Disease Modifying Antirheumatic Drugs in Early Rheumatoid Arthritis: A Longterm Observational Study

NIKOLAOS G. PAPADOPOULOS, YANNIS ALAMANOS, IOANNIS A. PAPADOPOULOS, NIKI TSIFETAKI, PARASKEVI V. VOULGARI, and ALEXANDROS A. DROSOS

ABSTRACT. ***Objective.*** To investigate the effectiveness, toxicity, and drug survival in an observational longterm study of patients with early rheumatoid arthritis (RA).

Methods. Four hundred twenty-eight patients with early RA were investigated between January 1987 and December 1995. All patients had a disease duration of less than one year and had not been previously treated with any disease modifying antirheumatic drug (DMARD). The following drugs were introduced at the doses specified: hydroxychloroquine (HCQ) (200–400 mg/day), D-penicillamine (D-Pen) (500 mg/day), sulfasalazine (SSZ) (2–3 g/day), auranofin (6 mg/day), intramuscular gold (IM gold, 50 mg/week), methotrexate (MTX) (0.15 mg/kg/week, per os), cyclosporin A (CSA) (3 mg/kg/day), azathioprine (AZA) (2–3 mg/kg/day), cyclophosphamide (CYC) (1–2 mg/kg/day).

Results. Three hundred eighty-three patients were treated with one DMARD for at least 6 months. Sixty-five percent of patients were seropositive. The disease duration was 9.2 (3.1) months and the followup period of 12.7 (4.8) years, ranging from 7 months to 13 years. The drugs of first choice were: D-Pen (32%), HCQ (30%), MTX (21%), CSA (8%), and IM gold (7%). After the 2nd, 3rd, and 4th prescriptions, MTX was the most popular drug (27%), while D-Pen and HCQ were prescribed less frequently. The longest drug survival was seen in MTX treated patients, followed by CSA, without significant differences between them. D-Pen, HCQ, and IM gold had the largest dropout rate. The main causes for drug discontinuation were drug inefficacy (HCQ), followed by adverse drug reactions (D-Pen).

Conclusion. It appears that MTX has the longest survival time, with CSA following in second place. The main reasons for discontinuation of treatment were drug inefficacy, followed by adverse drug reactions. (J Rheumatol 2002;29:261–6)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS DRUG SURVIVAL TOXICITY
METHOTREXATE CYCLOSPORIN A HYDROXYCHLOROQUINE

Rheumatoid arthritis (RA) is a chronic and destructive disease that demands longstanding therapy. Pharmacotherapy is the cornerstone of treatment and includes 2 kinds of drugs: The first comprises nonsteroidal antiinflammatory drugs (NSAID), which are given for their immediate analgesic and antiinflammatory effect, but which in general do not influence the disease process itself. The second comprises so-called disease modifying antirheumatic drugs (DMARD), which influence the disease process and also slow down joint and bone destruction[1-4]. In addition, small doses of steroids may also modify the RA disease process[5]. Until 1980 the number of DMARD available was limited and included intramuscular (IM) gold, hydroxychloroquine (HCQ), D-penicillamine (D-Pen), and azathioprine (AZA). After 1980, the rediscovery of sulfasalazine (SSZ) and the use of methotrexate (MTX) and cyclosporin A (CSA) resulted in a significant expansion of the therapeutic armamentarium for RA[6-9]. All these drugs are believed to have a positive influence on the outcome of RA. However, they differ with respect to their disease modifying properties and their toxicity profile[10,11]. Thus, rheumatologists and physicians must know (1) which drugs are most effective and for how long, (2) which are the most toxic, and (3) which of them have the most frequent and hazardous side effects.

We investigated the drug effectiveness, survival, and reasons for drug discontinuation during the disease course in a Greek observational longterm study of patients with early RA. We showed that MTX remains the drug with the best rate of continuation in therapy, followed by CSA. All the other DMARD had a poor survival time. Our results differ

From the Division of Rheumatology, Department of Internal Medicine, and the Department of Hygiene and Epidemiology, Medical School, University of Ioannina, Ioannina, Greece.

