

First, the agents are traditional DMARDs that have been used for years. Second, because all three agents are available in generic form, therapy is comparatively inexpensive. Third, the three drugs were being tested together.

Short-term and sustained results of this treatment combination were reported by O'Dell and colleagues (47, 48). Clinical responses were marked, and toxicity

was less than that seen in a group of patients treated with methotrexate as monotherapy (Table 1). Surprisingly, a recent report from the same group indicates that the combination of methotrexate and sulfasalazine is as effective as methotrexate and hydroxychloroquine (49). However, recent informal surveys at symposia and meetings indicate that many rheumatologists are not relying on this “triple therapy” as the most effective combination in methotrexate-refractory patients.

These paradoxes have yet to be resolved. It is unclear why more physicians are not using the combination of methotrexate, sulfasalazine, and hydroxychloroquine as a therapeutic mainstay in methotrexate-refractory patients. This suggests that the clinical responses reported in the excellent trials by O’Dell and colleagues (48, 49) may be less commonly observed in the general community. It is also problematic to posit a mechanism of action that would result in an equivalent therapeutic effect from the combinations of methotrexate with either of these agents. Because of these issues, triple therapy should be studied by other investigators in patients who are refractory to high-dose methotrexate so that its efficacy and the relative contribution of sulfasalazine and hydroxychloroquine can be better understood.

NEW DMARDs

Leflunomide and etanercept are effective when used as monotherapy (50–52). It is thought that infliximab, a foreign protein, must be administered with methotrexate to avoid an immune response to repeat dosing that would negate clinical efficacy (53). Methotrexate has thus been recommended for use with infliximab and has also been investigated in clinical trials in combination with the new DMARDs leflunomide and etanercept (54, 55).

Leflunomide has been observed to induce a clinical response equivalent (51) or inferior (56) to that of methotrexate, depending on whether methotrexate is used with (51) or without (56) supplemental folic acid. Although etanercept has been compared directly with methotrexate for early rheumatoid arthritis (57), comparison studies in patients with chronic rheumatoid arthritis are difficult because patients are already taking methotrexate in this setting (58, 59). The practitioner who wishes to rely on evidence-based medicine to dictate the clinical decision of whether to initially treat with

methotrexate or one of the new agents may have some difficulty with a variety of issues. How can the relative value of the data on the new DMARDs (Table 1) be judged? Were equivalent patients studied (that is, were patients similar in disease severity; duration; and serologic and genetic markers of disease severity, such as rheumatoid factor, failure of previous DMARDs, corticosteroid therapy, and joint counts at baseline)? Is it appropriate to calculate the relative costs of these agents when choosing initial therapy? Should the absence of long-term safety and efficacy data on new DMARDs limit their use early in the disease (that is, before therapy with methotrexate)?

Not all of these questions have defensible answers. For example, to achieve a greater effect on inhibition of bony destruction, it could be argued that patients with early rheumatoid arthritis should receive etanercept before methotrexate (46). Similarly, infliximab, when used with methotrexate, is statistically superior to methotrexate alone for the inhibition of radiographic disease (60). In the absence of definitive data on the long-term safety, tolerability, and sustained efficacy of the new DMARDs, it is still appropriate to use methotrexate initially and then combine agents as soon as the predictable plateau of methotrexate efficacy (34) is reached.

