Initial Disease Modifying Antirheumatic Drugs and Prednisolone Prescriptions for Patients with Rheumatoid Arthritis : A 15-year Study

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Abstract

Objective : To compare patterns and time trends of initial disease-modifying antirheumatic drugs (DMARDs) and prednisolone prescriptions for patients with rheumatoid arthritis (RA) by the rheumatologists at King Chulalongkorn Memorial Hospital, Bangkok, Thailand over a 15-year period, as well as their side effects.

Method : Medical records of all patients with RA seen at the Rheumatology Clinic from January 1983 to June 1997 with a duration of follow-up of 6 months or more were reviewed. Information on the disease, initial DMARDs prescriptions and their side effects, prednisolone use, dosage and side effect(s) were focused and compared among three 5-year periods (1983-1987, 1988-1992 and 1993-1997).

Results : 236 patients were included in this study. There were 44, 82 and 110 patients in the first, second and third period, respectively. Methotrexate (MTX) was the most frequently prescribed DMARD in all time periods. Dapsone and intramuscular (IM) gold were prescribed in the first period while antimalarial drugs and sulfasalazine (SSZ) were increasingly used in the second and third periods. Combination treatment of DMARDs was first used in the third period. Side effects from MTX were observed in patients with a longer duration of treatment ($p < 0.05$). Patients prescribed combined DMARDs did not develop more side effects compared with those who had monotherapy. Prednisolone was prescribed in 57.2 per cent of the patients, most being newly prescribed at the clinic. Mean starting dose of prednisolone was 8.9 mg per day. 64 patients took prednisolone together with non-steroidal antiinflammatory drugs (NSAIDs). Gastrointestinal side effects did not increase in these patients.

Conclusion : MTX was the most frequently prescribed DMARDs regardless of the time period. Antimalarial drugs, SSZ and combination of DMARDs (most were MTX + chloroquine) have been prescribed more in the last 5 years, while dapsone, auranofin and IM gold were rarely used as initial DMARDs. Low dose prednisolone was prescribed in more than half of the patients with RA. Side effects from DMARDs and prednisolone found in this study were comparable to previous reports.

Key word : Rheumatoid Arthritis, Disease-Modifying Antirheumatic Drugs, Prednisolone, Pattern of Prescription, Side Effects

OSIRI M, et al
J Med Assoc Thai 2000; 83: 217-224

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Disease modifying antirheumatic drugs (DMARDs) were believed to modify the inflammatory process and progression of rheumatoid arthritis (RA)[1]. They were once administered in patients with long-standing, active disease and well-established erosions in hand X-Rays. After a lot of studies in the pathogenesis of this disease, treatment with DMARDs will benefit patients with active inflammatory arthritis with disease duration not more than 2 years[2,3]. DMARDs are now prescribed much earlier and combination therapy is widely used[1,3]. However, which DMARDs is the most suitable for initial prescription is a subject of debate. It depends on 3 main factors : the disease, the patient and the doctor. Previous studies about variations among rheumatologists in the use of DMARDs were described[4-7].

Glucocorticoid was stratified as an antiinflammatory drug and it might act as a DMARD[8]. Some reports concluded that glucocorticoid could delay bone erosions in patients with RA[8,9]. Although most authorities recommended glucocorticoid use as bridging therapy,[10] a many RA patients cannot stop taking this drug, especially in Thailand where drugs can be bought at any drug store without a doctor's prescription. Glucocorticoid is also an ingredient in folk medicine which is usually self-prescribed by Thai people with rheumatic symptoms.

Since there are no studies about DMARDs prescription patterns in Thailand, we reported the initially used DMARDs by rheumatologists in King Chulalongkorn Memorial Hospital, Bangkok, Thailand over a 15-year period in Thai patients with RA and their side effects. We also studied prednisolone and its side effects on these patients.

MATERIAL AND METHOD

All records of patients with a diagnosis of RA seen at the Rheumatology Outpatient Clinic, King Chulalongkorn Memorial Hospital between January 1983 and June 1997 were reviewed.

Inclusion criteria were :

1) Before 1987, the patients must fulfill the 1958 American Rheumatism Association (ARA) criteria for the diagnosis of RA[11].

After 1987, the patients must fulfill the 1987 revised criteria of American College of Rheumatology (ACR)[12].

2) All patients were prescribed 1 or more DMARDs.

3) All patients must be followed continuously for at least 6 months after taking DMARDs.

Exclusion criteria were :

1) Patients with RA overlapping with other connective tissue diseases.

