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The Efficacy of Disease Modifying Anti-Rheumatic Drugs in Rheumatoid Arthritis in Local Patients of Karachi

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Abstract: The primary objective of the study is to assess the efficacy of the 'Disease Modifying Anti-Rheumatic Drugs (DMARDs) on the disease activity in Rheumatoid Arthritis (RA) in the local patients of Karachi. The secondary objective is to evaluate whether the combination of two concurrent DMARDs (Combination Therapy) is superior to a single DMARD (Mono-therapy). This is an open labeled retrospective case series. One hundred and five consecutive patients fulfilling 1987 ACR criteria for the diagnosis of RA were initially selected from the case notes of out patients department. Sixty nine patients fulfilled the inclusion criteria and were finally recruited for analysis. Details of the Tender Joint Count (TJC), Swolen Joint Count (SJC), Patient Global Assessment (PGA) and ESR were obtained at six weeks, three months, six months and one year. Out of the 69 patients studied 48 were in the mono-therapy group and 21 in the combination therapy group. Methotrexate (MTX) was the most commonly used single DMARD (75%) as well as the most frequent component of the combination groups (85%). The TJC, SJC and PGA analyses of all patients show that DMARDs are effective agents for clinically controlling RA activity. The speed of their beneficial effect is slow and unlike analgesics and NSAIDS, may take up to six weeks to start working. The 6 week responses showed 32.49% improvement in TJC, 33.19% improvement in SJC and 59% better responses in PGA. This response continued to show further improvement and at six months when TJC improved by 63.41%, SJC by 53.21% and PGA with 81% better responses. After 6 months the response reached a plateau but nevertheless maintained until 1 year with improvements in TJC by 66.23%, SJC by 56.48% and PGA with 88.23% better responses. The changes in ESR did not go parallel with the other three outcome measures. The mean baseline ESR of 56 reduced to 44 at 6 weeks but rose again gradually to 54 at 1 year. The sub-group analysis did not show the overall superiority of combination therapy over mono-therapy. DMARDs are effective in controlling disease activity in RA. Their effect starts slowly over 6 week and may take up to 6 months to show full benefits. The beneficial effect was maintained for at least 1 year. Sub-group analysis did not show any advantage of combination therapy over mono-therapy in this series of patients. Methotrexote being the most frequently used DMARDs in both groups and being most cost effective agent seems to be the most useful drug in RA in the developing world.

Key words: Rheumatoid arthritis, DMARDs, combination therapy, mono therapy

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that is associated with significant morbidity and mortality (Pincus *et al*., 2001). Altering the course of the disease is therefore of a pivotal significance. The role of Disease Modifying Anti Rheumatic Drugs (DMARDs) is now considered to alter the natural course of the disease especially if started very early (O'Dell, 2002). This opportunity in the early disease is sometimes regarded as the 'window period'. Even in the late or established disease, the use of DMARDs is associated with a better overall control of disease symptoms and possibly some alteration in the future progression of the disease

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(O'Dell *et al*., 2002). Most DMARDs exert their pharmacological effects insidiously over a period of 3 to 6 months. Well established DMARDs include methotrexate, sulfasalazine, anti-malarials (i.e., chloroquin and hydroxychloroquin) and leflunomide. Less often used agents include penicillamine, injectable gold and azathioprin. DMARDs can be used alone or as a combination of 2 to 3 different agents. Methotrexate being effective (Kremer and Lee, 1986) and best tolerated agent (Weinblatt *et al*., 1988) is a commonly used monotherapy. Its use is also associated with better outcomes (Choi *et al*., 2002). Hence, it is almost an essential component of most of the combination therapies as well. Many experts regard methotrexate as a gold standard therapy in RA and a parameter against which the efficacy of most of the other newer treatments including the biological therapy is measured. The concept of combining two or more DMARDs evolved in the mid-nineties. Several studies have suggested that various combinations involving methotroxate, sulfasalazine and hydroxychloroquin with or without a few month course of a tapering dose of oral prednisolone can be extremely useful in aggressive disease (O'Dell *et al*., 2002; Mottonen *et al*., 1999; O'Dell *et al*., 1996; Boers *et al*., 1997; Grigor *et al*., 2004; Goekoop-Ruiterman *et al*., 2005; Capell *et al*., 2007; Tugwell *et al*., 1995). Various other DMARD combinations have also been tried with variable results (Tugwell *et al*., 1995). The combination therapy may be a step-up regime (Capell *et al*., 2007) when a sequential addition of the 2nd and 3rd agent is made, a step down regime (Boers *et al*., 1997) when all the three agents are started together and then tapered gradually or a parallel regime when all the 3 agents are continued parallel (O'Dell *et al*., 2002; Mottonen *et al*., 1999; O'Dell *et al*., 1996) to each other from the outset.