It is clearly far too early in the process of gathering experience with these new drugs to be dogmatic about when or how they should be used. Yet there are compelling reasons to exchange the effects we are familiar with (pain, radiographic destruction, and disability) for those we are unfamiliar with and hope never to encounter (secondary treatment failures with new agents and an increased incidence of serious infections or malignancies). Physicians cannot ignore the potential for serious toxicity that is present when new drugs are prescribed to patients with a disease that lasts for decades. However, given what has been learned from the experience with DMARDs over the past four decades as well as the personal and societal costs of poorly controlled rheumatoid arthritis, it makes a good deal of sense to try something different, such as adding these new agents to methotrexate. Most but not all patients with rheumatoid arthritis are willing to exchange an immediate improvement in quality of life for the theoretical risk for an untoward event at an unspecified future time. This would be true for a patient with partial response to methotrexate monotherapy who begins taking a new DMARD in

combination or a patient with early disease who bypasses methotrexate and begins therapy with a newly approved agent. Because of the demonstrated significant clinical improvements that result when new DMARDs are added to methotrexate (Table 1), I believe that adding a new agent to methotrexate is preferable to stopping treatment with the drug and beginning a new DMARD. That is, methotrexate should be prescribed first because of our long-term experience with its safety and efficacy and our sophistication with the many issues associated with its use. It must be emphasized that this approach may not continue to be appropriate if new DMARDs are found to be safe and effective over prolonged treatment intervals or if new data demonstrate that even very expensive DMARDs are cost-effective early in disease because of decreased disability or fewer joint arthroplasties.

Leflunomide

Leflunomide is the only newly approved DMARD administered by the traditional oral route. It was developed specifically as an immunosuppressant and was tested in several animal models of autoimmune disease (61, 62) before it was studied in patients with rheumatoid arthritis (50). Leflunomide is thought to work by inhibiting dihydroorotate dehydrogenase in the intramitochondrial pyrimidine biosynthetic pathway, resulting in decreased levels of pyrimidine nucleotides, such as ribonucleotide uridine monophosphate. Dividing cells need to increase the pool of pyrimidine precursors eightfold to move from the G1 phase to the S phase of cell growth. In the presence of leflunomide, this pool can increase only twofold through cellular salvage pathways (63, 64). It is thus thought that clonal expansion of T cells in patients with rheumatoid arthritis who receive leflunomide would be inhibited, contributing to its mechanism of action (63, 64). Recently, it has been demonstrated that the leflunomide may also inhibit NF κ B activation (65) as well as tyrosine kinase activity (66), although the latter inhibition is probably not achieved in the doses used to treat rheumatoid arthritis (63).

Leflunomide is virtually entirely protein-bound and undergoes continuous enterohepatic recirculation (67). Its half-life is nearly 15 days, which means that effective antimetabolic levels will remain for many months after discontinuation of drug use. Leflunomide may, how-

ever, be efficiently removed from patients with the addition of the resin cholestyramine, which will bind the drug in the gut with ultimate removal in the stool. This strategy should be used if leflunomide therapy is discontinued in a woman of childbearing potential who wishes to conceive or who is not using a reliable form of contraception. It may also be used in the event of unacceptable toxicity, including transaminitis, gastrointestinal intolerance, rash, or alopecia. In a woman considering pregnancy, 11 full days of treatment with cholestyramine, 8 g three times daily, is required, along with blood sampling to ensure that the M1 metabolite of leflunomide is less than 0.02 μ g/mL. However, it is likely that shorter durations of treatment, such as 6 to 8 days, will be adequate to alleviate most other toxicities (67).

Leflunomide is actually a prodrug that undergoes hepatic metabolism in the liver to A77 1726, two thirds of which is excreted by the gut and one third of which is excreted by the kidney (67). Although leflunomide is not contraindicated in patients with renal impairment, it should be used with caution in this setting. Patients with hepatic compromise, including those who are regular heavy consumers of alcohol or those with a history of hepatitis, should probably not take leflunomide. Because no studies have examined the amount of alcohol, if any, that might be safely consumed with leflunomide, it is probably best to be conservative with this combination. Similarly, no studies have been performed in patients with histories of hepatitis.