2) Patients with juvenile rheumatoid arthritis (age at onset of disease less than 16 years).

3) Duration of DMARDs treatment less than 6 months.

Information on initially prescribed DMARDs was recorded, including type(s) of DMARDs, duration of disease at the first visit, duration of disease at the start of DMARDs, their side effect(s) and onset. Type of DMARDs included antimalarial drugs [chloroquine (CQ) and hydroxychloroquine (HCQ)], auranofin, intramuscular (IM) gold, methotrexate (MTX), sulfasalazine (SSZ), d-penicillamine, azathioprine (AZA), dapsone and cyclosporin A (CsA). Data on prednisolone included previous use of glucocorticoid (either from a doctor's prescription or folk medicine), prednisolone dosage, duration of prednisolone use, its side effect(s) and onset. Data on NSAIDs use were also recorded.

The deadline of all patients' last visits was the end of December, 1997. Any patient who was not available at the clinic 1 month or more than the appointment was considered to be lost to follow.

Three periods of 5 years time were selected to compare the patterns of DMARDs and prednisolone prescriptions as well as their side effects. (The first period, 1983-1987; the second period, 1988-1992; and the third period, 1993-1997).

Statistical analysis :

Continuous variables were compared by *t*-test or one way analysis of variance. Qualitative data were compared by chi-square test. p value < 0.05 was considered significant. Data was analyzed using SPSS/PC+ software.

RESULTS

Demographic Data :

The number of patients with RA seen at the Rheumatology Clinic, King Chulalongkorn Memorial Hospital from January 1, 1983 to June 30, 1997 was 236. All of them were followed for 6 months or more. There were 216 female (91.5%) and 20 male (8.5%) patients. All patients were prescribed DMARDs. Demographic data are summarized in Table 1.

Table 1. Demographic data of 236 patients with RA seen from 1983 to 1997.

Total No. of studied patients	236	%
the first period (1983-1987)	44	18.6
the second period (1988-1992)	82	34.7
the third period (1993-1997)	110	46.6
Sex (male : female)	20 : 216	8.5:91.5
Mean (±SD) age at onset of disease (yrs.)	41.8 ± 13.6	
Mean (±SD) dis. duration at first visit (mos.)	49.2 ± 49.8	
Rheumatoid factor positivity	151/217	69.6
Present of bone erosion in first hand X-ray	124/217	57.1
Mean (±SD) duration of follow-up (mos.)	49.5 ± 40.8	
No. of patients who loss to follow	102	43.2