N.G. Papadopoulos, MD, Fellow in Rheumatology; Y. Alamanos, MD, Assistant Professor of Hygiene and Epidemiology; I.A. Papadopoulos, MD, Rheumatologist; N. Tsifetaki, MD, Rheumatologist; P.V. Voulgari, MD, Rheumatologist; A.A. Drosos, MD, FACR, Professor of Medicine/Rheumatology.

Address reprint requests to Dr. A.A. Drosos, Department of Internal Medicine, University of Ioannina, 451 10 Ioannina, Greece.

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from others and this is probably due to the milder clinical profile of our patients and to the early immunointervention.

MATERIALS AND METHODS

Four hundred twenty-eight patients with early RA were diagnosed between January 1987 and December 1995, giving a RA prevalence of 0.5% in northwest Greece. The patients were recorded as inpatients and/or outpatients who were diagnosed or referred to our university hospital from the general hospital and from private rheumatologists, physicians, and orthopedists of the district of Ioannina[12]. The patients were followed up until December 1999, when the data were analyzed. Patients fulfilled the revised 1987 American College of Rheumatology (ACR) criteria for RA[13], had a disease duration less than a year, and had not previously been treated with any DMARD. Patients were fully informed about the disease process and the treatment regimen, and were followed according to the same protocol, using various DMARD, a few weeks after the diagnosis.

The choice of drug treatment was based on: (1) clinical and laboratory disease activity, (2) drug efficacy and toxicity, (3) patient's age, sex and fertility, (4) presence of other underlying conditions (diabetes mellitus, hypertension, blood dyscrasias, viral hepatitis), alcohol abuse, or other chronic diseases such as heart, lung and kidney failure, and (5) patient's opinion. The following drug regimens were introduced: HCQ (200 mg/day), D-Pen (initial dose 125 mg, increased by 125 mg every 2 weeks to a maximum dose of 500 mg/day), SSZ (enteric coated, initial dose 500 mg, increased by 500 mg every week to a maximal dose of 3000 mg), auronofin (AF) (6 mg/day), IM gold (started with a test dose of 10 mg, followed by 50 mg weekly during 24 weeks, thereafter 50 mg every 2 weeks, etc), MTX (0.15 mg/kg/week, per os), CSA (3 mg/kg/day per os), AZA (2-3 mg/kg/day), and cyclophosphamide (CYC) (1–2 mg/kg/day per os). In addition all patients received NSAID or small doses of steroids (prednisone 7.5 mg/day per os).

Treatment was never commenced with AZA or CYC, as these drugs are regarded as "3rd line" treatment in the classical pyramid[14]. During the observational period, combined DMARD treatment was not allowed. After commencing treatment, each patient was followed up every month for the first 6 months and every 2–3 months thereafter. Data concerning medication use at 1st, 2nd, 3rd prescription, etc. (start date, stop date, reason for changes: inefficacy, side effects) were all recorded. In addition, the clinical and laboratory variables according to the ACR criteria were recorded[15,16].

Definitions. Failure of drug treatment was defined as patients who stopped receiving the drug for more than one month because of lack of efficacy. Adverse drug reactions were defined as patients who had reactions that required them to stop receiving the drug because of life threatening conditions, or because of intolerability. Discontinuation was decided when patients presented failure of drug treatment or experienced adverse drug reactions. Lack of efficacy was defined when patients did not fulfill the American Rheumatism Association criteria for remission of RA[15].

Statistical analysis. Standard methods of survival analysis (Kaplan-Meier) were used, in which treatment termination due to side effects and/or lack of efficacy was taken as endpoint. Log rank tests were used to test survival differences among drugs. Each therapy course was considered to be independent from others. A Cox regression model was used to compare discontinuation rates among various DMARD adjusting for age, sex, rank order, presence of rheumatoid factor, and reason of drug discontinuation (inefficacy, side effects). In addition, Student's t test and chi-square test with Yates' correction were applied when indicated.

RESULTS

During the observational period (1987–99), 428 patients were investigated. Of these, 15 refused treatment. Thirty patients were withdrawn from the study before completing 6 months of therapy, 14 because of drug inefficacy, 2 due to loss to followup, and 14 because of adverse drug reactions. More specifically, 3 patients presented with hypersensitivity reactions to SSZ and 4 to IM gold injections. In addition, 3 patients complained of severe gastrointestinal reactions a few days after receiving MTX, 2 had severe diarrhea after receiving AF, one patient presented with leukopenia after treatment with AZA, and one presented with signs of myasthenia gravis 2 months after receiving D-Pen. Thus, 383 patients completed at least 6 months of treatment with DMARD. There were 273 women and 110 men with a mean age of 53.7 (14.6) years and disease duration 9.2 (3.1) months. Sixty-five percent were seropositive and the followup period was 12.7 (4.8) years, ranging from 7 months to 13 years.