It has been reported that leflunomide therapy itself is associated with elevated alanine aminotransferase and aspartate aminotransferase levels (twice the normal ranges in 6.6% and 6.0%, respectively) (68). Although we know that methotrexate can be a potent hepatotoxin (19), the same cannot yet be said about leflunomide. Only three liver biopsies have been performed in patients who were also receiving methotrexate, and the results of all three were benign (54). Nevertheless, liver damage is possible when methotrexate and leflunomide are used together (Table 1). It is reassuring that elevations in aminotransferase levels reported in patients receiving leflunomide or the combination of methotrexate and leflunomide return to normal quickly when use of the drug is discontinued and cholestyramine is administered (51, 54). Similarly, it is additionally reassuring that only one case of clinically significant liver disease (in a patient with insulin-dependent diabetes [69]) has been

Table 2. Monthly Costs of Disease-Modifying Antirheumatic Drugs

Drug	Monthly Cost*			
	Albany, New York	Cleveland, Ohio	Dallas, Texas	Atlanta, Georgia
Methotrexate (15 mg/wk)	53.48	74.50	75.99	70.59
Cyclosporine (175 mg/d)	208.02	283.99	189.00	182.00
Leflunomide (10 or 20 mg/d)	266.07	283.00	287.00	283.00
Etanercept (25 mg [8.3 doses/mo])	1210.65	1600.00	1622.00	1679.00
Infliximab†				
Year 1	915.00	900.00	870.00	907.50
Year 2	610.00	600.00	580.00	605.00

* Prices quoted for Albany represent the mean of three major pharmaceutical chains and hospital pharmacy. Prices for Cleveland, Dallas, and Atlanta represent a single major pharmaceutical chain. Prices for surgery represent approximate costs for uncomplicated surgery and hospital stay in Albany. Costs of postoperative care, drugs, and rehabilitation are not included. All prices were current as of June 2000.

† Prices represent a patient weighing less than 67 kg. The monthly cost would increase by 50% in patients weighing at least 67 kg and by 100% in patients weighing at least 100 kg. Prices represent nine or six infusions (year 1 or year 2, respectively) averaged over 12 months.

reported among patients with rheumatoid arthritis who are receiving methotrexate and are managed according to the 1994 guidelines of the American College of Rheumatology (ACR) (19). These suggested guidelines state that patients should be managed to maintain normal levels of serum aspartate aminotransferase by reduction of the methotrexate weekly dose (19). The appropriateness of this management strategy in patients receiving a combination of leflunomide and methotrexate would require a prospective study over many years, as well as hundreds of liver biopsies. In the absence of data, it is prudent for clinicians prescribing both drugs to reduce the dose of either agent in the event of a confirmed increase of aspartate aminotransferase levels into the abnormal range or a decrease in serum albumin level in a patient who is clinically stable or doing well.

The combination of leflunomide and methotrexate has been studied in a small open study that reported an ACR 20 response rate of 56% and an ACR 50 response of 36%. The ACR 20 response rate consists of a 20% improvement from baseline in both tender and swollen joints as well as 20% improvement from baseline in patient and physician evaluation of global arthritis activity; patient evaluation of pain; improvement in a validated health assessment questionnaire; and measurement of an acute-phase reactant, such as erythrocyte sedimentation rate or C-reactive protein; the ACR 50 response rate requires a 50% improvement in the same criteria as ACR 20 (Table 1). These responses represent clinically meaningful incremental improvements in patients who were already receiving the higher dosages of methotrexate (mean, 17.2 mg/wk) used for rheumatoid

arthritis. These results have recently been confirmed in a double-blind placebo-controlled study (70). Leflunomide costs approximately \$266 per month (Table 2).

Tumor Necrosis Factor Inhibition

Tumor necrosis factor (TNF) represents an attractive target for inhibition in patients with rheumatoid arthritis. The trimolecular cytokine is derived primarily from cells of a macrophage monocyte lineage and is known to stimulate the production of multiple mediators that drive the inflammatory process (71–74). For TNF to affect cellular events, it must first bind to a p75 and p55 receptor on the cell surface (75). These receptors are also shed into the circulation (76, 77) and will bind TNF, rendering the resultant TNF receptor–TNF circulating complex incapable of cellular activation.