yrs. = years; mos. = months; dis. = disease

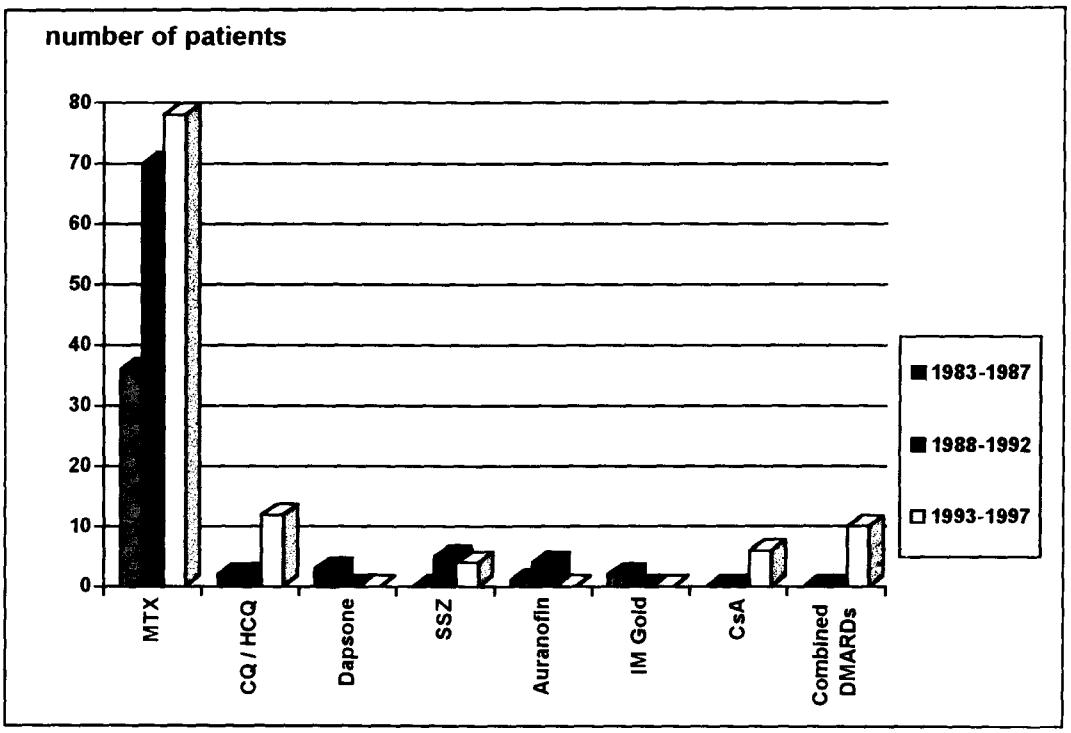

Fig. 1. Patterns of initial DMARDs prescription in King Chulalongkorn Memorial Hospital from 1983 to 1997.

MTX was the most common DMARD prescribed initially in the Rheumatology Clinic, King Chulalongkorn Memorial Hospital in all three time periods. 81.8 per cent, 85.4 per cent and 70.9 per cent of patients with RA were prescribed MTX as initial DMARD in the first, second and third period, respectively ($p<0.05$). The starting dose was 5 mg per week, most patients were prescribed 7.5 mg and the maximum dose was 10 mg per week. The second most prescribed DMARDs was dapsone in the first period, SSZ in the second period and antimalarial drugs (CQ and HCQ) in the third period. Details of DMARDs prescription in each time period are summarized in Fig. 1. Combination

therapy with two or more DMARDs was first started in the third period (1993-1997). From 10 patients who had combined DMARDs, 6 had MTX and CQ, 2 had MTX and SSZ. MTX+HCQ+IM gold and MTX+HCQ+SSZ were prescribed in one each.

There were 56 patients (23.7%) who developed side effects from DMARDs therapy. These side effects can be divided into 2 groups, first, major side effects which required discontinuation of DMARDs and minor ones which were mild and self-limited. Major side effects included leukopenia (white blood cell count $\leq$ 3,000/mm^3 or total neutrophil $\leq$ 1,500/mm^3), thrombocytopenia (platelet count <150,000/mm^3), hepatitis (serum AST or ALT > 3 times the normal limit with or without clinical manifestations), pulmonary injury (proved by chest X-Ray, pulmonary function test and bronchoscopy), renal impairment (serum creatinine > 1.5 mg/dl), proteinuria (24-hour urine protein > 0.5 g/d), retinopathy (irreversible retinal damage diagnosed by trained ophthalmologists), infection and persistent vomit or diarrhea. Minor side effects included a variety of signs and symptoms such as mild nausea, skin rash, skin hyperpigmentation, alopecia and hypertrichosis.

Side effects were found in 44 patients (23.9%) who were prescribed MTX as monotherapy and in 2 patients (20%) as combined therapy. MTX caused 19 major side effects which were hepatitis in 10 (52.6%), leukopenia in 5 (26.3%), thrombocytopenia in 2 (10.5%), lung injury and malignancy in 1 each (5.3%). The three most common minor side effects from MTX included alopecia in 11, nausea in 8 and oral ulcer in 2 patients. Patients who developed side effects from MTX had significant difference in mean duration of MTX use compared to those who had no side effects (37.0 *vs* 15.3 months; p<0.05).

No retinopathies caused by CQ or HCQ were observed in our study. CQ caused nausea/vomit in 1 (8.3%) and skin hyperpigmentation in 2 (16.7%). Proteinuria was reported in 1 of the two patients receiving IM gold while side effects from auranofin were mild, *i.e.* diarrhea in 2 (40%) and glossitis in 1 (20%). Combined MTX and CQ caused skin hyperpigmentation in 1 (16.7%) and combined MTX with SSZ caused nausea/vomit in 1 patient (50%). CsA caused hypertrichosis in 3 patients (50%) without report of major side effects.

Side effects in patients treated with combination therapy did not differ from those treated with a single drug. Mean duration of follow-up, however, was less in the combination therapy group (11.9 *vs* 51.2 months; p<0.0001).

102 patients were lost to follow (43.2%). Mean duration of follow-up in these patients was 31.7 months (range 6-121 months). 85 patients (83.3%) were prescribed MTX, 6 (5.9%) had CQ, 4 (3.9%) had SSZ, 2 each were prescribed auranofin, dapsone and CsA and 1 had IM gold. No explanation of why these patients were lost to follow-up is available.

