

# Contemporary Disease Modifying Antirheumatic Drugs (DMARD) in Patients with Recent Onset Rheumatoid Arthritis in a US Private Practice: Methotrexate as the Anchor Drug in 90% and New DMARD in 30% of Patients

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**ABSTRACT.** *Objective.* To describe therapies with disease modifying antirheumatic drugs (DMARD) and biological agents in patients with early rheumatoid arthritis (RA) who were receiving routine clinical care in 2001 in a private practice of 5 rheumatologists in Nashville, TN, USA.

*Methods.* A cohort of 232 patients with initial symptoms of RA in 1998 or later were enrolled between February and October 2001 into a longterm observational study, designed to evaluate treatments and longterm outcomes of RA. The baseline evaluation included review of all DMARD that had been taken since disease onset, clinical measures on a multidimensional health assessment questionnaire, joint counts, and laboratory measures.

*Results.* Among the 232 patients, methotrexate (MTX) was the first DMARD used in 192 patients (82.8%), including 3 in combinations. Since initiation of the first DMARD to the study visit, over a median interval of 12.1 months, 125 (66.1%) patients of the 189 whose initial DMARD was MTX as a single DMARD continued MTX as a single DMARD, 43 (22.8%) had another DMARD or biological agent added in combination with MTX, and 21 (11.1%) discontinued MTX. Since the onset of RA, 89.2% of the patients had taken MTX, 15.9% hydroxychloroquine, 3.9% sulfasalazine, 22.0% leflunomide, 9.5% etanercept, 4.3% infliximab, and 87.0% prednisone.

*Conclusion.* After a median duration of 12.1 months of DMARD therapy, almost 90% of patients with recent onset RA took MTX as the anchor drug. More than 60% took MTX as a single DMARD or in combination with traditional DMARD, while 30% took leflunomide, etanercept, or infliximab, usually in combination with MTX. (J Rheumatol 2002;29:2521–4)

## Key Indexing Terms:

EARLY RHEUMATOID ARTHRITIS

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The approach to treatment of patients with rheumatoid arthritis (RA) has changed considerably over the last 2 decades, with recognition that short term drug efficacy did not prevent severe longterm consequences in most patients<sup>1</sup>, with calls for early and aggressive use of disease modifying antirheumatic drugs (DMARD)<sup>2,3</sup>, and introduction of methotrexate (MTX)<sup>4</sup>, cyclosporine, leflunomide (LEF), etanercept (ETAN), infliximab (INFLIX), and anakinra (ANA), used singly and in combinations<sup>5</sup>. The efficacy of

new DMARD and combinations of DMARD for RA has been established through randomized controlled clinical trials, which are the optimal method to establish the efficacy of a drug. However, supplementary observational studies are required to establish longterm effectiveness as well as appropriate use of drugs in usual care<sup>6</sup>.

Relatively few data are available concerning the use of DMARD in usual care of patients with early RA. Paulus and colleagues<sup>7</sup> reported that 53–57% of patients with seropositive RA had been treated with MTX within the first 2 years of disease in 1993–1996. However, patterns of use of new DMARD and biological agents introduced since 1998 remain unknown. We analyzed DMARD and biological agents used in routine clinical care of 232 patients with early RA between January 1998 and October 2001 in a private practice of 5 rheumatologists in Nashville, Tennessee.

## MATERIALS AND METHODS

*Patients.* Patients with recent onset RA were receiving care from 5 full time rheumatologists at Medical Specialists of Nashville. More than 90% of

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patients whose symptoms began in 1998 or later and were seen between February and October 2001 consented to be enrolled in a longterm observational study, designed to evaluate treatments and longterm outcomes of RA. A total of 257 patients whose rheumatologists designated them as having RA were enrolled; the 232 who met American Rheumatism Association [now American College of Rheumatology (ACR)] criteria for RA<sup>8</sup> at some time are included in this report.

**Study design.** The patients were evaluated by one rheumatologist (TS) according to a standard protocol to evaluate RA (SPERA)<sup>9</sup>, which includes a multidimensional Health Assessment Questionnaire (MDHAQ)<sup>10</sup> with a modified HAQ (MHAQ) functional status scale<sup>11</sup> and visual analog scales to assess pain, fatigue and global status, a patient self-report questionnaire, joint count, laboratory tests, and review of all medications taken since onset of symptoms. The retrospective medication review was based on office medical records and supplemented by verifying details with the patient, included the date when a DMARD course was begun and, if relevant, discontinued, as well as DMARD combinations, prednisone, and nonsteroidal antiinflammatory drugs (NSAID).

**Statistical analyses.** Data were analyzed using the Statistical Package for the Social Sciences (SPSS 10.0; Chicago, IL, USA) for the personal computer.