There have been suggestions from local studies that RA may have a less aggressive spectrum and course in Asians than the Caucacians (Moran *et al*., 1986; Veerapen *et al*., 1993; Hameed and Gibson, 1996). Despite that the disability index noted in Pakistani RA patients is higher than the same observed in the Caucacians (Hameed and Gibson, 1996). The main reason for this is thought to be the relative lack of timely and appropriate DMARD intervention in our local patients. Similar conclusions were also drawn in a review article highlighting the RA disease burden and management strategies in the developing countries (Kalla and Tickly, 2003). Literature evidence on the use of DMARDs in local patients is limited to two studies done on methotrexate alone (Baig, 2007; Ali *et al*., 2006). It is therefore logical to study as to how our local patients with RA respond to different DMARDs in general as a group and to various DMARDs regimen.

MATERIALS AND METHODS

This is a retrospective case series. Case notes were obtained from the outpatients' record of the Baqai Rheumatology Unit (BRU) of Baqai Medical University. 105 consecutive patients who presented between April 2000 and July 2001 and fulfilled the 1987 ACR (American College of Rheumatology Revised criteria 1987) criteria for RA were initially screened. Out of 105 patients 90 Patients were started on DMARDs. Out of 90 patients 21 patients were excluded due to either incomplete data or had a recent exposure to DMARDs in the 3 months prior to entry in the study or presence of co-morbid conditions such as renal impairment, diabetes and other concurrent painful conditions such degenerative and metabolic bone diseases. Out of 90 patients 69 patients satisfied the inclusion criteria. Their demographic information, basic disease characteristics such as disease duration, Rheumatoid Factor positivity, Tender Joint Count (TJC), Swollen Joint Count (SJC), Patients' Global Assessment (PGA) and ESR were recorded. Details of medications including analgesics, NSAIDS, DMARDs and steroids were obtained. The use of analgesics, NSAIDS and local intra-articular injections of corticosteroids as rescue analgesia was permitted. Mean percentage change from the baseline was calculated in four main outcome measures as primary response indicators to DMARD therapy i.e. (1) Tender joint count (TJC) (2) Swollen joint count (SJC) (3) Patients' Global Assessment (PGA) and (4) ESR. These parameters are routinely recorded in patients' case-notes on each visit. Serial observations were obtained at baseline, 6 weeks, 3 months, 6 months and 1 year. The choice of DMARD was made by a consultant Rheumatologist on the basis of 'methotrexate first' principal. Only those patients who had problems with methotrexate in the past or who had a current contra-indication to it were put on other DMARDs which were sulfasalazine, chloroquin and azathioprin in the same order. Similarly the decision to put the patient on combination therapy was made by the same physician (i.e., the Rheumatologist) using his clinical judgment of the disease severity.

We also used a modified ACR-20, 50, 70 (modified after American College of Rheumatology responses-20, 50, 70) to look at the number and percentage of patients achieving 20, 50 and 70% reduction in TJC and SJC only.

The PGA was obtained on the simple three point scale of patients' overall feeling i.e., B if they feel better, S if they feel the same and W if they feel worst than before. Each response category was then expressed as a percentage of patients.

Statistical analysis: The mean values in SJC, TJC, PGA and ESR at various specified observation time were compared to the baseline mean values using the difference of mean test. For comparing the two treatment groups i.e., monotherapy and combination therapy ANOVA technique was used to observe the difference between the mean changes of the two sample observations at subsequent time intervals. For comparing modified ACR20, 50 and 70 responses of TJC and SJC the test for comparing percentages was performed and the results were compared with p-value.