Etanercept

Etanercept is an artificial bioengineered molecule derived from Chinese hamster ovary cells grown in tissue culture. Its structure consists of two p75 TNF receptors attached to an IgG1 Fc region of a human immunoglobulin molecule. This construct is administered subcutaneously twice weekly (mean half-life, approximately 3 days) and is capable of significantly lowering levels of circulating TNF. This is the first agent for rheumatoid arthritis that requires long-term self-administration with a needle. Some patients may not wish to have this responsibility or may lack the manual dexterity or access to another caregiver required for its use. Etanercept is effective when compared with placebo in pa-

tients with rheumatoid arthritis (52). The most common side effects are erythema and pruritis at the injection site, and these reactions usually disappear after 3 months of regular dosing (58). While an increased mortality rate was observed in patients with septic shock receiving etanercept (78), only a small number of serious adverse events have been reported in patients with rheumatoid arthritis who receive etanercept as monotherapy (52, 58) or in combination with methotrexate (79). Nevertheless, because of concern about the development of infectious complications with the use of etanercept, the FDA recently changed the labeling of the compound to include a directive warning against its use in patients with a history of, or predisposition to, serious infections, such as pneumonia or cellulitis (80). Tumor necrosis factor also contributes to effective immune surveillance for malignancies (81, 82). However, no increased incidence of tumors has been reported during 2 years of TNF inhibition with etanercept (83).

Tumor necrosis factor inhibition is associated with an increase in the incidence of positivity for antinuclear antibodies; a few patients have developed full-blown systemic lupus syndromes (84). It is therefore appropriate to obtain a baseline antinuclear antibody and DNA antibody in patients beginning etanercept and to remain vigilant for the development of lupuslike clinical features. Etanercept will also bind to lymphotoxin in the circulation (85). The clinical relevance of this interaction is presently unknown. Repeated dosing with etanercept may also be associated with the development of nonneutralizing antibodies to the drug. These antibodies do not seem to be clinically relevant, although more information about them and their potential effects on clinical response is needed. Several cases of demyelinating disease have recently been reported in patients with rheumatoid arthritis receiving etanercept (86). The significance of this observation is unclear.

When etanercept is added to higher doses of weekly methotrexate used to treat patients with rheumatoid arthritis, a clinically meaningful response results (Table 1). At 24 weeks, ACR 20 response rates of 71% are observed in patients already receiving a mean weekly methotrexate dose of 19.0 mg; ACR 50 and 70 response rates are 39% and 15%, respectively. (The ACR 70 response rate requires a 70% improvement in the same criteria as ACR 20 and ACR 50.) Most patients have little difficulty self-administering the injection. Initial

etanercept therapy is often accompanied by an improvement in psychological state or mood, which can be marked in certain patients. Whether this phenomenon is due to the rapid clinical improvements seen with the drug or an independent central nervous system effect is unknown. Because etanercept costs approximately \$1200 to \$1600 per month (Table 2), many insurance plan administrators insist on documentation of methotrexate failure before etanercept can be added. Some plans will approve the use of etanercept with the mandate that clinical efficacy be reassessed after 6 months of treatment to verify continued eligibility. The Veterans Administration Health System in New York State also requires that a patient with rheumatoid arthritis have failure of both methotrexate and leflunomide to be eligible to receive etanercept.

Infliximab

Infliximab is a chimeric antibody whose target is TNF. It is administered intravenously in an outpatient setting. The hypervariable region of the antibody is murine in origin, while the remainder of the immunoglobulin consists of a human IgG1 Fc heavy chain and partial κ light chain. Because of the chimeric nature of the antibody, it should have less potential to generate an immune reaction than a fully murine molecule but more potential than a fully humanized construct. Repeat intravenous administration has been associated with the development of clinically relevant human antichimeric antibodies. Because of this, infliximab has been studied with simultaneous methotrexate dosing to abrogate the response of these antibodies, which could limit the long-term effectiveness of the intervention (53). The weekly methotrexate dosage used with infliximab was 7.5 mg per week. This was said to be identical to the weekly dosage of methotrexate that was commonly prescribed in Europe when European investigators planned their study (53).

