

Treatment of Rheumatoid Arthritis with Combination of Disease Modifying Anti-Rheumatic Drugs: A Three-year follow-up study

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Abstract

Rheumatoid arthritis is a multisystem disease causing substantial morbidity. Disease modifying anti-rheumatic drugs induce clinical remission in such patients. The study aims to find out the efficacy of these drugs in producing disease remission in patients of rheumatoid arthritis reporting even at the later stage of illness.

A prospective study was carried out in 61 patients of rheumatoid arthritis. Mean duration of illness was 2.9 years, age ranging from 20-65 years. The patients were followed up for a mean period of 20.29 ± 9.79 months (range 6-36 months). Chloroquine phosphate - 150 mg/day, Methotrexate -7.5 to 15.0 mg/week Sulfasalazine 500-2000 mg/day were given in saw-tooth strategy regime. Clinical response was measured for clinical markers of synovial inflammation. Disease control was achieved in 39 % of the patient at 6 months and in 60% of patients in 24 months, still maintaining at 50% improvement in clinical markers. Chloroquine and Methotrexate was the most commonly used combination (52.5%) for achieving remission,without any major adverse effects.

Disease modifying anti-rheumatic drugs have a role in achieving disease remission even in comparatively later stages of illness. Methotrexate and Chloroquine can be safely given for longer period. Side effects can be monitored by periodic check up.

Key words : Rheumatoid Arthritis, Disease Modifying Anti-Rheumatic Drugs, Saw-tooth strategy, Disease remission, Outcome measures, Adverse effects.

Introduction:

Rheumatoid Arthritis (RA) is a chronic multisystem disease causing substantial morbidity and socio-economic impact. It has been demonstrated that 50% of the patients suffering from RA will have significant impairment of their work activities after 10 years of diagnosis^{1,2}. Since the pathogenesis of RA is obscure, the treatment remains empirical and the mechanisms of action

of disease modifying anti-rheumatic drugs (DMARDS) are not clearly understood^{3,4}. However, there is strong evidence that DMARDS can alter the short-term course of the disease^{5,6}. Treatment of RA with DMARDS is problematic because of various adverse effects and drugs also tend to loose their effectiveness with time.

It is also reported that only 5 - 15% of the patients of RA in whom there was initial response to a DMARD will continue benefit from the drug therapy after 5 years^{4,7,8}. Increasing knowledge about the pathogenesis and long-term morbidity and the importance of early treatment in RA has led to

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a more aggressive approach⁹. And, clinical trials with DMARDS in early RA indicate definite decrease in radiographic progression when inflammation is effectively suppressed, suggesting that the inflammatory process is at least the major factor in joint destruction¹⁰. Individual DMARDS have to be changed repeatedly, in order to find out the most effective and least toxic drug for the individual patient. Since the traditional pyramid approach has become ineffective in suppressing the rheumatoid inflammation and in preventing joint destruction in most RA, new treatment strategies have been proposed¹¹⁻¹³. In our set up, we find the majority of the cases of RA reporting to us in the later stage of illness. Hence, the present study aimed to find out the efficacy of DMARDS in producing disease remission and arresting progression of disease process in RA patients even at the later stage of illness and to find out the toxicity and tolerance of DMARDS used thereof.

Patients and Methods

A prospective study was carried out in sixtyone patients of classic RA fulfilling the revised criteria of American College of Rheumatology 1987¹⁴, attending the Department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences, Imphal. The inclusion criteria were RA patients with duration of illness more than 6 months with history of unsuccessful treatment but without history of any DMARD therapy. Patients with functional classification stage IV of American College of Rheumatology, pregnant woman or woman of childbearing age group without contraceptive cover were excluded from the study group. So also, the patients with history of liver, renal, haematological, cardio-pulmonary or active peptic ulcer disease and with visual difficulties were also excluded.

There were 5 male and 56 female patients. The patient characteristics were given in table 1. The period of study was from January 1997 to

December 1999.

