Use of combination therapy in the routine care of patients with rheumatoid arthritis: Physician and patient surveys

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ABSTRACT

Aims

To describe the utilization of combination therapy in the treatment of rheumatoid arthritis (RA).

Methods

Review of published articles and abstracts, and patient/physician questionnaire data.

Results

Combination therapy was rarely used in the early 1980s and is now (1999) used for about 25% of RA patients in the US. Physician and patient surveys indicate that methotrexate plus hydroxychloroquine is the most commonly used combination in North America, and physician surveys indicate that methotrexate plus sulfasalazine is the most commonly used combination in Europe. Patient questionnaire data indicate that 13.4% of patients in the US take methotrexate and hydroxychloroquine, and between 11% and 15% of patients with recent onset of RA receive treatment with disease-modifying antirheumatic drug (DMARD) combinations.

Conclusions

Combination therapy with agents such as hydroxychloroquine and methotrexate is used in up to 25% of RA patients in the US, but the use of "aggressive combination therapy" is unusual. Whether combination therapy as currently practiced is beneficial remains to be determined.

Introduction

Aggressive early treatment of rheumatoid arthritis (RA) has been encouraged as the optimal approach to prevent joint deformities and minimize functional losses (1-3). Combination therapy, or the simultaneous use of more than one disease-modifying antirheumatic drug (DMARD) is one form of such aggressive therapy.

Early studies of combination therapy generally included patients with well-established disease who had "failed" one or more second-line drugs. However, recent clinical trials have been directed toward newly diagnosed RA patients (4-8). The results of clinical trials of combination therapy have been mixed, with findings ranging from advantages with combinations (9-13) to no difference between combinations and monotherapy (5, 14-23). Most studies showing advantages with combinations have included methotrexate and/or low-dose prednisone. Certain DMARD combinations have been associated with increased toxicity (13, 14, 22-27), primarily those which included gold, penicillamine, or hydroxychloroquine. To date most combinations have been studied in only one report, and replicated studies of various combinations are limited (6). More recent studies have included new therapies such as leflunomide (Arava), etanercept (Embrel), and infliximab (Remicade), both as single-drug treatments and in combination with methotrexate (28-32). Critical, comprehensive reviews of the results of the major studies of combination DMARD therapies in RA have also been published (4-8).

There is a general consensus that acceptance of combination therapy among practicing rheumatologists, for at least some patients, has been growing over the last 15 years - at least according to physician surveys (33-36). One recent summary of current treatment for RA indicates that combination therapy has become the " . . . rule rather than the exception" (37). In this review we examine the prescribing patterns for combination therapy by reviewing the literature from both physician surveys and patient questionnaires.

Physician surveys

Several surveys of practicing rheumatologists confirm a dramatic increase in the use of DMARD combinations over the last ten years, although universal or

routine use of combinations in clinical care has not been documented. In a study of 92 Canadian and 77 Australian rheumatologists in 1986, Bellamy and Brooks reported that 45% of Canadian and 31% of Australian rheumatologists who responded to the questionnaire prescribed antimalarials with gold therapy, and a smaller fraction of the surveyed physicians used the combination of antimalarials and penicillamine (38). Eleven years later O'Dell (1997) reported that 99% of 200 randomly selected members of the American College of Rheumatology (ACR) who responded to his survey prescribed combination therapy (36). He estimated that combination therapy was used in about 24% of the responding clinicians' patients.

Other recently conducted surveys of Canadian, European, and US rheumatologists have not found as high a percentage of usage as that described by O'Dell; however, they asked slightly different questions. O'Dell focused on the willingness to prescribe combinations of DMARDs. Others have examined the circumstances in which rheumatologists choose combination therapy. Maetzel and colleagues surveyed all Canadian rheumatologists plus a geographically stratified 10% sample of US rheumatologists concerning their first and second choice of DMARDs based on the severity of their patients' RA. For aggressive RA, about 13% of the Canadian and US physicians reported that they would select some form of combination therapy as their first treatment choice (34). Forty-one percent of Canadian and 38% of US rheumatologists reported that they would add another DMARD if methotrexate had been ineffective for a patient (34).