In a subsequent dose-ranging study, 3 mg/kg and 10 mg/kg of infliximab were compared and methotrexate was given with placebo infusions (60). The two dose regimens were administered at both 4- and 8-week intervals after an initial loading schedule of doses administered at 0, 2, and 6 weeks. All four active infliximab regimens exhibited statistically superior ARC 20 responses compared with those seen in patients receiving methotrexate and placebo infusions. No differences were

Table 3. Cost of Total Hip or Knee Arthroplasty*

Variable	Cost, \$
Total hip arthroplasty	
Surgeon	5000
Operating room	3000
Implant (prosthesis)	3300–4500
Anesthesia	1248
Operating room supplies	700
Hospital stay, drugs	2010–2680
Total knee arthroplasty	
Surgeon	5000
Operating room	3000
Implant (prosthesis)	3500–5200
Operating room supplies	700
Anesthesia	1196
Hospital stay, drugs	2010–2680

* Prices for surgery represent approximate costs for uncomplicated surgery and hospital stay in Albany, New York. Costs of postoperative care, drugs, and rehabilitation are not included. All prices were current as of June 2000.

observed in the ACR 20 responses across the four active study groups. The magnitude of the response is similar to that reported when either leflunomide or etanercept is added to methotrexate (Table 1) (54, 55). Human antichimeric antibodies to infliximab were observed in 3 of 27 patients (11.1%) who terminated treatment prematurely while receiving 25 mg of weekly methotrexate (59). Of interest, ACR 70 responses were significantly more common with the higher dose of 10 mg/kg administered every 8 weeks than with the 3-mg/kg dose administered at the same interval (59). The frequency of any infection increased at the 10-mg/kg dose only. Three malignancies were observed, all in patients receiving the 10-mg/kg dose every 4 weeks.

Infliximab is approved by the FDA for treatment of rheumatoid arthritis on a mg/kg of body weight basis. The FDA recently approved an increase in the dose of infliximab to up to 10 mg/kg in order to achieve the desired clinical response (87). The wholesale price of the 100-mg vial is approximately \$480, and a 70-kg patient would receive three vials ($70 \text{ kg} \times 3 \text{ mg/kg} = 210 \text{ mg}$ per dosing). It is currently recommended that no portion of a vial be discarded. In the 70-kg patient, with rounding, three vials would be administered at a wholesale cost of \$1440 per dosing. Medicare will reimburse intravenous infusion performed in the office, but non-Medicare patients usually go through the same sequence of steps described for etanercept in order to qualify for coverage. Because of the differing costs for patients of different weight, it is possible that infliximab may be less

cost-effective for large patients than for small patients (Table 2). Infliximab binds TNF at the cell surface, which is not possible with etanercept. The therapeutic implications, if any, of this difference in biological activity are currently unclear.

Although no episodes of anaphylaxis have been reported with intravenous infusion of infliximab, a few cases of hypotension have been observed (53). Headache and respiratory congestion may occur and are treated by slowing the infusion or pretreating with acetaminophen or antihistamine.

COSTS

The new agents are costly. Before the final decision can be made on whether the substantial additional expense is warranted, data must be available to indicate whether the slowing of radiographic damage observed with all of these agents through 12 to 24 months, when used in combination with methotrexate, can be sustained. If so, then it follows that joint arthroplasties can be avoided (Table 3), along with disability. A nondisabled patient may continue to work; pay taxes; and fulfill his or her personal role as a spouse, parent, and functional, vital member of society. The worth of these outcomes is thus both tangible and intangible, and it is difficult to assign an accurate or adequate value to the latter. Open long-term observational studies must be performed to demonstrate to society that utilization of these expensive interventions not only is appropriate now but is cost-effective in the long term. The costs depicted in Table 3 provide an objective representation of annual costs of new agents that may be added to methotrexate to achieve improved outcomes. These agents must be considered in the context of a lifelong disease and must take into account whether disability can be avoided with their use.