Study design

Assessment for the clinical variables was done at entry (baseline), at 1 to 2 months interval for the first 6 months and thereafter at 3 to 6 months interval. The clinical variables tested were swollen joint count (JS), tender joint count (JT), range of motion (ROM) of the joints, grip strength in Kg/cm² (using grip dynamometer), duration of morning stiffness in minutes and pain using visual analogue scale (VAS) of 100 mm. Baseline investigations for RA factor, C-Reactive protein, haemogram, liver function test (LFT), kidney function test (KFT) and radiological investigations viz. X-ray of the wrist and hand, chest X-ray were also done. Investigations like LFT, KFT, haemogram were done at 3 months interval if no untoward adverse effects were reported. Ophthalmologic examination was carried out every six months for all the patients receiving Chloroquine for its potential ocular toxic effects.

DMARD therapy

DMARDS were instituted on saw-tooth strategy regime¹¹ using Chloroquine phosphate 150 mg/day, Methotrexate 7.5 to 15mg/week, Sulfasalazine 500-2000 mg/day. As has been outlined in the objective of the present study, most of our patients have reported in the later stage of illness. Single DMARD was instituted for mild and moderate disease activity while double or triple drugs combination was instituted for severe disease activity and for those reporting at later stage of illness.

Concurrent therapy

Non-steroidal anti-inflammatory drugs were given on regular basis for the initial period of 10 to 14 days and thereafter as and when needed basis. Intra-articular steroid injection was also given, if required to control acute local inflammation of the joint. But no systemic corticosteroids were

administered during the study period.

Outcome measures

The main end point was the improvement of patients' condition by at least 50 per cent among the clinical variables measured with special consideration to joint counts, pain, and morning stiffness and grip strength. We have considered 50 percent improvement as clinically relevant and the treating physicians could readily recognise the change. We have taken into consideration of the Modified Paulus composite criteria¹⁵ and preliminary improvement criteria of American College of Rheumatology¹⁶ for measuring the treatment response. The criteria were JS decreased by 50 percent, JT decreased by 50 percent, absence of morning stiffness or less than 30 minutes duration. Besides, the evaluations of additional measures like grip strength and pain improvement in patients' and physician's global assessment in VAS was also considered.

Table 1: Showing patient characteristics (n = 61).

Male: Female	5:56
Mean age of the patients	48.97 ± 11.74 years (range 25 - 65)
Mean duration of illness	2.71 ± 1.90 years (range 0.5 - 6.00)
Mean duration of follow-up	20.29 ± 9.79 months (range 6 - 36)
RA factor positivity (%)	26 (42.6%)
Extra-articular manifestation, vasculitis	1

Statistical analysis:

Differences in the mean values of the outcome variables were evaluated by using two-tailed student's t-tests, after putting the data in a computer using dbase. The statistical significance

for all the variables were put at p<0.05.

Results:

All the patients received at least one DMARD during the study period. DMARD therapy with the number of patients receiving them are shown at Table 2. Chloroquine and Methotrexate were the most frequently used combination of DMARDS as received by 32 patients (52.5%). 18 patients i.e. 30% received either Chloroquine or Methotrexate while only 6 patients [10%] needed all the three drugs viz. Chloroquine, Methotrexate, Sulfasalazine for the control of disease remission.

Table 2. Showing number of patients (%) receiving DMARDS as single or in combination.

DMARDS	Number of Patients	% of Patients
CQ	8	(13)
MTX	10	(16)
CQ+MTX	32	(52.5)
CQ+SLZ	4	(6.6)
MTX+SLZ	1	(1.6)
CQ+MTX+SLZ	6	(10)

CQ = Chloroquine, MTX = Methotrexate, SLZ= Sulfasalazine

Table 3 shows the number of patients receiving treatment with each specific DMARD at a specific period of time. Chloroquine was the commonest initial DMARD instituted in 46 patients (75%) while 23 patients (37%) received Methotrexates as the initial single DMARD. For lack of therapeutic response, combination of DMARDS were instituted in the following 3 to 6 months. Mean cumulative time of DMARDS used in combination for achieving disease remission was 9.6 months without any significant adverse effects in 43 patients (70%).

There were 37 patients (60%) who received combination of 2 DMARDS at a single point of time. 18 patients (30%) took only one DMARD for achieving clinical remission. Of the total patients

only 6 patients discontinued DMARD therapy due to adverse effects requiring temporary withdrawal of DMARD. 10 patients needed addition of another DMARD or change to another DMARD for lack of response in 3 to 6 months period, as shown in Table 4. We observed improvement in the clinical markers of the disease viz. JS, JT, ROM of the joints, grip strength, morning stiffness duration and improvement in pain scored by 3 to 6 months of the DMARD therapy. Significant improvement was sustained at the end of 24 months with the continuation of DMARDS. Table 5 shows changes in the mean values in the clinical variables mentioned above.

