

Efficacy & Tolerance of Low Dose Methotrexate in Rheumatoid Arthritis

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Introduction

- COPCORD study observed prevalence of rheumatological disorders in Bangladesh
- Prevalence of RA is 0.397%
- So an estimated 5,16,100 people are affected with RA in Bangladesh

Hypothesis

- Low dose MTX (7.5mg/wk) is an effective & safe DMARD for Bangladeshi RA patient population

Why Methotrexate?

- Low cost
- Easy to administer
- Compliance is better
- Early clinical response
- Retards progression of radiographic erosions
- Gold standard in treatment of RA

Comparison of price of different DMARDs

Drug	Dose	Unit price (Taka)	Monthly cost of drug (Taka)
Methotrexate 2.5mg	7.5 - 15 mg wkly	4	48 (7.5mg/ wk)
Leflunomide	20 mg daily	5	150
Sulphasalazine 500mg	1 g BID	5	600
Azathioprin 50mg	50 mg BID	8	480
Hydroxychloroquine 200mg	400 mg daily	25	1500
Oral gold	3 mg BID	Not readily available in market	
Gold (inj)	50 mg IM wly	Not readily available in market	
Penicillamine 250mg	250 mg daily	11	330

Objectives

- Quantify *efficacy* of MTX in low dose
- Observe *intolerance* to MTX in low dose

Materials & Methods

The place & Time

- Rheumatology Clinic, Shaheed Suhrawardy Hospital, Dhaka
- From October 2001 to April 2003

Patients included

- Suffering from active RA
- Age 16-65 yrs
- Consented to take part

Randomization

- Computer generated randomization chart in blocks of 4
- Envelopes containing drug or placebo arranged in sequence
- Serial number of the envelope corresponded to the order of enrollment
- Allocation took place immediately after confirmation of enrollment

Methods

- Double blind randomized placebo controlled study
- IG received
 - MTX, 7.5 mg/ wk
- CG received
 - Placebo
- Both groups also received
 - Indomethacin 75 mg/ day
 - Omeprazole 20 mg/ pantoprazole 40 mg daily
 - Folic acid 5 mg/ wk
- Each pt was evaluated monthly for six months

Outcome Measures

Efficacy

- TJC (tender joint count)
- SJC (swollen joint count)
- MS (morning stiffness in minutes)
- VAS (visual analogue scale of pain)
- PGA (physicians global assessment)
- HAQ DI (disability index of health assessment questionnaire)
- ESR (erythrocyte sedimentation rate)
- ACR 20 (American College of Rheumatology Response Criteria)

Tolerance

Clinical:

- Nausea
- Vomiting
- Diarrhea
- Cough
- Sore throat
- Lymphadenopathy

Laboratory:

- Total counts of WBC & platelet
- Hemoglobin
- Alanine aminotransferase
- Serum creatinine

Results

- 132 subjects enrolled
- 99 pts visited at least twice
- 7 visits completed by 43 pts – 22 in IG & 21 in CG
- Baseline characteristics of 2 groups were similar
- Disease activity significantly ↓ at 6 mo in both groups
- Reduction of activity more prominent in IG
- Significant number of pts in IG achieved ACR20 criteria