RESULTS

The demographic features of the 69 study patients showed that the average age was 42 years and the average disease duration was 5.1 years (6 months to 30 years). 56 females and 13 males (F:M ratio 4.5:1). Fifty four patients (79%) were Rheumatoid Factor (RF) positive. Mean baseline TJC was 21.48 (±10.17) and SJC was 9.86 (±8.87). Mean baseline ESR (56.33±34.89). Forty eight patients (69.56%) were given a single DMARD (mono-therapy)while 21 (30.42%) patients were given two different DMARDs (combination therapy group). In mono-therapy methotrexate was used in 36 patients (75%), sulfasalazine in 6 patients (12.5%), chloroquin sulfate in 3 patients (6.25%) and azathioprin also in 3 patients (6.25%). The combination therapy group consisted of methotrexate plus chloroquin in 10 patients (47.61%), methotrexate plus sulfasalazine in 8 patients (38.09%), azathioprin plus sulfasalazine in 2 patients (9.52%) and sulfasalazine plus penicillamine in 1 patient. Methotrexate was the most commonly used single DMARD (75%) as well as most frequently used component of combination therapy i.e., 85%. The average dose of methotrexate used in monotherapy group was 15 mg once weekly and that in the combination group was 12.5 mg once weekly. Similarly the average doses for sulfasalazine and chloroquin were 2G daily and 250 mg daily, respectively. Azathioprin was used in a dose of 1.5-2 mg kg^{-1}. Adverse effects were acceptable and observed in 12.9% of patients. Gastro-intestinal symptoms, rashes and transient reversible increase in Alanine Transaminase (ALT) were the main problems reported. There was no drug withdrawal in any group.

Table 1 shows TJC and SJC of all patients as a group. The mean baseline TJC was of moderate severity (21.48). With DMARD treatment this started to reduce at 6 weeks (14.38-a reduction of 32.49%) and more markedly at 6 month (6.91-a reduction by 63.41%). The response was maintained but reached a plateau at 12 months (6.38-a reduction of 66.26%). The SJC also showed similar response trends. The baseline means SJC was 9.86 for all patients. It also started to improve as early as 6 weeks (6.46-a reduction of 32.49%) and continued to show progressive improvement until 6 months (3.74-a reduction of 53.21%) after which the response though was still maintained but reached a plateau at 12 months (2.94-a reduction of 56.48%). The PGA responses (Fig. 1a) were available at 3, 6 and 12 months and were better in 59, 81

Table 1: Mean values in Tender Joint Count (TJC) and Swollen Joint Count (SJC)

Parameters	Base line	Mean±SD	p- value
6 week			
Monotherapy			
TJC	21.25±10.53	14.08±8.16	<0.000
SJC	9.44±8.33	6.08±5.33	0.021
Combination therapy			
TJC	22.00±9.52	15.05±8.39	0.016
SJC	10.81±10.10	7.33±6.83	0.199
Total			
TJC	21.48±10.17	14.38±8.18	<0.000
SJC	9.86±8.87	6.46±5.81	0.008
3 months			
Monotherapy			
TJC	21.25±10.53	9.30±5.67	< 0.000
SJC	9.44±8.33	4.60±4.02	< 0.000
Combination therapy			
TJC	22.00±9.52	9.00±5.14	< 0.000
SJC	10.81±10.10	4.80±3.63	0.016
Total			
TJC	21.48±10.17	9.21±5.48	< 0.000
SJC	9.86±8.87	4.66±3.88	< 0.000
6 months			
Monotherapy			
TJC	21.25±10.53	6.97±4.59	<0.000
SJC	9.44±8.33	3.74±3.27	<0.000
Combination therapy			
TJC	22.00±9.52	6.79±5.43	<0.000
SJC	10.81±10.10	3.74±2.44	0.005
Total			
TJC	21.48±10.17	6.91±4.86	<0.000
SJC	9.86±8.87	3.74±2.98	0.0001
One year			
Monotherapy			
TJC	21.25±10.53	6.22±4.57	<0.000
SJC	9.44±8.33	2.78±2.43	0.002
Combination therapy			
TJC	22.00±9.52	6.56±7.22	<0.000
SJC	10.81±10.10	3.13±2.89	0.006
Total			
TJC	21.48±10.17	6.38±5.87	<0.000
SJC	9.86±8.87	2.94±2.62	<0.000

Values are expressed as Mean±SD

Table 2: ESR

Parameters	Baseline Monotherapy (n = 48) combination therapy (n = 21)	6 weeks Monotherapy (n = 20) combination therapy (n = 9)	3 months Monotherapy (n = 17) combination therapy (n = 8)	6 months Monotherapy (n = 13) combination therapy (n = 9)	1 years Monotherapy (n = 6) combination therapy (n = 10)
Monotherapy	57.02±31.88	50.3±25.1	61.47±30.92	50.62±38.93	66.33±32.6
p-value		0.064	0.871	0.125	0.599
Combination therapy	54.48±36.22	28.67±20.9	37.38±19.04	45.56±23.57	44.3±20.50
p-value		0.054	0.36	0.948	1.000
Total patients	56.25±33.01	43.59±25.6	53.76±29.57	48.55±32.93	52.56±26.97