Table 4 : Showing number of DMARDS prescribed, DMARDS discontinued due to adverse effects or needing addition of another DMARD for lack of efficacy in the study group (n= 61)

Number of DMARDS prescribed	Number of patients(%) receiving DMARDS	Number of patients stopped DMARDS due to adverse effects	Number of patients needing additional DMARD for inefficiency
1	18 (30%)	2 (1MTX+1CQ)	8
2	37 (60%)	2 (1MTX+CQ) (1CQ+SLZ)	2
3	6(10%)	2 (MTX+CQ+SLZ)	0

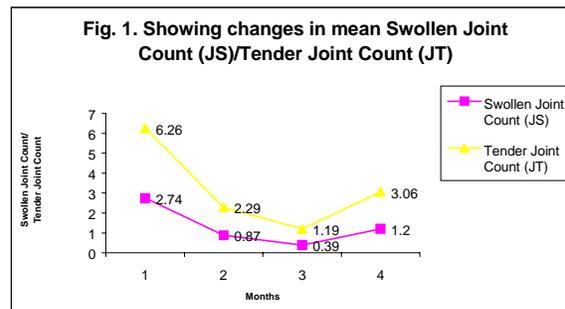
CQ = Chloroquine, MTX= Methotrexate, SLZ= Sulfasalazine,

Table 5: showing change in mean value ± standard deviation in clinical variables at the end of 3,6,24 months from baseline (0 month).

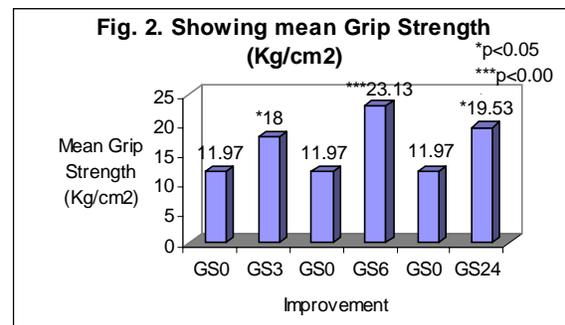
Variables	Months			
	0	3	6	24
No. of Swollen Joint	2.61 ± 1.58	0.87 ± 1.05	0.39 ± 0.88	1.20 ± 1.78
No. of Tender Joint	6.26 ± 2.71	2.29 ± 1.81	1.19 ± 1.55	3.06 ± 2.63
Range of Motion	115.97 ± 60.40	173.06 ± 89.43	203.22 ± 108.90	177.33 ± 70.40
Grip strength (kg/cm2)	11.97 ± 7.39	18.00 ± 9.03	23.13 ± 8.84	19.53 ± 9.37
Morning stiffness (hrs.)	2.35 ± 0.84	0.27 ± 0.46	0.02 ± 0.89	0.56 ± 0.79
Pain (in VAS)	100	49.35 ± 16.57	31.29 ± 26.45	36.33 ± 29.30

Figure 1 shows the changes in the mean

values of JS and JT at 3, 6, 24 months of DMARD therapy. Mean value of the number of JS got significantly reduced from 2.61 ± 1.58 to 0.87 ± 1.05 at 3 months ($p < 0.01$) and to 0.39 ± 0.88 ($p < 0.001$) at 6 months. After 24 months, the improvement in the mean JS was still significant ($p < 0.05$). Mean value of number of JT also significantly reduced at 3 months ($p < 0.001$). Reduction in mean value of JT was still significant at 24 months follow-up ($p < 0.001$).



Improvement in the mean values of ROM of the joints was also significant by the end of 6 months ($p < 0.001$) and the significance was still maintained at the end of 24 months ($p < 0.01$). We also observed significant improvement in the mean values of grip strength at 3 months ($p < 0.05$) and still more significant at the end of 6 months ($p < 0.001$) as shown at figure 2. Moreover, the improvement in the mean scores of morning stiffness and pain remained significant from 3 months to 24 months of DMARDS therapy ($p < 0.001$) as shown in figure 3 and figure 4.