Randomized: 132 pts

IG: 66

CG: 66

Lost to follow-up ≤ 2 visits: 28

Lost to follow-up ≥ 3 visits: 09

Lost to follow-up ≤ 2 visits: 33

Lost to follow-up ≥ 3 visits: 08

Excluded : 04

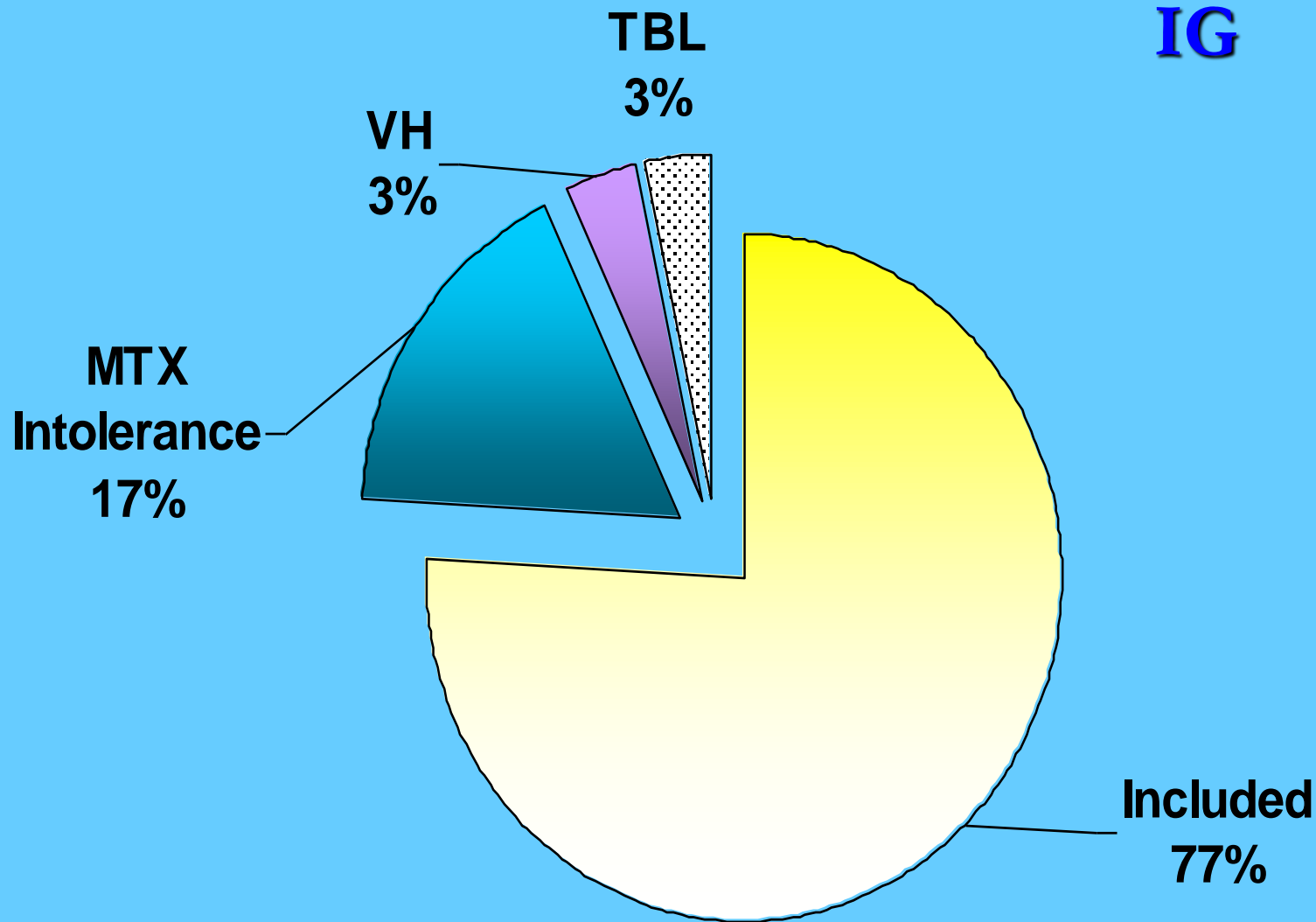
Excluded : 07

**Final analysis:
22**

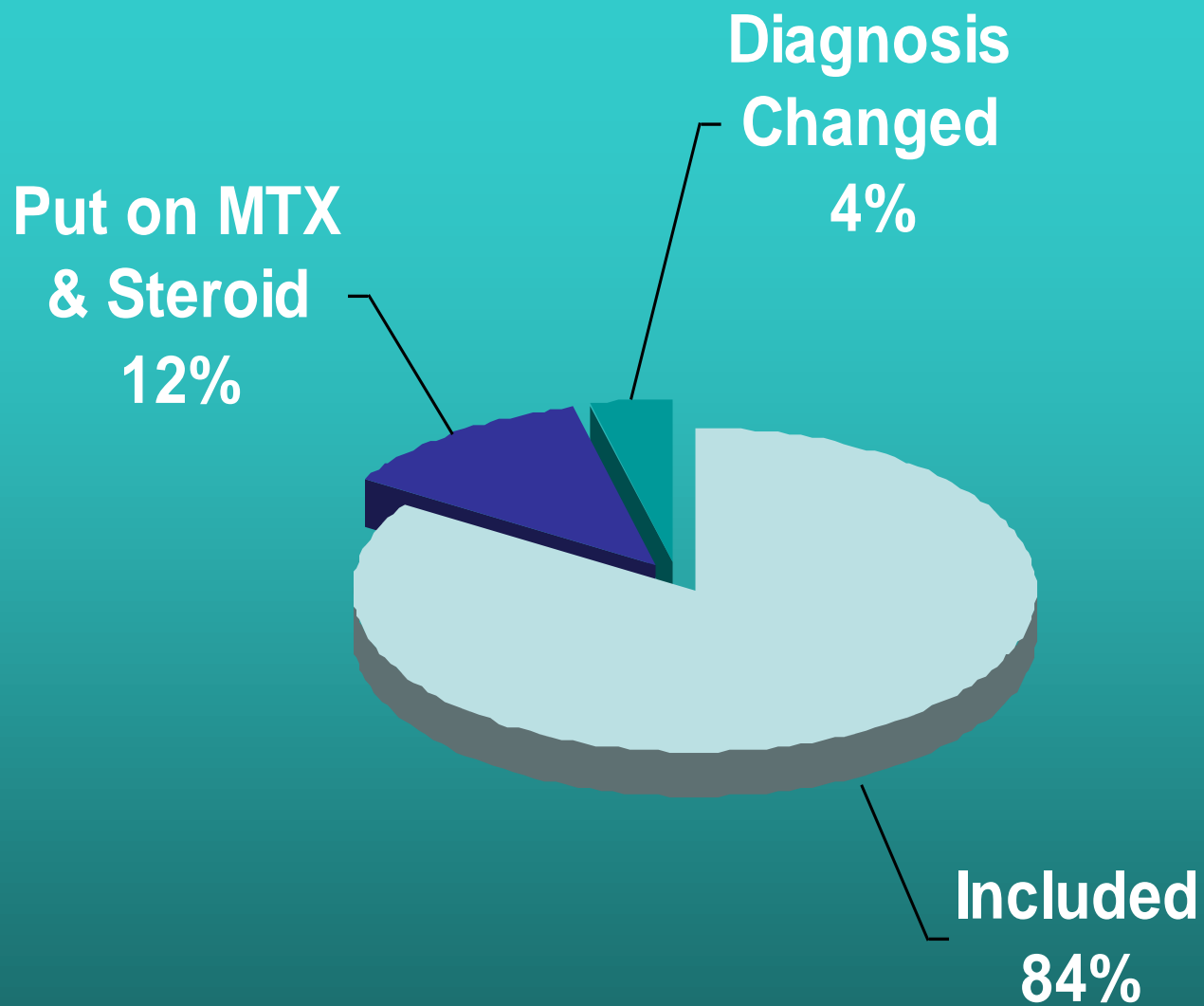
**Final analysis:
21**

Withdrawal & Why