Moreland and colleagues reported similar results from a survey of European and US rheumatologists (35). Of those responding, 24% of US and 10% of European rheumatologists reported that they would use combination therapy for moderate disease. Further, 58% of US and 32% of European rheumatologists reported that they would use combination therapy for severe RA (35).

Wolfe and colleagues posed a different question in their survey of 645 US rheumatologists (33). They asked clinicians to rate the effectiveness of different DMARDs in single therapy and in combination therapy (i.e., their best choice for combination therapy) after one and four years of treatment. Combination therapy was rated as good or excellent by 70% of the respondents after one year of treatment and by 44% after four years. In contrast, methotrexate was rated as good or excellent by 90% of the responding rheumatologists after one year of treatment and by 66% after four years.

Physician surveys have indicated some degree of agreement about which combinations are most effective. O'Dell's study of 200 US rheumatologists found that methotrexate with hydroxychloroquine (84%) and methotrexate with sulfasalazine (52%) were the two most popular DMARD combinations (36). Moreland and colleagues also reported that methotrexate and hydroxychloroquine was the DMARD combination chosen by the majority of US rheumatologists, while the European rheumatologists in this survey favored methotrexate and sulfasalazine (35). Both European and US clinicians would select methotrexate, hydroxychloroquine, and sulfasalazine for triple therapy (35).

Patient surveys and clinical chart reviews

Physician reports of their prescribing practices provide only estimates of the use of combination DMARD therapy in the treatment of RA, however. To assess the actual use of combinations, we surveyed 3,604 patients with RA from the practices of 303 geographically diverse US rheumatologists between August 1998 and April 1999 (39), using a self-report questionnaire (CLINIHAQ). We asked patients about their current and past use of various DMARDs and prednisone. DMARD usage was high, with 94.1% of the patients having received at least one such drug since the onset of their disease. Current usage included 51.1% taking one DMARD, 19.3% two, 5.7% three, and 0.5% four DMARDs, while 23.3% reported taking no current DMARD. Thus, about one-fourth of the patients were taking combination therapy, a figure virtually identical to that suggested by O'Dell (36).

The most common two-drug combination was methotrexate and hydroxychloroquine taken by 8.7% of all patients, followed by methotrexate and sulfasalazine taken by 1.3% (39). The most frequently used three-drug combination was methotrexate, hydroxychloroquine, and sulfasalazine, used by 2.1% of all patients. Not surprisingly, these combinations were the same ones identified by O'Dell (36), Moreland *et al.* (35), and Maetzel *et al.* (34) as the most popular in each of their surveys of US rheumatologists.

Table I reviews the reports of various patient groups or chart reviews to determine which medication(s) patients are actually taking. Several of the investigations are available only in abstract form, and details of the methodologies as well as demographic and clinical characteristics of the patients are limited. The data indicate clearly that the prescription of combination therapy has increased from being rare in the 1980s [as few as 2% of patients received combination therapy in 1981 (40) and 1986 (41)] to as many as 25% in the late 1990s.

Recent studies (42, 43) that examined drug use in early disease (duration < 2 years) indicate that 11-15% of patients may begin therapy with combination medications. Wolfe and colleagues asked 740 patients with a disease duration of < 6 months (and who being followed by 142 different US rheumatologists) about their DMARD usage. Sixty-four percent had received at least one DMARD, while 15% had used combination DMARDs, including 14% who were taking methotrexate plus hydroxychloroquine and 1% who were using triple therapy with hydroxychloroquine, sulfasalazine, and methotrexate (43).

The North American Rheumatoid Arthritis Disease Management Study Group, which began a cohort study of patients with "early" RA in 1996 (n = 326), reported that 11% were taking combination therapy, of whom 8% were prescribed a combination of hydroxychloroquine and methotrexate (42). Studies with small samples (< 70 patients) have reported higher percentages. Illei and colleagues (44) reported that 35% of 46 patients with early synovitis from a single clinic were treated with combination DMARDs during the first year, and 56% were receiving combinations by year two. The International Rheumatoid Ar-

Table I. Use of combination disease-modifying antirheumatic drug (DMARD) therapy for rheumatoid arthritis (RA), as reported by patients.