RATIONAL RECOMMENDATIONS

Unless there is a contraindication to the use of methotrexate, most patients with rheumatoid arthritis should receive this agent. The dose should be increased to tolerance after obtaining a baseline chest radiograph, starting folic acid to help avoid many nuisance toxicities (21, 22), and monitoring liver enzymes at recommended intervals to avoid hepatic toxicity (19). For patients with mild disease (those who have no evidence of erosions and easily controlled synovitis), hydroxychloroquine or

Table 4. Treatment with Disease-Modifying Antirheumatic Drugs in Patients with Moderate or Severe Active Rheumatoid Arthritis

Indication	Action	Reference
If patient has persistent synovitis and evidence of radiographic erosions	Start oral methotrexate	13–16, 26, 27
	Obtain baseline chest radiograph	18, 20
	Establish normal hepatic and renal function	19
	Start folic acid	21, 22
	Switch to parenteral methotrexate	28
If patient has inadequate response to oral methotrexate and folic acid	Add sulfasalazine and hydroxychloroquine or add leflunomide	47, 48
If patient has inadequate response to parenteral methotrexate		
If patient has inadequate response to methotrexate, sulfasalazine, and hydroxychloroquine	Discontinue sulfasalazine and hydroxychloroquine, add leflunomide	54, 70
If patient has toxicity or inadequate response	Discontinue leflunomide, add etanercept	55, 79
If patient has toxicity or inadequate response	Discontinue etanercept, add infliximab	59, 60

sulfasalazine may be used. Treatment recommendations for patients with moderate or severe disease are outlined in Table 4.

Because of improved bioavailability, a change to subcutaneous dosing (28) should be strongly considered if a patient has not achieved an adequate response to 20 mg of oral methotrexate per week. If a patient has persistent synovitis while receiving parenteral methotrexate in the range of 20 to 25 mg per week, another DMARD should be added. The choice of which agent or agents to add at this point is somewhat arbitrary. Such issues as insurance coverage, perceived convenience, and both patient and physician preference must be considered.

Although a single group of investigators reported impressive clinical benefits resulting from the addition of hydroxychloroquine and sulfasalazine to methotrexate, their findings must be confirmed by others. It is not clear whether the perception of relatively low reliance on this strategy amongst rheumatologists is due to a different experience or simply the desire to move on and try new agents. Triple therapy is relatively inexpensive and is therefore easier to access for patients with limited resources.

At this time, the clinical response rate and overall toxicity reported for leflunomide, etanercept, and infliximab do not clearly show that one of these agents is better than the others when used with methotrexate (Table 1). Therefore, until further data are generated that would provide evidence for a judgment of superiority, it is reasonable to use the least expensive drug (leflunomide) first. If the methotrexate–leflunomide combination fails, then the decision to use either etanercept or infliximab will depend on insurance coverage or patient preference. Because of toxicity concerns and

the emergence of new DMARDs, cyclosporine has become a less attractive choice for combination with methotrexate.

FINAL THOUGHTS

A combination of methotrexate and leflunomide with either etanercept or infliximab needs to be investigated in clinical trials. The financial costs of these combinations of DMARDs would be significant but must be weighed against the potential savings associated with maintaining function while avoiding disability, decreased earning capacity, and reconstructive joint arthroplasties (Table 3). Randomized head-to-head studies are needed to determine which of the several combinations of new and existing drugs are most effective and safe for rheumatoid arthritis, a disease that has ruined far too many lives.

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