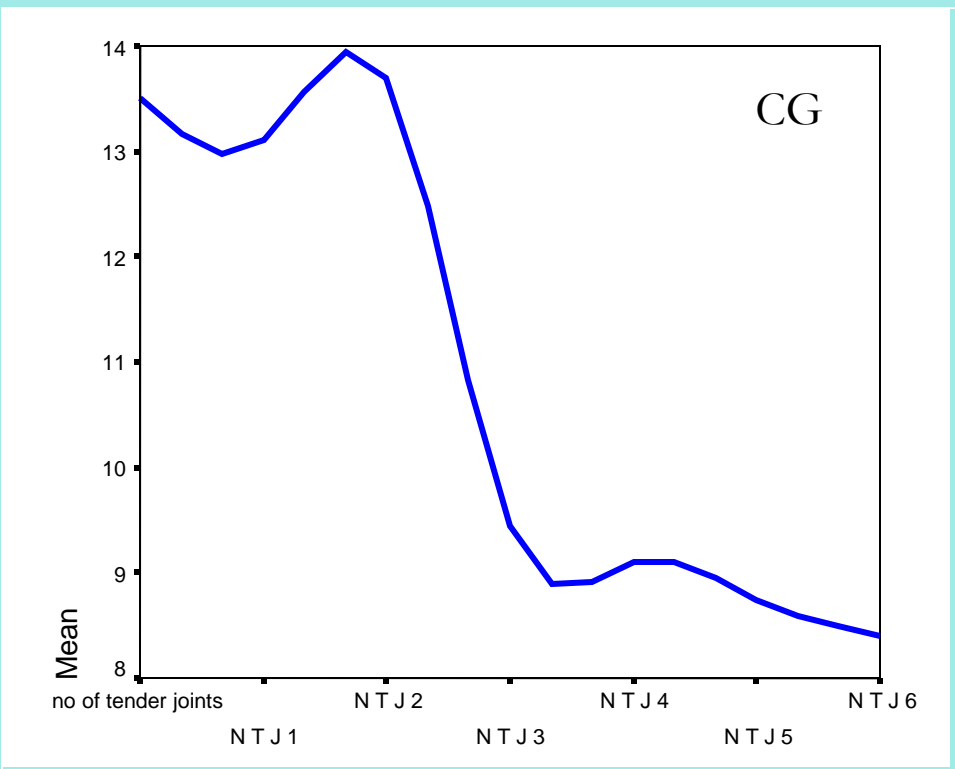
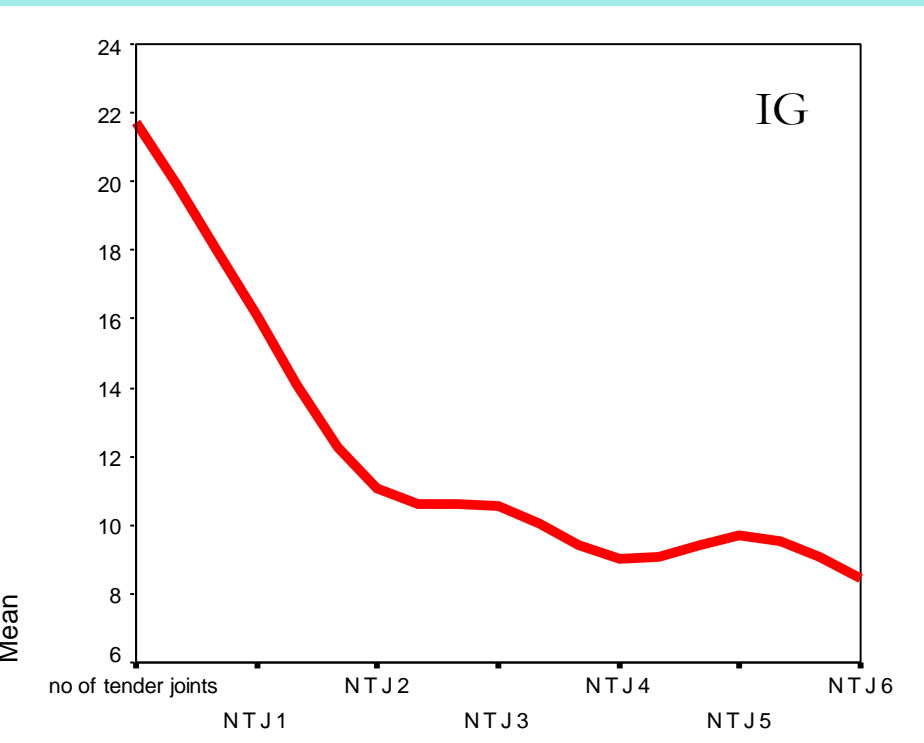
- 7 pts were withdrawn from the IG
 - 5 pts - intolerance to MTX (GI complaints)
 - 1 pt - viral hepatitis
 - 1 pt - TB lymphadenopathy
- 4 pts withdrawn from CG
 - 3 due to increased disease activity & put on steroid & MTX
 - 1 due to change of diagnosis