NSAIDs were prescribed in 164 patients (69.5%). No significant difference was detected in the prescription of NSAIDs at each time period. 64 out of 135 patients (47.4%) took NSAIDs together with prednisolone. No adequate data on side effects from NSAIDs were recorded.

Data on prednisolone prescription are shown in Table 2. Ninety three patients were prescribed prednisolone for the first time at the Rheumatology Clinic while 45 patients had previously used steroid and most of them (41 patients; 91.1%) were continuously prescribed this drug from the clinic.

Side effects from prednisolone were observed in 34 patients (25.2%) including hypertension in 11 (8.1%), Cushingoid appearance in 7 (5.2%), diabetes mellitus in 4 (3.0%), infection in 3 (2.2%) and peptic ulcer and upper gastrointestinal bleeding in 2 (1.5%). From these 2 patients, 1 had concomitant NSAIDs treatment.

Comparing the three periods of 5-year duration, there were no statistic significances in the differences of mean age of disease onset, mean duration of disease at first visit, mean duration of disease when DMARDs (were) started, mean treatment duration before starting DMARDs, number of patients who were lost to follow-up, mean duration of disease when prednisolone was started, mean of first prednisolone dosage, number of patients having prednisolone and NSAIDs.

Statistic significances (p<0.05) were observed in the number of patients receiving prednisolone therapy especially those who were newly prescribed prednisolone in the second period (1988-1992), number of patients prescribed combined DMARDs in the third period (1993-1997) and mean onset of side effects from DMARDs. Details and *p* value are shown in Table 3.

Table 2. Details on prednisolone prescription from 1983-1997.

		%
Total No. of patients receiving prednisolone	135	57.2
The first period (1983-1987)	23	52.3
The second period (1988-1992)	57	69.5
The third period (1993-1997)	55	50.0
No. of patients previously had prednisolone	45	
No. of patients newly prescribed prednisolone	93	
Mean (±SD) prednisolone dosage at start (mg/d)	8.9 ± 3.7*	
Mean (±SD) duration of prednisolone used (mos.)	42.8 ± 36.7	

mos. = months

Table 3. Differences in data on patients with RA being seen in each time period.

	1983-1987	1988-1992	1993-1997	p value
Mean age of disease onset (yrs.)	37.6	41.5	43.4	0.61
Mean dis.duration at 1st visit (mos.)	57.3	49.8	45.8	0.44
Mean dis. duration at DMARDs start (mos.)	60.8	51.1	47.4	0.33
Mean treatment duration before DMARDs (mos.)	3.5	1.3	1.6	0.42
No. of pts. had combined DMARDs	0	0	10	**0.003**
No. of pts. who loss to follow	22	39	41	0.22
Mean dis. duration at prednisolone start (mos.)	57.4	47.5	36.5	0.21
Mean dosage of prednisolone(mg/d)	9.2	9.4	8.2	0.24
No. of pts. had prednisolone	23	57	55	**0.02**
No. of pts. newly had prednisolone	13	46	34	**0.003**
No. of pts. had pred.+NSAIDs	14	25	25	0.36
Mean onset of SE. from DMARDs (mos.)	50.4	21.5	12.3	**0.004**
Mean onset of SE. from prednisolone (mos.)	57.0	19.7	17.2	0.15

dis. = disease; yrs. = years; mos. = months; No. = number; pts. = patients; SE. = side effects

Patients who were prescribed combined DMARDs had significantly longer disease duration compared to those who had monotherapy. Mean duration from the first visit to initiation of DMARDs was slightly shorter in the combination DMARDs treatment group, but no statistic significance was observed. Data are shown in Table 4.

Mean (± SD) duration of follow-up was 88.8 (± 58.8) months in the first period, 61.4 (± 30.7) in the second and 24.9 (± 13.6) months in the third period.

DISCUSSION

Our study is the first to describe the time trends and patterns of initial DMARDs prescription for RA patients by rheumatologists in Thailand. There have been reports of individual variations in the use of DMARDs and no definite agreement has been made on which is the best DMARDs to prescribe initially. Previous studies from Western countries reported MTX and SSZ were mostly prescribed[13-15]. Recent reports described an increasing use of MTX as the main drug in moderate and severe diseases by British and American rheumatologists[16,17].

MTX was the most frequently used DMARDs as initial therapy in our study regardless of the time periods. The reasons for choosing MTX as initial DMARD could be due to its rapid onset of action, convenience to administer and affordable price[18]. MTX was first effectively used in patients with RA in 1951[19]. In the 1980's it was prescribed worldwide and a lot of studies on this drug were conducted[20-23]. Its disadvantages include the requirement of frequent blood tests, severe, although rare, side effects and the development of resistance[18,24]. Nevertheless, MTX was the only DMARDs which RA patients used continuously for more than 5 years[25,26].