Values are expressed as Mean ±SD

Table 3: Mean values of TJC and SJC compared in two treatment groups

Time period	Therapy	N	Mean±SD	p-value
Base line	Monotherapy	48	21.25±10.53	0.780
	Combination therapy	21	22.00±9.53	
6 weeks	Monotherapy	48	14.08±8.16	0.656
	Combination therapy	21	15.04762±8.4	
3 months	Monotherapy	47	9.35±0.067	0.841
	Combination therapy	20	9.00±5.14	
6 months	Monotherapy	35	6.97±4.6	0.897
	Combination therapy	19	6.78±5.45	
1 year	Monotherapy	18	6.22±4.57	0.869
	Combination therapy	16	6.56±7.23	

Table 4: Modified ACR (20, 50 and 70%) responses of Tender Joint Count (TJC) and Swollen Joint Count (SJC)

		6 Weeks Mono (n = 48) Comb (n = 21)		3 Months Mono (n = 47) Comb (n = 20)		6 Months Mono (n = 35) Comb (n = 19)		1 Years Mono (n = 18) Comb (n = 16)	
Number of %		TJC	SJC	TJC	SJC	TJC	SJC	TJC	SJC
≥20 (%)	Monotherapy	83.33(40)	68.75(33)	95.74(45)	78.72(37)	97.14(34)	74.28(26)	94.44(17)	66.67(12)
	Combination	85.71(18)	71.42(15)	100(20)	70 (14)	94.73(18)	68.42(13)	93.75 (15)	75(12)
	p-value	0.58	0.63	0.04	0.09	0.34	0.33	0.86	0.28
≥50 (%)	Monotherapy	14.58(7)	12.5(6)	48.93 (23)	29.78(14)	65.71 (23)	57.14 (20)	77.77 (14)	50(9)
	Combination	9.52(2)	4.76(1)	50(10)	30(6)	73.68 (14)	52.63 (10)	81.25(13)	50(8)
	p-value	0.21	0.03	0.86	0.97	0.20	0.50	0.61	1.0
≥70 (%)	Monotherapy	2.08(1)	4.16(2)	17.02 (8)	17.02 (8)	40 (14)	31.42 (11)	50(9)	38.88(7)
	Combination	4.76(1)	0	25(5)	5(1)	52.63 (10)	26.31(5)	62.5 (10)	43.75 (7)
	p-value	0.18	0.03	0.09	0.004	0.06	0.41	0.14	0.56

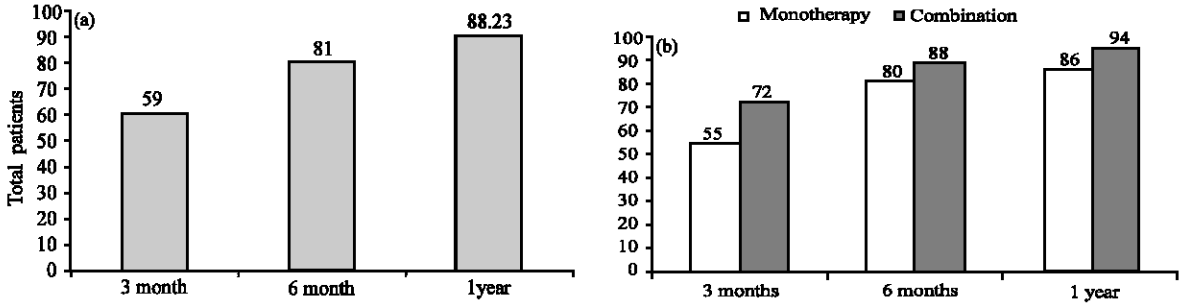

Fig. 1: (a) PGA show better response all patients and (b) PGA (on 3 point scale) in the two DMARDs groups

and 88.23% of patients respectively. The ESR trends were entirely different (Table 2). The baseline mean ESR of 56.25 reduced modestly (22-24%) until 6 months but then rose again close to baseline levels at one year.