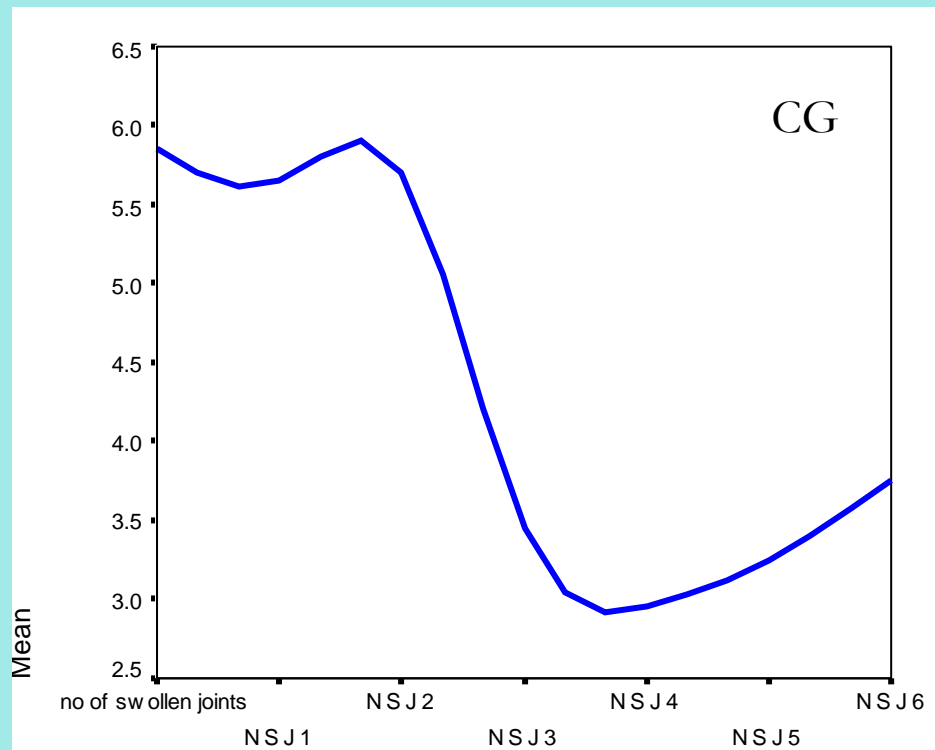
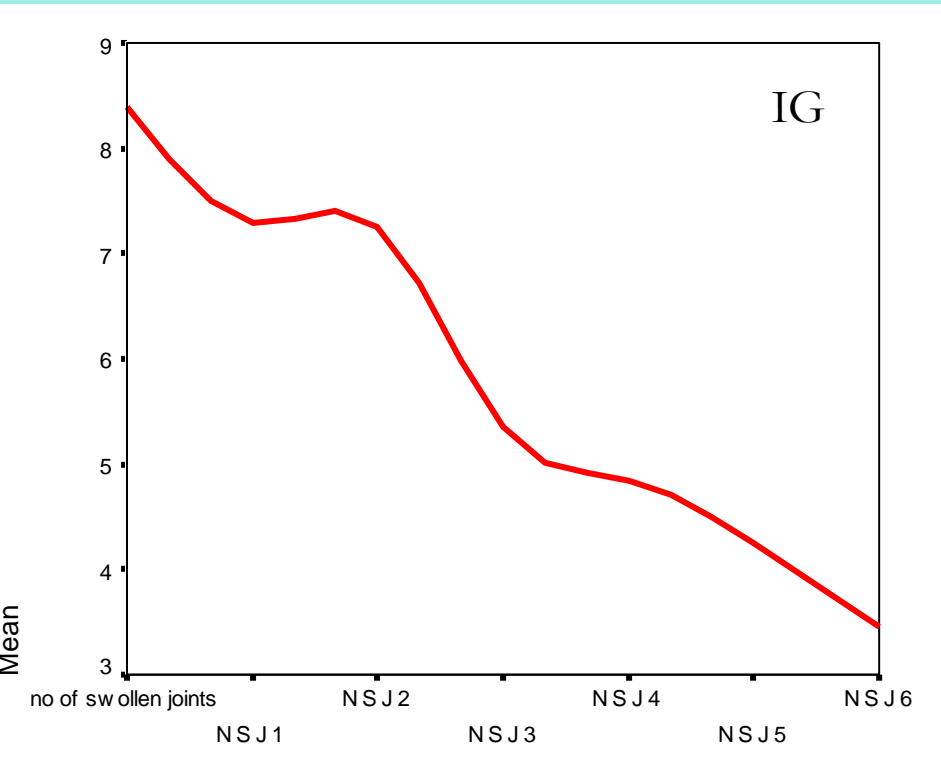
CG