Because of the small number of prescriptions of AF, SSZ, AZA and CYC, survival analysis was applied only for HCQ, D-Pen, MTX, CSA, and IM gold. During the observational period a DMARD was prescribed 800 times in 383 patients. The numbers of patients and the rank order of prescriptions of the various DMARD are shown in Table 1.

The drugs of first choice were D-Pen (32%) and HCQ (30%) followed by MTX (21%), CSA (8%), and IM gold (7%). MTX was the most popular DMARD at the 2nd prescription, while D-Pen and HCQ were prescribed less frequently (Table 1). After the 3rd, 4th, and 5th prescriptions the most commonly prescribed DMARD were MTX (27%), HCQ (20%), D-Pen (19%), CSA (8%), and IM gold (7%) (Table 1). The low use of SSZ and high use of D-Pen in our population is related to the type of practice and training in rheumatology in our clinic. Rheumatologists were more familiar with D-Pen for a relatively long period of time[17].

The longest drug survival, independent of the reason for failure (inefficacy and/or adverse reactions), was seen in MTX treated patients, followed by CSA. There was no statistically significant difference between these 2 drugs. D-Pen, HCQ, and IM gold had the largest dropouts. Survival curves of these drugs presented significant differences compared with survival curves of MTX and CSA ($p < 0.05$) (Figure 1). The probability to continue with MTX after 5 years was 55%. This probability was 44% for CSA, 25% for IM gold, 19% for HCQ, and 17% for D-Pen. The main causes for drug discontinuation were drug inefficacy (HCQ) followed by adverse drug reactions (D-Pen and IM gold) (Table 2). MTX was found to be one of the safer DMARD

Table 1. Drug prescription frequency.

Drug	Prescriptions (%) 1st	2nd	3rd	Total
Methotrexate	82 (21)	75 (39)	28 (28)	212 (27)
Hydroxychloroquine	115 (30)	18 (9)	11 (11)	157 (20)
D-penicillamine	122 (32)	23 (12)	4 (4)	154 (19)
Cyclosporin A	33 (8)	12 (6)	2 (2)	61 (8)
IM gold	21 (5)	13 (7)	11 (11)	53 (7)
Others	10 (3)	52 (27)	45 (45)	163 (21)
Total	383	193	101	800

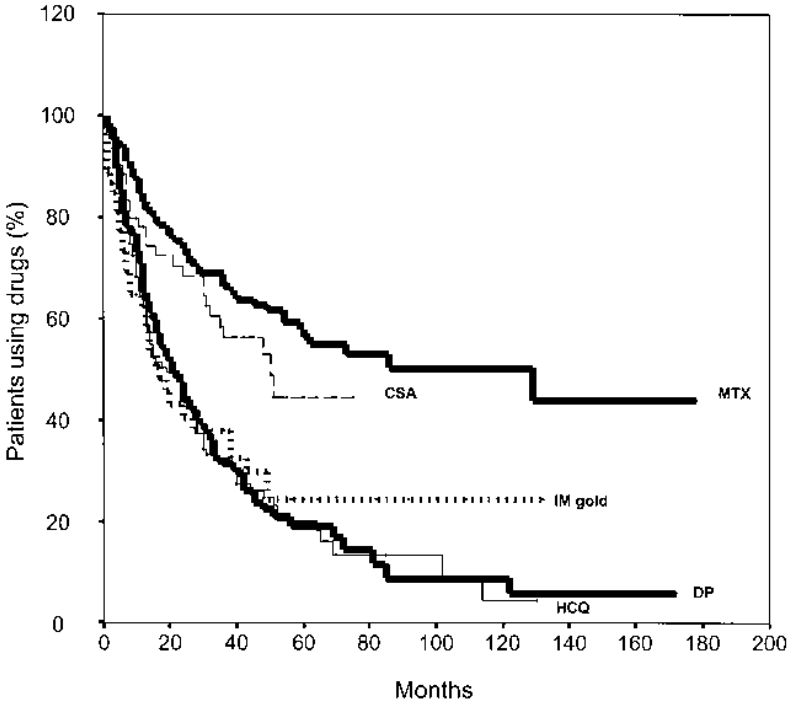

Figure 1. Drug survival time overall, n = 637 (included: all therapy courses; censored: therapy courses that did not reach an endpoint).