## RESULTS

**Patients.** The mean age of the 232 patients was 53.9 (16–88) years (Table 1); 77.2% were female, 89.7% were Caucasian, and 73.5% were rheumatoid factor positive. The median duration of symptoms was 5.1 months before the diagnosis, and the median duration of disease at study visit was 20.9 months.

At the study visit, 22 (9.5%) patients had RA symptoms for less than 6 months, 45 (19.4%) had symptoms 6–12 months, 64 (27.6%) 12–24 months, and 101 (43.5%) more than 24 months.

Table 1. Demographic and clinical status measures in 232 patients with recent onset RA.

	Mean (median) or Number (% of total)
Demographic measures	
No. of patients	232
Age, yrs	53.9 (53.7)
Female	179 (77.2%)
Caucasian	208 (89.7%)
Education, yrs	12.8 (12.0)
Other disease measures	
Duration of disease, mo	21.3 (20.9)
Positive rheumatoid factor	169 (73.5%)
Outcome measures	
MHAQ, 0–3	0.52 (0.38)
Pain score, 0–10	4.2 (4.1)
Patient estimate of global status, 0–10	3.8 (3.8)
Fatigue score, 0–10	5.1 (5.0)
Psychological distress, 0–9.9	2.6 (2.2)
Morning stiffness, min	70.8 (45.0)
No. of symptoms, 0–60	10.6 (9.0)
Swollen joint count, 0–42	8.8 (7.5)
Tender joint count, 0–42	8.5 (6.0)
ESR, mm/h	30.4 (27.0)
Physician estimate of global status, 0–10	3.7 (3.0)

MHAQ: Modified Health Assessment Questionnaire (functional status scale on multidimensional HAQ); ESR: erythrocyte sedimentation rate.

**Treatment with DMARD.** The first DMARD was begun at a median of 5.5 months after the first symptoms of RA; it was MTX in 189 (81.5%) patients, hydroxychloroquine (HCQ) in 15 (6.5%), sulfasalazine (SSZ) in 2 (0.9%), LEF in 6 (2.6%), MTX+HCQ in 2 (0.9%), and MTX+ETAN in 1 (0.4%) patient (Table 2). At the study visit, 152 (65.5%) patients were taking a single DMARD, 59 (25.4%) patients were taking combination DMARD therapy, and 21 no DMARD other than prednisone, which was taken by 18 of these 21 patients. The 152 patients taking a single DMARD included 130 (56.0% of all patients) taking MTX, 4 (1.7%) HCQ, 1 (0.4%) SSZ, 14 (11.0%) LEF, 2 (0.9%) ETAN, and 1 (0.4%) INFLIX. The 59 patients taking combinations included 55 (23.7% of all patients) taking MTX, 17 (7.3%) HCQ, 3 (1.3%) SSZ, 23 (9.9%) LEF, 14 (6.0%) ETAN, and 8 (3.4%) INFLIX in combinations (Table 2).

Over the median of 12.1 months of DMARD treatment (with a median of 20.9 months since the first RA symptoms), 207 of the 232 patients (89.2%) had taken MTX (median dose 12.5 mg; range 5–25 mg), 37 (15.9%) HCQ, 9 (3.9%) SSZ, 51 (22.0%) LEF, 22 (9.5%) ETAN, and 10 (4.3%) INFLIX at some time, either as a single DMARD or in combinations (Table 2). Among the 232 patients, 128 (55.2%) had taken only 1 DMARD, 58 (25.0%) had taken 2, 27 (10.3%) had taken 3, 3 (1.3%) had taken 4, and 2 (0.9%) patients had taken 5 DMARD; 17 patients had taken no DMARD (other than prednisone), 9 of whom were at their first visit.

During the interval from DMARD initiation to the study visit, 125 patients of the 189 whose initial DMARD was MTX (66.1%) continued to take MTX as a single DMARD, 43 (22.8%) continued MTX in combination with another DMARD, and 21 (11.1%) discontinued MTX. Only 3 of 17 patients who had begun HCQ or SSZ as a single DMARD continued to take this single DMARD; 7 had another DMARD added, and 7 discontinued this DMARD. Among other initial therapies, 4 of 6 who began LEF continued this single drug, while the 2 of 3 patients who were initially treated with combination therapy continued the same therapy.

**Treatment with prednisone.** Among the 232 patients, 201 (87.0%) had taken prednisone for 2 weeks or more at some time during their treatment for RA. At the study visit, 139 (59.9%) patients were taking prednisone. The median dose of prednisone was 5 mg. Of those 139 who took prednisone at the study visit, 23 (16.4%) were taking less than 5 mg a day, 71 (51.1%) were taking 5 mg a day, 9 (6.5%) were taking 6–9 mg a day, 23 (16.4%) were taking 10 mg a day, and 13 (9.3%) were taking more than 10 mg a day.