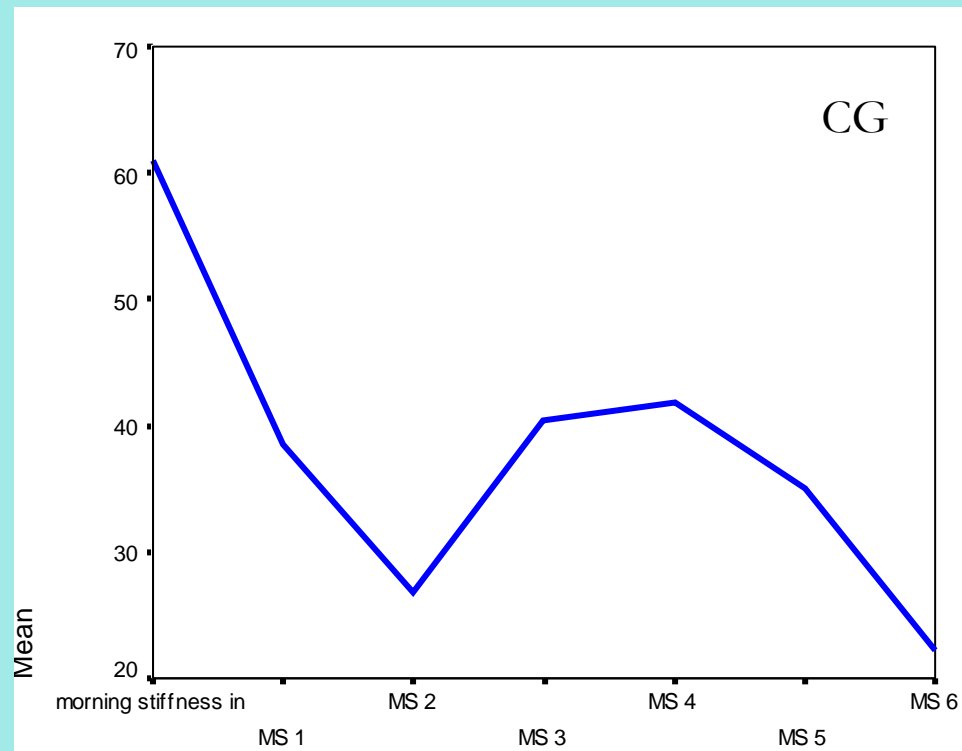
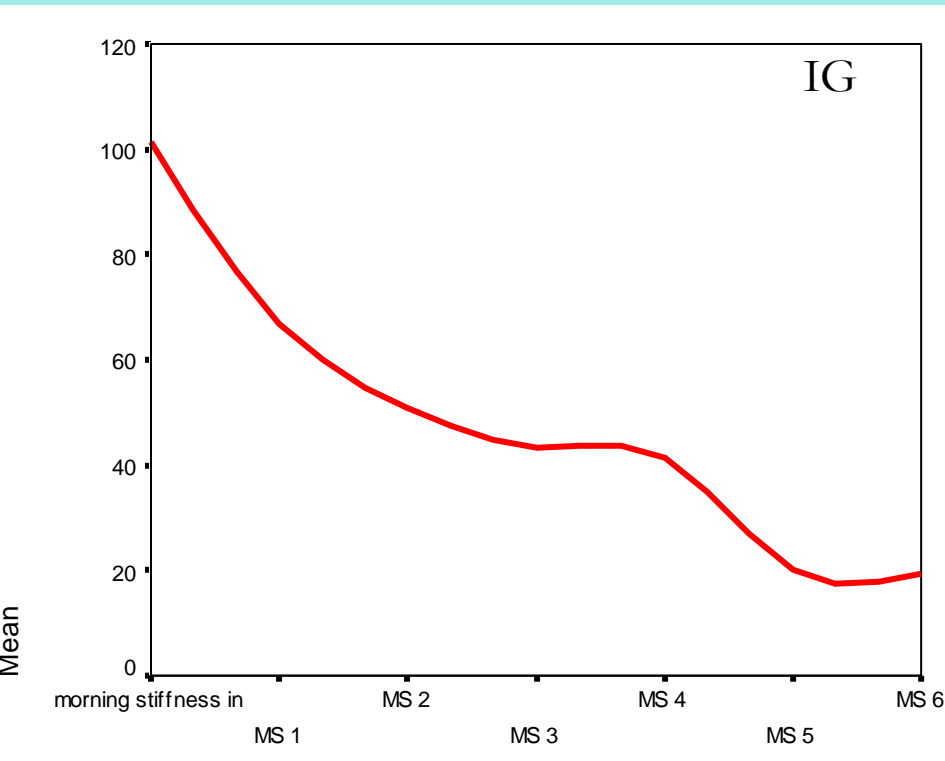
Mean TJC in 7 visits



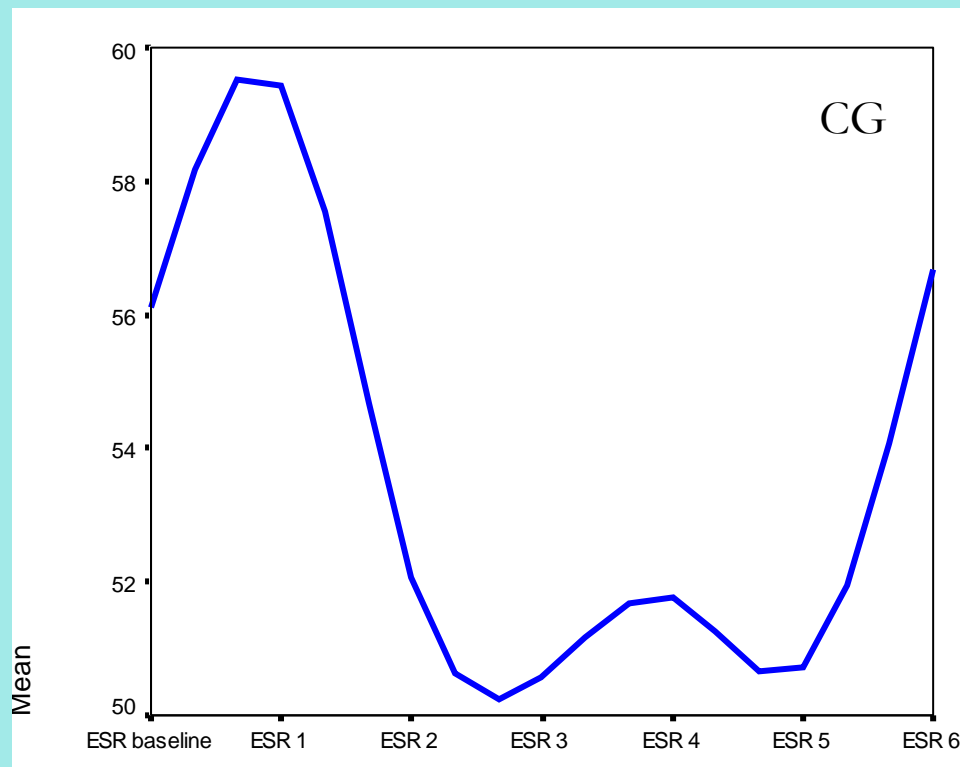
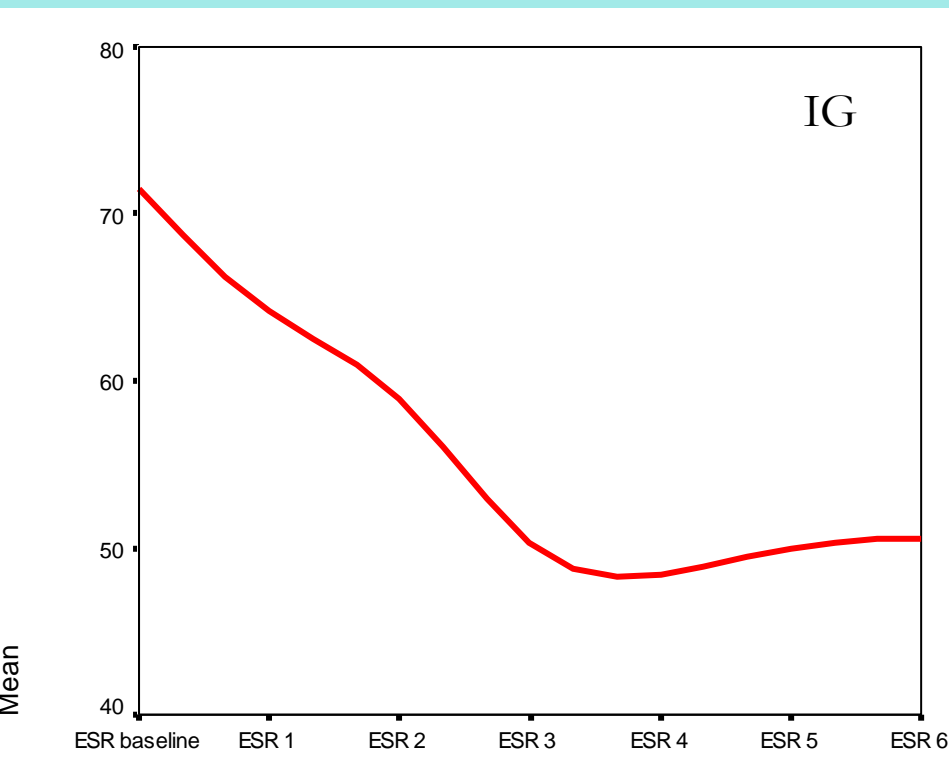
Mean SJC in 7 visits