In the subgroup analysis of mono-therapy and combination therapy groups, there were no significant differences in the mean percentage changes of TJC and SJC in both groups (p-value >0.05) (Table 3). On comparing the modified ACR 20, 50 and 70 responses of the two groups combination therapy showed a slight superiority that was statistically significant only up to 3 months ($p<0.05$). After that and until 1 year there was no difference between groups ($p>0.05$) (Table 4). The PGA response rate was slightly better in the combination therapy group (Fig. 1b) but could not reach the statistical significance ($p>0.05$). The mean ESR response in the combination therapy group was marginally better only until 6 months but again wasn't statistically significant ($p>0.05$).

DISCUSSION

Studies such as this, despite limitations reflect the importance of local and regional data in determining the effective strategies for a tighter control of rheumatoid arthritis in our population. This study confirms the beneficial role of DMARD therapy in controlling the disease activity even when started at a relatively late stage. Disease duration of 5.1 years is comparable to the same observed by O'Dell *et al.* (2001). As mentioned earlier that the conventional scales such as ACR 20, 50, and 70 or DAS-28 were difficult to apply in retrospective studies, the outcome measures we used in this study i.e., TJC, SJC, PGA and ESR are well accepted components of most international disease activity scales. In fact, a large study called RADIUS (Weaver *et al.*, 2006) used a modified ACR response rate which didn't even include ESR/CRP due to unavailability. There is no doubt, however, that such real time DMARD studies more closely represent the true clinical scenario than the more formally designed ones. In our study over 80% of patients had TJC20 and SJC20 responses, over 70% had TJC50 and SJC50 responses and over 50% had TJC70 and SJC20 responses in both groups. This response rate is somewhat similar to that observed in earlier studies done on our local patient population where methotrexate was found to be effective in almost 75-80% of cases (Ali *et al.*, 2006; Baig, 2007). However this response rate is greater than what is generally observed in other populations e.g., Caucacians (Mottonen *et al.*, 1999). One explanation to this varied response could be the genetic influences which may determine the response to methotrexate (Ali *et al.*, 2006).

The slow onset of clinical response to DMARD is well known. As per this study it could take up to 6 weeks to initiate an effect and up to 6 months to show full benefit. It is, therefore extremely important to counsel the patients what to expect of these agents. This in turn may improve compliance which is an important issue amongst the ethnic Asian communities living in the Europe (Helliwell and Ibrahim, 2003) as well as a frequently observed problem in our local patients.

Present study does not endorse the overall superiority of combination therapy. Only small differences were noticed in some parameters at 6 weeks and 3 months only. The results are very close to the evidence available in the literature which is either equivocal or only marginally in favor of combination therapy (Verhoeven *et al.*, 1998; Smolen *et al.*, 2005; Donahue *et al.*, 2008; Dougados *et al.*, 1999; Haagsma *et al.*, 1997). Despite methodological limitations, this study provides some food for thought since no literature is available on this issue in our population. In general, head to head comparison of two different treatment groups is technically difficult in retrospective studies anyway. The baseline TJC, SJC and ESR, however, were not greatly varied in the mono-therapy and the combination therapy groups. Hence their efficacy relative to each other could be compared. Future prospective studies with more stringent patient selection criteria might give a better answer to this issue.

The relative lack of effect on ESR despite improvements in synovitis was also observed in studies by O'Dell *et al.* (2002), Mottonen *et al.* (1999) and Capell *et al.* (2007). This could be because of the known observation that in late and established disease ESR is a less sensitive marker than CRP. The later therefore could be a more appropriate marker in future studies.

CONCLUSION AND RECOMMENDATIONS

DMARDs are useful agents in controlling the disease activity in RA in local patients of Karachi. Their mode of onset is slow but once started is well maintained for at least one year. Present study does not endorse the superiority of the combination DMARD therapy. DMARDs, in particular Methotrexate, should remain the mainstay of therapy to alter the natural course of the disease in countries like us. For reasons of having a lesser disease load and severity, financial constraints and increased risk of infections, the newer therapies such as Anti Tumor Necrosis Factor Alfa (Anti-TNFα) are unlikely to have a significant impact in reducing the overall disease burden of RA in Pakistan. These biological therapies could however be useful in certain individual cases. Future research resources should therefore be directed at assessing the disease burden, exploring innovative ways to use old DMARDs and developing better strategies to make use of glucocorticoids in a novel yet judicious ways. A nation-wide campaign of early aggressive use of DMARDs could potentially transform the whole outlook of this menacing and chronic disabling disease.

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