Table 4. Differences in data on patients with RA being treated with single and combined DMARDs.

	Type of initial DMARDs		p value
	monotherapy	combination therapy	
Mean disease duration at first visit (mos.)	47.7	83.1	**0.028**
Mean disease duration when started DMARDs (mos.)	49.6	84.5	**0.029**
Mean duration from first visit to DMARDs initiation (mos.)	1.9	1.4	0.72
Mean duration of follow-up (mos.)	51.2	11.9	**<0.0001**

mos. = months

We found side effects from MTX in 23.9 per cent of patients treated with this drug, which was comparable to a previous report[26]. Hepatitis was the most common major side effect found in these patients. The others were leukopenia, thrombocytopenia and lung injury. These findings did not differ from previous studies[27,28].

The second and third most prescribed DMARDs in each time period were different, dapsone and IM gold are hardly prescribed as initial DMARDs nowadays, as well as auranofin which was mostly used in the second period. Antimalarial drugs(CQ and HCQ) and SSZ were increasingly prescribed in the third period. Their side effects, if existed, were mild and reversible in our study. CsA was first prescribed in the 1993-1997 period but most patients were lost to follow-up or had to change to other DMARDs (most had MTX) due to the high expense of the drug and monitoring laboratory tests.

Recent data showed that initial combination therapy of DMARDs was more effective than monotherapy[29-31]. Recommendation of initial " triple therapy" and a "step-down" strategy was proposed[16,31,32]. In our study, initial therapy with combined DMARDs was first used in the third period. All patients in this group had longer duration of disease than those who received single DMARD. Although side effects from combined DMARDs did not differ from those from monotherapy. We recommended a longer period of patients follow-up since most DMARDs usually developed after long term use.

Prednisolone was prescribed in more than half of the patients which was higher than most reports from Western countries[5,6]. Although some of the patients used this drug before attending the clinic, a statistically significant number of patients had newly been prescribed prednisolone. Although prednisolone was recommended as a "bridging" drug,[10] most patients who once took prednisolone could not stop using this drug as the overall mean duration of prednisolone use was 3.5 years. Mean onset of side effects from prednisolone was 2 years after taking this drug. Its side effects varied from Cushingoid features, hypertension, diabetes to osteopenic fracture of the lumbar spine. Decreased dosage or termination of prednisolone can cause severe myalgia/arthralgia as withdrawal symptoms or exacerbate synovitis. Most patients were not willing to stop taking this drug in spite of its hazardous side effects. In our study, gastrointestinal side effects from combination of NSAIDs and prednisolone did not increase compared to prednisolone alone. However, the number of patients with these side effects was too small to make a conclusion.

SUMMARY

Our study concluded that MTX was the most favorite DMARD prescribed initially for patients with RA in Thailand while combination of MTX with other DMARDs are increasingly used. Low dose prednisolone was prescribed significantly in the 1988-1992 period. Most DMARDs caused mild adverse reactions and could be used continously without termination of these drugs. Combination therapy of DMARDs and combined DMARDs with prednisolone did not increase side effects from DMARDs while combined prednisolone with NSAIDs did not demonstrate a higher incidence of side effects from prednisolone alone.

(Received for publication on May 29, 1998)

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การใช้ยาปรับและชะลอกระบวนการของโรครูมาติก กับ เพรดนิโซโลน ในการรักษาผู้ป่วยโรคข้ออักเสบรูมาตอยด์ ในช่วงระยะเวลา 15 ปี