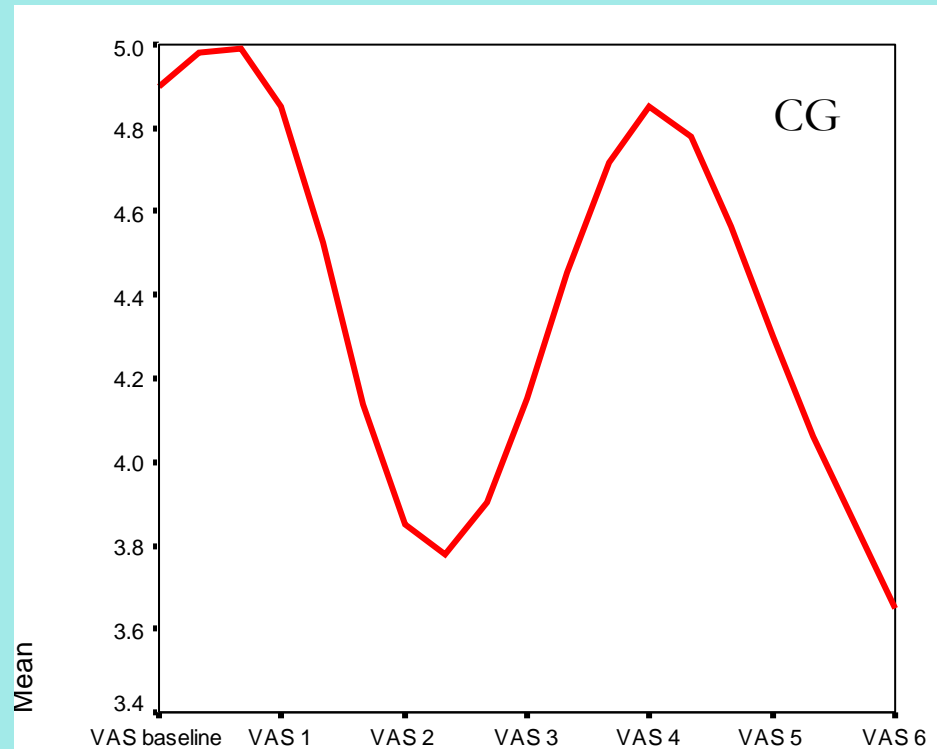
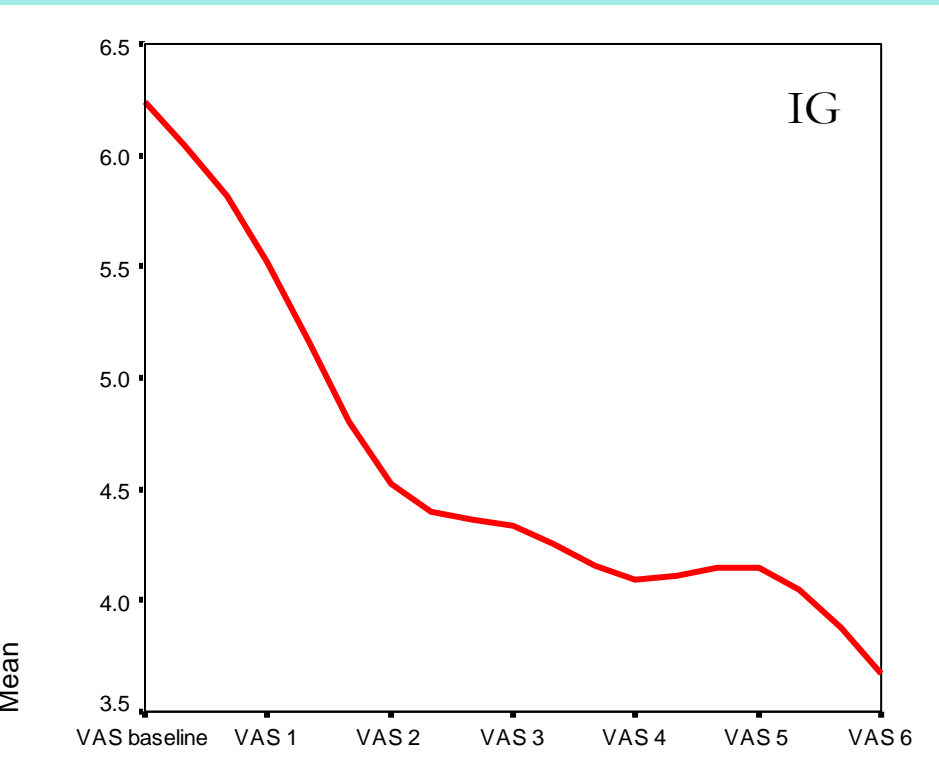
Mean MS in 7 visits