Study	Study methods	Year/Ref.	No.	Disease duration	Age (yrs.)	Female (%)	Any combin.	MTX + any	MTX + HCQ	Other comb.	Triple therapy
Ward & Fries	Review of data collected in 1981	1998 (40)	305	14.2 yrs.	54.9	83.0	1%				
Owen *et al.*	Community survey; Tasmania sample	1986 (41)	380	12 yrs.	60	72.5	1.6%				
Nowlin *et al.*	Chart review for years 1993-1996	1998 (46)		13.5 yrs.	56.6	65.5					
	1993		139				12.2%				
	1994		234				10.7%				
	1995		268				13.4%				
	1996		237				10.5%				
Ward & Fries	Review of data collected in 1996 (reflects lifetime use)	1998 (40)	126				12.2%				
Wolfe *et al.*	Survey of a geographically diverse sample	1997 (43)	750	4.6 mos.	54.3	72.6			14%		1%
Int. RA Group*	Clinic sample from Canada	1997 (45)	68	< 5 yrs.	—	77.9		26%		44%	
Int. RA Group*	Clinic sample from the US	1997 (45)	60	< 5 yrs.	—	76.7		28%		28%	
Illei *et al.*	Early synovitis cohort	1997 (44)	46	< 1 yr.			35%				
Illei *et al.*	One year follow-up synovitis cohort	1997 (44)	46	~ 2 yrs.			56%				
Wang *et al.*	Clinic sample reflecting lifetime use	1998 (48)	581	18.9 yrs.	61.6	81.0	65%		24.7%		
NARA Group**	Inception cohort recruited in 1996	1998 (42)	326	Early			11%				
Pal & Amlesh	Random sample; 4 British practices	1998 (47)	142				2.1%				
Wolfe *et al.*	Survey of a geographically diverse US sample	1999 (39)	3,604	8.7 yrs.	60.6	76.0	25.6%		13.4%	3.9%	2.1%

*International Rheumatoid Arthritis Disease Management Group; ** North American Rheumatoid Arthritis Disease Management Study Group
Any combin. = any combination of more than one DMARD; MTX + any = methotrexate + any DMARD; MTX + HCQ = methotrexate + hydroxychloroquine; Other comb. = any other combination of DMARDS; Triple therapy: combination of three DMARDs.

thritis Disease Management Group, reporting from a total of 26 clinics in Canada (n = 68 patients) and the US (n = 60 patients), indicated that > 60% of the patients were being treated with combination DMARD therapy (45).

Chart reviews from specific clinics show that the percentages of patients who received combination DMARD therapy ranged from 2% to 13% at any point in time (46, 47). However, the percentage of patients who had used combination DMARD therapy at any time approached 65% for patients with established disease for > 5 years (48).

Discussion

The results of these physician and patient surveys do not address the question of the effectiveness of combination therapy. Combination therapy is a "modern" idea, but only makes sense if it is effective, i.e., more effective than single-drug therapy. The current increase in combination therapy may not reflect long-term effectiveness, but rather factors such as short-term efficacy in clinical trials, beliefs, the availability of drugs, the efficacy of specific second-line agents, and other practice issues.

The degree to which combination therapy may add effectiveness to routine rheumatologic care has not been determined. The fact that treatment with more than one DMARD by US rheumatologists was seen for only 25% of patients suggests that clinicians have yet to be convinced of the value of combination DMARD therapy for most patients. Future longitudinal investigations of these patients should help to determine the possible benefits of, and adverse responses to, combination therapy for RA.

Summary

Combination therapy, or the simultaneous use of more than one DMARD for the treatment of RA has increased dramatically over the last 15 - 20 years. While early studies of combination therapy generally involved patients who had failed one or more DMARDs, recent clinical trials have been directed toward newly diagnosed patients with RA. Surveys of physicians and patients indicate that about 25% of patients are prescribed one or more DMARDs. The most commonly used two-drug combinations are methotrexate plus hydroxychloroquine in the US and methotrexate plus sulfa-

salazine in Europe. Methotrexate plus hydroxychloroquine plus sulfasalazine is the most frequently selected three-drug combination in both Europe and the US. Further clinical trials and long-term observational studies of various drug combinations should help to clarify the optimal approaches toward improved outcomes for patients with RA.

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