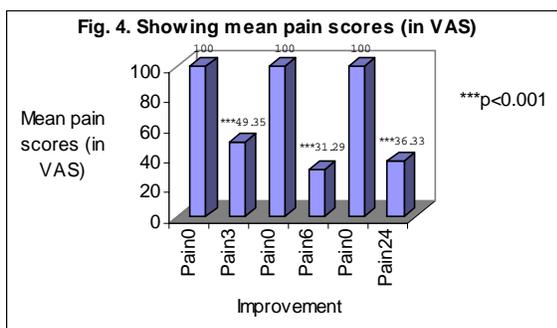
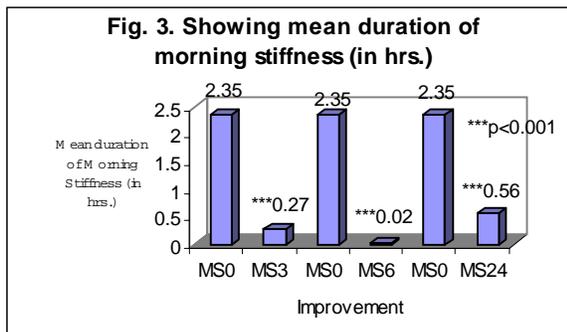


Table 3. Showing number of patients receiving treatment with each specific DMARDS at a specific period of time.

DMARDS	MONTHS					
	0	3	6	12	24	36
HCQ	46	42	44	18	4	
MTX	23	30	40	28	12	12
SLZ	2	3	6	2	1	

CQ =Chloroquine, MTX=Methotrexate, SLZ=Sulfasalazine

In the present series, 31 patients (51%) were followed up for 6 to 12 months while 24 patients (39%) were followed up for 24 to 36 months. The patients have been followed up for a mean duration of 20.29 ± 9.79 months (range 6 to 36 months). Out of the total 61 patients, 24 patients i.e. 39% achieved clinical remission at the end of 6 months follow up. Out of 24 patients followed up for two years 15 patients (60%) maintained clinical remission. 50% improvement in clinical markers

were maintained in these patients. However, remission was temporary if DMARDS was stopped after the remission, as was observed in 4 such patients showing relapse of signs and symptoms within 2 months of stoppage of DMARDS therapy.

Toxicity and adverse reactions:

6 patients needed to stop DMARDS therapy temporarily or switch to another DMARDS due to adverse reactions. 1 patient receiving Chloroquine developed blurring of vision at 3 months and switched to Methotrexate. 1 patient receiving Methotrexate developed anaemia at 6 months, for which 2 units of whole blood transfusion was given. The patient had a history of dependence on non-steroidal anti-inflammatory analgesic drugs before being admitted into the present study. 2 patients receiving Methotrexate and Chloroquine combination developed severe nausea and liver function abnormalities at 6 months. Liver function test alteration was in the form of altered Albumin and globulin ratio but with SGOT and SGPT levels maintained within 2 times the normal value. 2 patients receiving combination of all the three drugs developed nausea, loss of appetite and dizziness at 6 to 10 months. 1 patient receiving Chloroquine and Methotrexate developed vasculitis which was rather an extra-articular manifestation of the disease.

Discussion

The treatment of RA with DMARDS are now a days started early in the course of the disease with the aim to achieve clinical remission as early as possible. However, complete remission of RA is rare, inspite of the currently available DMARDS therapy modalities^{17,18}. Although early treatment seems to be the common denominator in all newer strategies, it is also generally agreed that aggressive therapy should be used in severe RA and even in comparatively later stage of illness¹⁹.