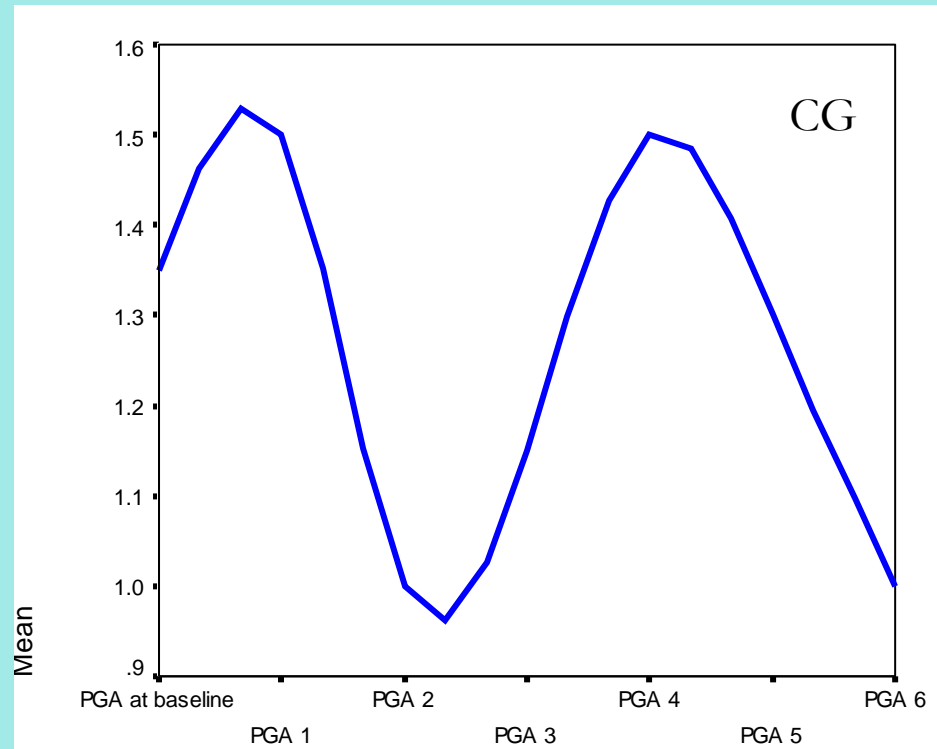
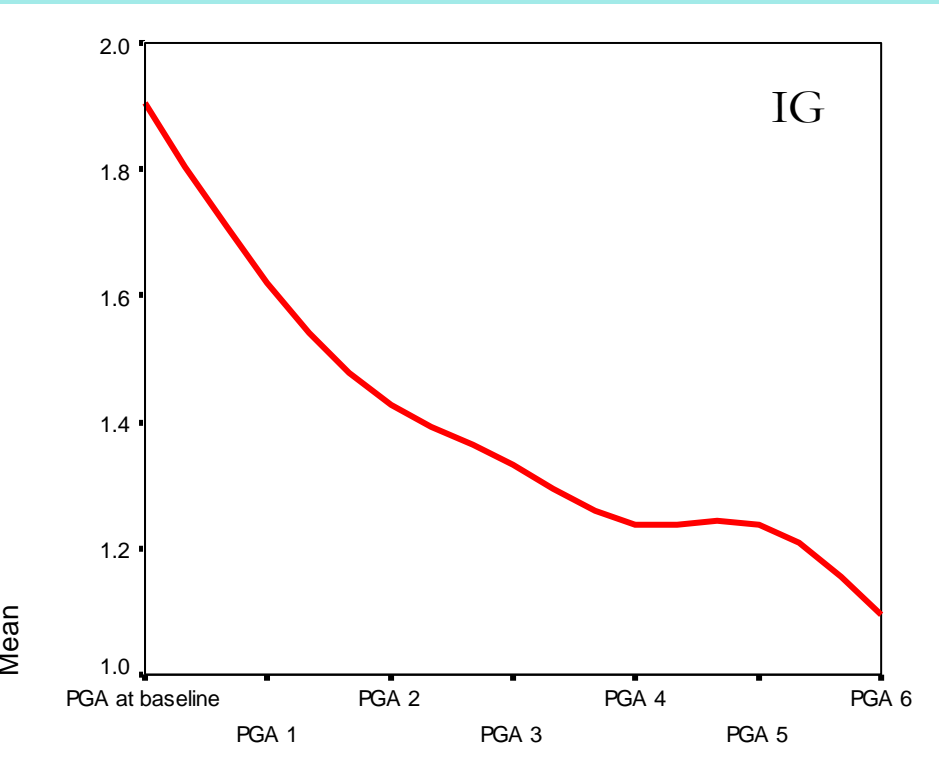
Mean ESR in 7 visits