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ได้ศึกษาย้อนหลังจากประวัติผู้ป่วยที่ได้รับการวินิจฉัยแน่นอนว่าเป็นโรคข้ออักเสบรูมาตอยด์ ที่มารับการรักษาที่คลินิกโรคข้อ โรงพยาบาลจุฬาลงกรณ์ ตั้งแต่เดือนมกราคม พ.ศ. 2526 ถึงเดือนมิถุนายน พ.ศ. 2540 โดยผู้ป่วยต้องได้รับการรักษาต่อเนื่องเป็นระยะเวลาอย่างน้อย 6 เดือนขึ้นไป ได้เปรียบเทียบลักษณะทางคลินิกของผู้ป่วย, ชนิดของยากลุ่มปรับและชะลอกระบวนการของโรครูมาติกที่แพทย์สั่ง การใช้ยาเพรดนิโซโลน รวมถึงผลข้างเคียงจากยาทั้งสองในผู้ป่วยโรคข้ออักเสบรูมาตอยด์ โดยแบ่งระยะเวลาที่มารับการรักษาเป็น 3 ช่วง ช่วงละ 5 ปี คือ ช่วงแรกตั้งแต่ มกราคม 2526 ถึง ธันวาคม 2530, ช่วงที่สอง มกราคม 2531 ถึง ธันวาคม 2535 และช่วงที่สาม มกราคม 2536 ถึง มิถุนายน 2540 ผลการศึกษาพบว่าผู้ป่วยโรคข้ออักเสบรูมาตอยด์ทั้งหมดที่ศึกษามี 236 ราย เป็นผู้ป่วยมารับการรักษาในช่วงแรก 44 ราย, ช่วงที่สอง 82 ราย, ช่วงที่สาม 110 ราย กลุ่มยาปรับและชะลอกระบวนการของโรครูมาติก ตัวแรกที่แพทย์นิยมสั่งให้ผู้ป่วย คือ เมโธเทร็กเซท ทั้ง 3 ช่วงเวลา, แดพโซน และสารเกลือทองชนิดฉีดเข้ากล้ามเป็นยาที่นิยมใช้รองลงมาในช่วงแรก แต่ในช่วงที่สองและสามเป็นยากลุ่มรักษามาลาเรีย (คลอโรควินและฮัยดรอกซีคลอโรควิน) กับซัลฟาซาลาซีน ช่วงที่สามเริ่มมีการใช้ยาปรับและชะลอกระบวนการของโครูมาติกร่วมกันตั้งแต่ 2 ชนิดขึ้นไป โดยส่วนใหญ่เป็นเมโธเทร็กเซทร่วมกับคลอโรควิน ผลข้างเคียงจากเมโธเทร็กเซทพบในผู้ป่วยที่ได้รับยามานานอย่างมีนัยสำคัญ เมื่อเทียบกับผู้ป่วยที่ได้รับยาในช่วงเวลาอันสั้น (37 : 15.3 เดือน : $p < 0.05$) ผู้ป่วยที่ได้รับยา 2 ชนิดขึ้นไปไม่พบว่าเกิดผลข้างเคียงมากกว่าผู้ป่วยที่ได้รับยาเพียงอย่างเดียว ร้อยละ 57.2 ของผู้ป่วยในการศึกษานี้ได้รับเพรดนิโซโลน ซึ่งส่วนใหญ่เป็นการสั่งจากแพทย์ ขนาดเริ่มต้นของเพรดนิโซโลนโดยเฉลี่ยเท่ากับ 8.9 มิลลิกรัมต่อวัน มีผู้ป่วย 64 รายได้รับเพรดนิโซโลนพร้อมกับยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ แต่ไม่พบว่าผลข้างเคียงทางระบบทางเดินอาหารเพิ่มขึ้นในผู้ป่วยกลุ่มนี้ โดยสรุปจากการศึกษานี้ เมโธเทร็กเซทเป็นยากลุ่มปรับและชะลอกระบวนการของโรครูมาติกที่แพทย์นิยมใช้มากที่สุดในระยะ 15 ปีที่ผ่านมา ช่วง 5 ปีหลังนี้มีการใช้ยารักษามาลาเรีย, ซัลฟาซาลาซีนและใช้ยา 2 ชนิดขึ้นไปร่วมกันมากขึ้น ในขณะที่ยาบางชนิดแทบไม่ได้ใช้เป็นยาตัวแรกในระยะหลังเลย ได้แก่แดพโซน, สารเกลือทองทั้งแบบกินและฉีดเข้ากล้าม ผู้ป่วยมากกว่าร้อยละ 50 ในการศึกษานี้ได้รับเพรดนิโซโลนขนาดต่ำ (ไม่เกิน 10 มิลลิกรัมต่อวัน) ผลข้างเคียงจากยากลุ่มที่ปรับและชะลอกระบวนการของโครูมาติกและเพรดนิโซโลนที่พบในการศึกษานี้ไม่แตกต่างจากรายงานของต่างประเทศ

คำสำคัญ : โรคข้ออักเสบรูมาตอยด์, ยากลุ่มปรับและชะลอกระบวนการของโรครูมาติก, ยาเพรดนิโซโลน, การใช้ยา, ผลข้างเคียง

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จดหมายเหตุทางแพทย์ ฯ 2000; 83: 217-224

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