In the present study disease remission was

achieved in 39% of patients at the end of 6 months. Burhoo AM²⁰ reported that at 8 to 10 weeks all the 20 patients had shown complete remission with low dose Methotrexate at 7.5 to 15mg /week with encouraging results till 6 months follow up period. In our series, out of 24 patients followed up for 2 years, 15 patients (60%) showed maintenance of remission of the disease with the continuation of DMARDS. In a 2 year double blind randomised study, O'Dell and colleagues²¹ compared Methotrexate alone (7.5-15 mg/week), Sulfasalazine (1gm/day) with hydroxyChloroquine 400 mg /day combination or all the three drugs. The primary endpoint of their study was also 50% improvement in the composite symptoms of arthritis as comparable to those of our study. Fifty of 102 patients had a 50% improvement at 9 months and maintained at least the same degree of improvement for the two year period without evidence of major side effects. Of these, 24 of 31 patients received all the three drug combination, 14 of 35 patients were treated with Sulfasalazine and hydroxyChloroquine and 12 of 36 patients were treated with Methotrexate alone. In our study, 37 of 61 patients (70%) needed combination of DMARDS, out of which 6 patients received all the three drugs while 32 patients (52.5%) received Methotrexate and Chloroquine combination. 60% of patients in our series maintained 50% clinical improvement at the end of two years as compared to 49% of patients in O'Dell et al series²¹.

Mottonen et al²² carried out a prospective study in 142 patients treated according to saw-tooth strategy using gold sodium thiomalate, Sulfasalazine, Methotrexate, hydroxy Chloroquine, d-penicillamine etc. They observed clinical remission in 20% of patients at end of first year and in 27% of patients after 2 years of DMARDS therapy. The difference in the percentage of patients who achieved clinical remission at 2 years (i.e 27%) in the series of Mottonen et al²², may be because of the severity of the cases (51% of them

were in Steinbrocker functional class II to IV) and injectable gold (sodium aurothiomalate) being the most common initial DMARDS used in 82% of patients. The above findings indicate that it is not too late to institute DMARDS treatment in RA patients, even in whom erosions have appeared already.

Clegg and colleagues²³ reported an interesting study where 121 patients who had responded to a combination of Methotrexate and Hydroxy Chloroquine were randomized to one of three continuation therapy protocols for control of flare of the disease activity viz., (group I - 40 patients) on hydroxychloroquine with pulse Methotrexate, (group II - 41 patients) on Hydroxychloroquine with placebo pulse, (group III- 40 patients) on placebo with pulse Methotrexate. They observed that patients improved on a combination of Methotrexate and hydroxy Chloroquine. And continuation of Methotrexate or Hydroxy Chloroquine delayed the onset of flares. In our study also, after clinical remission was achieved we continued with either Chloroquine or Methotrexate. As such combination therapy of 2 or 3 DMARDS were given with a mean cumulative period of 9.6 months only. Other series also recorded the mean duration of combination therapy for 13.2 months²².

In our series, 6 patients out of 61 patients (10%) needed to stop DMARD therapy because of adverse reaction as comparable to that of O'Dell et al²¹ which has similarity of DMARDS used and moreover the moderate duration of follow-up as well, upto 24 to 36 months duration. The higher percentage (29%) of adverse effects encountered in Mottonen T et al series²² may be because of different drug combinations and probably also for comparatively longer period of follow-up (mean 6.2 years) .

Chloroquine was the most commonly used initial DMARD in 46 patients (64%) while 23

patients (32%) received Methotrexate as initial DMARD in the present study. One important observation we have found in our series was that patients taking Chloroquine decreased to 18 patients at 1 year while patients taking Methotrexate kept on increasing by 6 months (40 patients) and at 1 year (28 patients). It appears that Methotrexate has moderate potency in controlling the disease activity as compared to Chloroquine. Better clinical remission was achieved in patients receiving combination therapy taking Chloroquine and Methotrexate as also observed by other workers^{21,23}.

Conclusions

DMARDS with more aggressive approach like saw-tooth strategy has a role in inducing disease remission even at a comparatively later stage of RA. DMARDS treatment seems to retard the progression of the disease in patients of RA. The present finding showed that DMARDS substitution can be made safely for those becoming ineffective or showing toxic effects. The beneficial effects of continued treatment with DMARDS may be extended for longer periods. Methotrexate and Chloroquine can be safely given for longer periods (upto 3 years in the present series) without any major side effects. However, despite initiation of early aggressive therapy, RA may continue to progress in some patient. In this group with progressive disease, in spite of continued aggressive treatment with DMARDS, treatment with drug combinations should be tried as early as possible. Moreover, the role of newer biological agents and how they will perform as combination therapy in such patients needs to answer critical questions in near future. For this we need to review the combination therapy and to encourage appropriately designed studies to answer these questions.

