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Original Research Article

Incidence and clinico-immunological assessment of patients of rheumatoid arthritis in Gorakhpur district, Uttar Pradesh, India

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease manifesting itself in various extra-articular signs and progressive articular damage. The present study was designed to find out the incidence and clinico-immunological characteristics of patients with RA.
Methods: This one-year observational study involved 150 adult patients attending orthopaedics department at Nehru Hospital, B.R.D. Medical College, 2010. Each patient was subjected to clinical, functional, radiological and laboratorial examination after taking informed consent. SPSS software was used for data analysis.
Results: Nearly 36% patients had some radiological changes in the form of surrounding osteopenia articular erosion, joint space narrowing and degenerative changes. All NSAIDs when used alone showed poor fall in values of acute phase reactant i.e. ESR and CRP. Maximum fall in acute phase reactant was obtained by treatment with combination therapy of NSAID + hydroxychloroquine + methotrexate + sulfasalazine. NSAIDs did not prevent radiological progression of disease and in more than 50% radiological progression continued however when NSAIDs used with any DMARDs show radiological regression. Maximum radiological regression was caused by combination therapy of NSAID + hydroxychloroquine + sulfasalazine + methotrexate.
Conclusions: All NSAIDs produced poor fall in values of acute phase reactants and radiological progression continued in majority of patients, when a DMARD or combination of DMARDs were used with NSAIDs response was much better and relief was obtained earlier, and remission was sustained for longer duration.

Keywords: CRP, DAS, ESR, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease manifesting itself in various extra-articular signs and progressive articular damage.[1] Clinical onset of this disease may be variable; it generally begins with symmetrical involvement of the small joints, pain, morning stiffness, and limitation of movement for more than 1 hour. Although the metacarpophalangeal (MCP) joints, the proximal interphalangeal (PIP) joints, the wrists, the metatarsophalangeal (MTP) joints and the knee joints are the most frequently involved joints, RA may also involve other ones.[1] Early initiation of aggressive treatment and frequent assessment and monitoring of RA activity allows timely adoption of appropriate therapies. This is important in preventing progression of the disease.[2] There is scarcity of data about incidence, and clinico-immunological assessment of RA, in Northern India. Therefore, the present study was designed to find out the incidence and clinico-immunological characteristics of patients with RA.

METHODS

This study has been conducted on 150 patients suffering with rheumatoid arthritis, attending outpatient department and admitted in Orthopaedics ward at Nehru Hospital, B.R.D. Medical College, Gorakhpur 2010 after taking permission from the institutional ethical committee. A thorough history was recorded, and each patient was subjected to clinical, functional, radiological and laboratorial examination after taking informed consent. Treatment was given and Follow up examination was done. The probable cases of rheumatoid arthritis were selected on the basis of three or more of the following criteria.

- Morning stiffness- Duration>1hour, lasting>6 weeks
- Arthritis of three or more joint areas (soft tissue swelling or effusion lasting>6 weeks)
- Symmetric arthritis- At least one area>6 weeks
- Rheumatoid nodule
- Serum rheumatoid factor
- Radiographic changes- As seen on anteroposterior films of wrist and hand.

For treatment purpose, patients were categorized into two main categories, mainly on basic of total duration of illness.

I. Mild to moderate disease

- Duration of disease upto 1 year
- No or minimal joint deformity
- None or minimal radiological changes.

II. Chronic, severe disease

- Duration of disease greater than one year
- With joint deformities
- Radiological changes at presentation

In category i.e. mild to moderate disease, patients were given non-steroidal anti-inflammatory drugs (NSAIDS) alone or with one disease modifying antirheumatic drug (DMARD). NSAIDS which were used in the study were indomethacin, naproxene, etoricoxib, etodolac.

In category i.e. severe chronic disease, patients were given treatment with non-steroidal anti-inflammatory drugs combined with some disease modifying anti-steroidal anti-rheumatic drugs mainly hydroxychloroquine, sulfasalazine, methotrexate and leflunomide.

In few cases, presenting with severe acute symptoms of disease, corticosteroid mainly methylprednisolone was supplemented along with NSAID.

Follow up visits: Patients were called 3 weekly or monthly depending on severity of disease, patient's cooperation and convenience.

Laboratorial analysis and grading:

ESR

- A → More than 40 mm fall in first hour.
- B → Fall between 20-40 mm.
- C → Less than 20 mm fall.

C-reactive protein

- A → Decrease of more than 4 mg/dl.
- B → 1-4 mg/dl decrease.
- C → Less than 1 mg/dl decrease.

Radiological evaluation

- A → Regression (healing of joint erosions maintenance of joint space, remineralization of osteoporosed areas).
- B →No further radiological deterioration.
- C →Progression (increasing osteopenia, joint space narrowing and joint erosion during the course of treatment).

The final results regarding response to various drugs were evaluated as:

- Good - Four or more A (>4 A)
- Fair - Five or more B (>5 B) Or
- Three A or + two more B (3A>2B)
- Poor – Four or more C (>4 C)

Assessment of patients was also done by calculating the disease activity score (DAS).