Mean VAS of Pain of 7 Visits



Mean PGA in 7 Visits



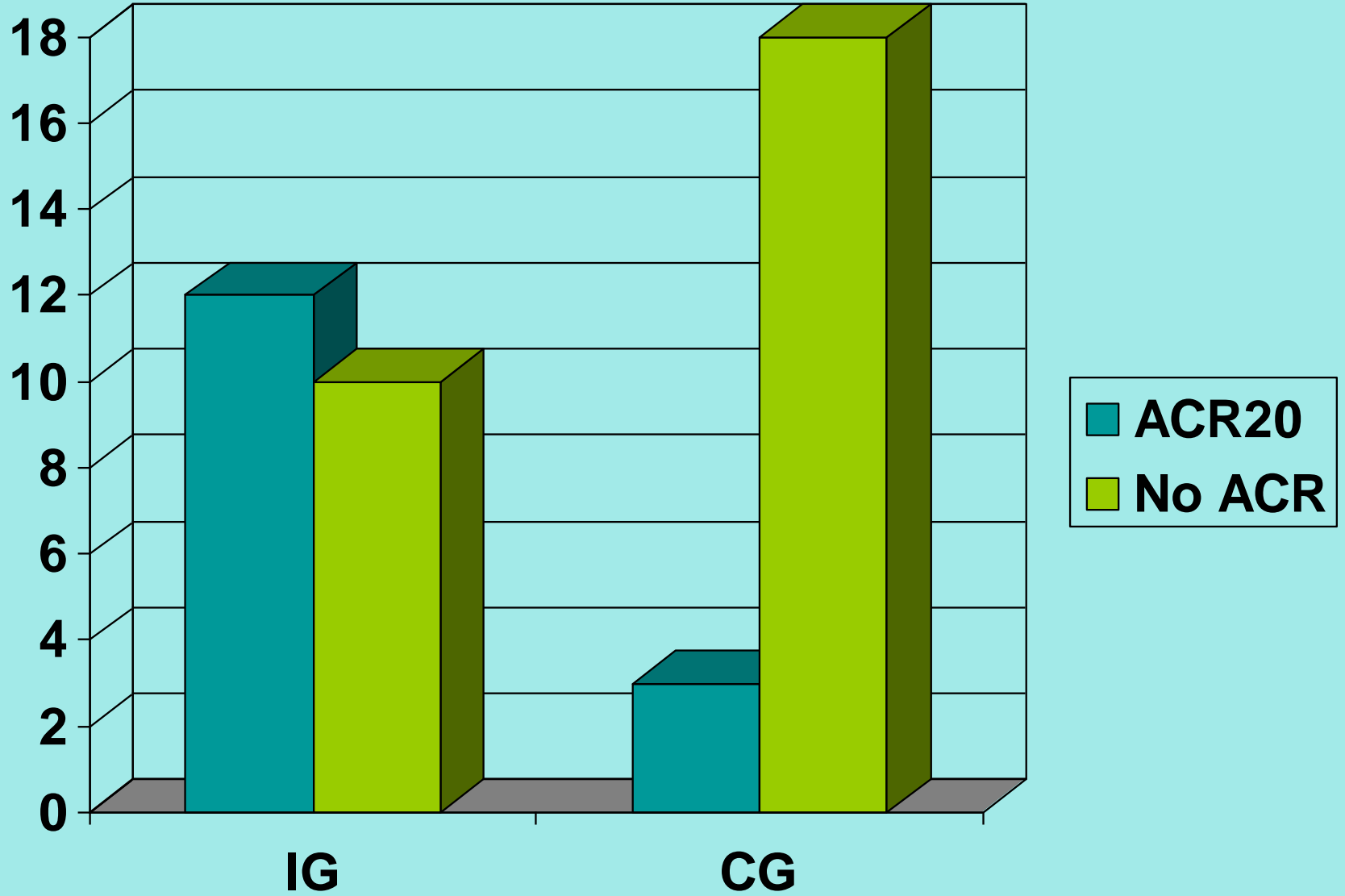
How much Effective?

- Efficacy was quantified by measuring ACR20 achievement
- ACR 20 indicate 20% decrease in:
 - TJC
 - SJC
 - 3 of 5: PGA, Disability, VAS, ESR, PtsGA

ACR20 Criteria Fulfillment in Both Groups

			placebo	methotrexate	Total
ACR Criteria	No ACR	Count	18	10	28
		Expected Count	13.7	14.3	28.0
		% of Total	41.9%	23.3%	65.1%
ACR20		Count	3	12	15
		Expected Count	7.3	7.7	15.0
		% of Total	7.0%	27.9%	34.9%
Total		Count	21	22	43
		Expected Count	21.0	22.0	43.0
		% of Total	48.8%	51.2%	100.0%

Pearson Chi-Square: 7.66 df=1 P=0.006



Comparison of Intolerance to MTX

		placebo	methotrexate	Total
Intolerant	Count	0	5	5
	Expected Count	2.2	2.8	5.0
	% of Total	.0%	10.4%	10.4%
Tolerant	Count	21	22	43
	Expected Count	18.8	24.2	43.0
	% of Total	43.8%	45.8%	89.6%
Total	Count	21	27	48
	Expected Count	21.0	27.0	48.0
	% of Total	43.8%	56.3%	100.0%

Pearson Chi-Square: 4.3 df=1 $P=0.037$

Limitations

- Small sample size
- Drop out rate was high
- Pts global assessment was not done
- No provision for increasing dose of MTX
- Quantification of radiological changes not done

Conclusion

- MTX is effective in RA even at low dose
- Some pts may need to stop the drug due to adverse effect
- No serious biological adverse events
- It is reasonably well tolerated at a dose of 7.5 mg weekly

Thank You