References

1. Yelin E., Callahan L. The economic cost and social and psychological impact of musculoskeletal conditions. *Arthritis Rheum* 1995; 38:1351-1362.
2. Yelin E, Henke C, Epstein WV. The work dynamics of the person with rheumatoid arthritis. *Arthritis Rheum* 1987; 30:507-512.
3. Cash JM, Klippel JH. Second line drug therapy for rheumatoid arthritis. *N Engl J Med.* 1994; 19:1368-1375.
4. Kushner I. Does aggressive therapy of rheumatoid arthritis affect outcome? *J Rheumatol* 1989; 16:1-4
5. Van der Heijde DMFM, Van Riel PL, Nuver-Zwart IH, Van de Putte LBA. Sulphasalazine versus hydroxychloroquine in rheumatoid arthritis : 3 years follow up (letter). *Lancet* 1990; 335:539.
6. Hannonen P, Mottonen T, Hakola M, Oka M. Sulphasalazine in early rheumatoid arthritis : a 48 week double blind, prospective, placebo-controlled study. *Arthritis Rheum* 1993; 36:1501-1509.
7. Wolfe F, Hawlay DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis : a 14-year prospective evaluation of 1017 consecutive patients. *J. Rheumatol* 1990; 17:994-1002.
8. Situnayake RD, Grindulis KA, McConkey B. Long term treatment of rheumatoid arthritis with Sulphasalazine, gold or Penicillamine : a comparison using life-table methods. *Ann Rheum Dis* 1987; 46:177-183.
9. Emery P, Solomon M. Early rheumatoid arthritis time to aim for remission. *Ann Rheum Dis* 1995; 54 (12) : 944-947.
10. van de Putte LBA. Chronic arthritis : Why the joint ? *Scand J Rheumatol* 1995; 24 (suppl 101) : 7-9.
11. Fries JF. Reevaluating the therapeutic approach to rheumatoid arthritis : the "saw tooth" strategy. *J Rheumatol* 1990; 17:12-15.
12. Wilske KR, Healey LA. Remodelling the pyramid : A concept whose time has come. *J Rheumatol* 1989; 16:565-567.
13. Wilske WS, Clough JD. Therapy for rheumatoid arthritis combinations of disease modifying

- drugs and new paradigms of treatment. *Semin Arthritis Rheum* 1991; 21 (suppl 1): 21-34.
14. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31 (3):315-324.
 15. Paulus HE, Egger MJ, Ward JR, Williams HJ. Analysis of improvement in individual rheumatoid arthritis patients treated with disease modifying anti-rheumatic drugs based on the patients treated with placebo. *Arthritis Rheum* 1990; 33:477-484.
 16. Felson DT, Anderson JJ, Boers M et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38:727-735.
 17. Alarcon GS, Blackburn WE Jr, Calvo A, Castaneda O. Evaluation of the American Rheumatism Association preliminary criteria for remission in rheumatoid arthritis: a prospective study. *J Rheumatol* 1987; 14:93-96.
 18. Pinals RS, Masi AT, Larsen RA. Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; 24:1308-1315.
 19. Pincus T, Callahan LF. Remodelling the pyramid or remodelling the paradigms concerning rheumatoid arthritis - lessons from Hodgkin's disease and coronary artery disease. *J Rheumatol* 1990; 17:1582-1585.
 20. Burhoo Ali Mohmad. Methotrexate as remission inducing agent in rheumatoid arthritis. *Indian J Phys Med Rehabil* 1997-98; 8-9:31-36.
 21. O'Dell JR, Haire CE, Erikson N et al. Treatment of rheumatoid arthritis with Methotrexate alone, sulfasalazine and Hydroxy Chloroquine, or a combination of all three medications. *New Eng J Med* 1996; 334 (20): 1287-1291.
 22. Mottonen T, Paimela L, Ahonen J et al. Outcome in patients with early rheumatoid arthritis treated according to the 'Saw tooth' strategy. *Arthritis Rheum* 1996; 39:996-1005.
 23. Clegg DO, Dietz F, Duffy J et al. Safety and efficacy of Hydroxy Chloroquine as maintenance therapy for rheumatoid arthritis after combination therapy with Methotrexate and Hydroxy Chloroquine. *J Rheumatol* 1997; 24:1896-1902.