with the least amount of adverse drug reactions. Side effects often developed during the first 6 months and consisted mainly of nausea and vomiting. Another common side effect was an increase in the liver enzymes, but this was a rare reason for treatment termination (Table 2). Therefore, inefficacy was the main reason for MTX discontinuation. CSA was second to MTX in our study, with the least amount of side effects, the most common being uncontrolled hypertension, increased serum creatinine, gingival hyperplasia (one patient), and hypertrichosis (one patient) (Table 2, see other side effects). The above side effects were very rare (6.5%). Multivariate analysis showed that the risk for discontinuation was significantly higher for D-Pen, IM gold, and HCQ, but not for CSA, compared to MTX (Table 3).

IM gold was 3rd in our survival study. Less than 50% of the patients were still using the drug after 2 years of treatment. Lack of efficacy and toxicity were the main reasons for drug discontinuation (22.6% each). Rashes were the most prominent side effect.

HCQ is one of the safer DMARD but also the most ineffective. Fifty percent of patients discontinued treatment during the first 2 years due to inefficacy. Concerning the side effects, ocular involvement was the most common reason for discontinuation. No patient experienced symptoms of eye involvement, i.e., scotomas, diplopia, or visual loss. However, during ophthalmologic monitoring 9 patients presented pigmentary changes expressed mainly as premaculopathy, which is considered a reversible condition[18].

D-Pen had a low survival time mainly due to adverse reactions (24.6%). Cutaneous and renal involvement were the main reasons for D-Pen discontinuation.

Table 2. Discontinuation of therapy due to side effects.

Side Effects	Methotrexate, n = 212	Cyclosporin A, n = 61	D-Penicillamine, n = 154	IM Gold, n = 53
Cutaneous	—	—	17 (11)	10 (18.9)
Hematologic	4 (1.9)	—	—	—
Renal	—	1 (1.6)	10 (6.5)	1 (1.9)
Hypertension	—	1 (1.6)	—	—
Liver	4 (1.9)	—	—	—
Gastrointestinal	12 (5.7)	—	4 (2.6)	1 (1.9)
Ocular	1 (0.5)	—	—	—
Pulmonary	1 (0.5)	—	—	—
Others	—	2 (3.3)	7 (4.5)	—
Total	22 (10.5)	4 (6.5)	38 (24.6)	12 (22.6)

Values in parentheses are percentages.

Table 3. Cox regression hazard ratios, with MTX as reference category, adjusted for sex, age, rank order, rheumatoid factor, and reason of termination.

DMARD	Hazard Ratio	95% CI	p
Cyclosporine	1.42	0.91–2.21	0.12
D-Penicillamine	1.72	1.23–2.41	0.001
IM gold	2.37	1.57–3.57	0.001
Hydroxychloroquine	2.11	1.54–2.89	0.001

DISCUSSION

We investigated 383 patients with early RA who were diagnosed during the period 1987–95 and followed until the end of 1999. We showed that MTX remains the DMARD with the best rate of continuation of therapy. We observed that 50% of our patients continue having a beneficial effect after 120 months of therapy. However, in a Dutch inception cohort study, the median survival time of MTX was 23 months[19], while Wolfe, *et al* reported a median survival time of about 53 months[20]. A similar, median drug survival time was also reported in a longterm observational study from Spain[21]. Differences between our results and those mentioned are probably due to: (1) disease activity and severity, (2) disease duration, (3) previous use of DMARD, (4) the rank order of drug prescription, (5) the use of steroids in a small number of patients in our study, and (6) possibly, variation in rheumatologic practice.

In our study multivariate analysis showed that MTX and CSA presented significantly lower risk of discontinuation after controlling for several potential cofounders. Further, we treated patients with early RA before bone and cartilage damage developed. No patient had previously been treated with other DMARD. In addition, there were no differences between the various DMARD regarding their rank order of prescription. Thus, drugs with high rank order like HCQ and D-Pen were discontinued earlier than those with low rank order, such as CSA. Finally, another explanation for the better survival time of MTX in our patients is that Greek patients with RA have a milder disease, and may respond better to early intervention[22,23].