**Treatment with NSAID.** Among the 232 patients, 225 (97.0%) had taken NSAID for 2 weeks or more at some time during their treatment for RA. At the study visit, 135 (58.2%) patients were taking NSAID regularly. The most commonly used NSAID at study visit were celecoxib in 38

Table 2. Percentage of patients taking DMARD in a cohort of 232 patients with recent onset RA.

DMARD	No. (%) of Patients Taking as the 1 <sup>st</sup> DMARD	No. (%) of Patients Taking DMARD at Study Entry	No. (%) of Patients Who Had Ever Taken This Drug Only or in Combinations
MTX only	189 (81.5)	130 (56.0)	207 (89.2)
HCQ only	15 (6.5)	4 (1.7)	37 (15.9)
SSZ only	2 (0.9)	1 (0.4)	9 (3.9)
LEF only	6 (2.6)	14 (6.0)	51 (22.0)
ETAN only	0	2 (0.9)	22 (9.5)
INFLIX only	0	1 (0.4)	10 (4.3)
MTX + HCQ and/or SSZ	2 (0.9)	16 (6.9)	
MTX + LEF	0	20 (8.6)	
MTX + ETAN	1 (0.4)	8 (3.4)	
MTX+ ETAN + HCQ	0	3 (1.3)	
MTX+ INFLIX	0	8 (3.4)	
LEF + ETAN	0	3 (1.3)	
Other DMARD	0	1 (0.4)	
No DMARD	17 (7.3)	21 (9.1)	

DMARD: disease modifying antirheumatic drug; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; ETAN: etanercept; INFLIX: infliximab.

(28.2%) patients, diclofenac in 21 (15.6%), rofecoxib in 19 (14.1%), and naproxen in 15 (11.1%) patients. At any time, 111 (47.8%) of the patients had taken celecoxib, 79 (34.1%) had taken rofecoxib, and 6 (2.6%) had taken meloxicam for 2 weeks or more.

*Analysis of clinical status measures.* The 59 patients who took LEF, ETAN, or INFLIX were significantly younger, had longer duration of disease, were more likely to be positive for rheumatoid factor, have higher psychological distress scores, more symptoms on a symptom checklist, and higher patient global status scores than the 173 patients who did not take these agents ( $p < 0.05$ ). Multidimensional Health Assessment Questionnaire scores were also somewhat higher, although not statistically significantly ( $p = 0.056$ ), and swollen and tender joint counts were slightly higher in patients who took LEF, ETAN, or INFLIX. No differences in the 2 groups were seen according to pain scores, fatigue scores, morning stiffness, or physician global scores.

## DISCUSSION

This cross-sectional study extends the observations of Paulus and colleagues<sup>7</sup> that 53–57% of patients with early RA from 1993 to 1996 took MTX. In the series reported here, 82.8% of 232 patients in 1998–2001 took MTX as the initial DMARD (including 3 in combination DMARD regimens), and 207 (89.2%) took MTX at some time. At the study visit at a median of one year after initiation of DMARD therapy, 185 patients (79.7%) were taking MTX, including 130 (56.0%) as a single DMARD and 55 (23.7%) in combination with one or more other DMARD.

The use of DMARD in this study differs markedly from

studies a decade ago in the USA and recent reports from European centers. In 1990, in 7 US rheumatology private practices only 30% of patients took any DMARD and 3.9% took MTX within the first 2 years of RA<sup>12</sup>. In a cohort of 70 Finnish patients with early RA in 1995–1996, SSZ was the initial therapy for almost all of 70 patients<sup>13</sup>. In 384 patients with early arthritis in the Norfolk Arthritis Register (NOAR) from the United Kingdom<sup>14</sup>, SSZ was taken by 60.7% of 183 patients who took DMARD, while only 6 of the 384 patients took MTX as the first DMARD. In a series of 383 patients from Greece with RA for less than one year between 1987 and 1995, MTX was the first DMARD taken by 21.4% of the patients who took DMARD<sup>15</sup>.

It remains unknown whether it is appropriate that 56% of patients in this cohort continue to take MTX without LEF, ETAN, or INFLIX. A longterm clinical trial to compare MTX monotherapy to combination DMARD therapy would appear to be an optimal strategy that is ethically reasonable<sup>16</sup>, but support for such a longterm clinical trial or clinical protocol<sup>17</sup> is not available. Therefore, further observational studies would appear necessary to determine the potential longterm benefits of the new DMARD.

Limitations of our study include a small number of patients, and the recruitment of all patients from only one treatment locale. It would appear to be a reasonable intellectual and ethical responsibility of other rheumatologists to conduct similar analyses of consecutive patients with RA under their clinical care, with plans to monitor longterm outcomes.

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