Comparing our results with others, we demonstrated that MTX has high effectiveness, low toxicity, and a very good survival time[24,25]. However, there is a difference in the toxicity profile of MTX between our study and that of De La Mata, *et al*[21], who state that 37% of their patients discontinued treatment due to side effects, while our percentage was significantly lower.

Another important finding in our study is that CSA came second in survival time after MTX. However, the number of patients, the time of use, and our experience with this drug are clearly lower than other DMARD, since CSA was introduced in clinical practice at the beginning of the 1990s. During the last 10 years this drug has been found to be very useful not only in suppressing disease activity, but also in decreasing the rate of radiological progression in RA[26]. Recent studies have shown that CSA in early RA is effective, well tolerated, and safe in longterm use[27,28]. More recently, Ferraccioli, *et al* also reported that CSA is effective and safe and may inhibit the radiological progression of joints, after 60 months of treatment[29].

Our results clearly showed that the rate of continuation of treatment in patients taking CSA is very good. We also demonstrated that the drug survival time of CSA is superior to D-Pen, HCQ, and IM gold injections. In addition, it had a better survival time than MTX concerning adverse drug reactions, with only a few patients developing hypertension or gingival hyperplasia, and only one having renal failure requiring CSA dropout. In previous studies the majority of RA patients treated with CSA showed high percentage of hypertension and renal dysfunction, which have limited its testing in longterm studies. In these studies they treated severe, refractory RA with a long disease duration using high dose CSA (≥ 5 mg/kg/day)[30,31]. It is well known that administration of high dose CSA can result in the loss of renal function. However, renal function in RA depends on many other factors such as the RA disease process causing glomerulonephritis, interstitial nephritis, or amyloidosis and the effect of various DMARD and NSAID on renal function[32,33].

The differences between our results, which are unique (good survival time, no serious side effects), and others' findings are probably due to: (1) the early intervention, before the systemic manifestations and joints and bone deformities develop, (2) the use of small doses of CSA in our study, (3) the suppressive effects of steroids used in some patients, and (4) close followup and monitoring; and finally (5) another explanation for the low rate of renovascular side effects of CSA in our study, i.e., the effects of the Mediterranean diet of our patients[34].

All the other DMARD had a poor survival time. The majority had to be stopped within a few months to a few years because of poor efficacy (HCQ) or intolerable side effects (D-Pen, IM gold). Sixty months after treatment only 10–20% of patients taking HCQ, D-Pen, or IM gold continued with this treatment. These findings are in agreement with previous reports showing that D-Pen and IM gold therapy have many side effects[35].

Variations in the choice of DMARD have been reported in various studies[36-39]. Several determinants have been identified as responsible for this variation. Some physicians are more familiar with a particular drug. Others use less toxic DMARD or use cytotoxic agents (MTX, CSA, AZA) in advanced and refractory disease. But the most important determinant is the type of rheumatology being practiced (private, hospital, etc.) and the training in rheumatology[40]. In our study, patients were diagnosed and followed up in a tertiary university center and had been treated early, by 5 expert rheumatologists well trained in our university hospital. Initially we followed the classic treatment pyramid approach[14]. The fact that HCQ was one of the most popular DMARD reflects the practice using the former treatment pyramid, in which the mildest drug was used first. The same was true for D-Pen, which was one of the preferred drugs in the 1980s. At that time, MTX was considered very toxic and was used carefully only after the failure of all other DMARD. These conceptions were inverted in the 1990s, when several studies proved that MTX was well tolerated and had a low toxicity profile. Thus we observe MTX

becoming the most popular drug prescribed. At this time, CSA entered the armory of DMARD.

In summary, there is a clear difference in the survival time between the various DMARD in patients with early RA. MTX remains the drug with the best rate of continuation of therapy, followed by CSA. Patients treated with a single drug had a poor drug survival time after 6 to 7 years. Combination therapy with MTX and CSA might improve efficacy after this point. Future research is necessary to prove the superiority of combination therapy, according to "a step up or a step down strategy," versus monotherapy.

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