DAS can be calculated as follows:

$$0.56 \times \sqrt{(t_{28})} + 0.28 \times \sqrt{(SW_{28})} + 0.70 \times \text{Ln (ESR)} + 0.014 \times GH = 0.014 \times GH$$

Here, t_{28} = Tender joints (of 28 counted); SW_{28} = Swallen joints (of counted); ESR = Erythrocyte sedimentation rate; GH = General health status (100 mm-VAS); Score-DAS 28 >5.1= High disease activity; DAS 28 < 3.2 = Low disease activity; DAS 28 <2.6 = Remission

SPSS software was used for data analysis.

RESULTS

53 (35.33%) patients were in age group 30-40 years, followed by 45 (30.0%) in 40-50 years age group, 24 (16%) were in third decade, 18 (12%) in sixth decade and 10 (6.67%) in seventh decade. Out of 150 patients, 108 (72.0%) were females and only 42 (28.0%) were males.

Pain was the most common presenting symptom in 134 (89.35%) patients followed by morning stiffness in 116 (77.33%) and joint swelling in 88 (58.67%) patients. Fifty-two (34.67%) patients had prodromal symptoms before starting of definite joint disease. Forty-six (30.67%) patients had joint deformities and 12 (8.0%) patients had subcutaneous nodule. Associated systemic illness was present in 22 (14.67%) patients. Ninety-six (64.0%) patients had no radiological findings or only soft tissue swelling could be demonstrated at the time of presentation and 54 (36.0%) cases had some radiological changes. Most common radiological change present was osteopenia of surrounding bones, presenting in 44 (29.33%) patients, joint space narrowing in 28 (18.67%) patients. Bony erosions and late degenerative changes were seen only in 14 (9.33%) and 11 (7.33%) patients respectively.

Table 1: Subjective improvement in functional capacity after drug therapy.

Name of drugs	Total no. of patients	Improvement in functional capacity with graded					
		Full squatting normal walking grip strength normal		Difficulty in squatting limping present grip strength weak		Walk with support, squatting not possible, grip much weak	
		No.	%	No.	%	No.	%
Indomethacin	12	04	33.30	05	41.67	03	25.00
Naproxen	12	04	33.30	04	33.33	04	33.33
Etoricoxib	12	03	25.00	04	33.33	05	41.67
Etodolac	12	03	25.00	05	41..67	04	33.33
NSAID + hydroxychloroquine	16	10	66.67	03	20.00	02	13.33
NSAID +sulfasalazine	15	12	80.00	02	13.33	01	06.67
NSAID + methotrexate	15	02	50.00	01	25.00	01	25.00
NSAID + prednisolone	04	09	56.25	05	31.25	02	12.50
NSAID + hydroxychloroquine + sulfasalazine	16	12	75.00	03	18.75	01	06.25
NSAID + hydroxychloroquine + sulfasalazine + methotrexate	22	19	86.36	02	09.10	01	04.54
NSAID + leflunomide	14	11	78.57	02	14.28	01	07.15

Table 1 shows that maximum improvement in functional capacity was in patients taking combination therapy of hydroxychloroquine + sulfasalazine+ NSAID + in 19 (86.36%) patients, followed by in patients taking NSAID + methotrexate in 12 (80.0%) and taking NSAID + leflunomide in 11 (78.57%) patients. NSAID used alone cause minimal improvement in functional capacity.

Table 2: Fall in ESR values with drug therapy.

Name of drugs	Total no. of patients	Fall in ESR values with grades					
		40 mm fall in 1st hour		20-40 mm fall in 1st hour		$>30^0$ restriction	
		No.	%	No.	%	No.	%
Indomethacin	12	01	08.40	04	33.33	07	58.30
Naproxen	12	00	00.00	03	25.00	09	75.00
Etoricoxib	12	01	08.4003	03	25.00	08	66.67
Etodolac	12	00	00.00	04	33.33	08	66.67
NSAID + hydroxychloroquine	16	07	46.67	06	40.00	02	13.33
NSAID +sulfasalazine	15	09	60.00	05	33.33	01	06.67
NSAID + methotrexate	15	02	50.00	01	25.00	01	25.00
NSAID + prednisolone	04	07	43.75	07	43.75	02	12.5
NSAID + hydroxychloroquine + sulfasalazine	16	09	56.25	05	31.25	02	12.50
NSAID + hydroxychloroquine + sulfasalazine + methotrexate	22	18	81.82	03	13.63	01	04.55
NSAID + leflunomide	14	09	64.28	03	21.43	02	14.29

Table 2 shows that maximum fall in ESR was caused by Combination therapy group of NSAID + sulfasalazine + hydroxychloroquine + Methotrexate in 18 (81.82) patients, followed by NSAID + leflunomide and NSAID + methotrexate in 9 (64.28%) and 9 (60.0%) patients respectively. NSAIDS used alone cause minimal decrease in the ESR.

Table 3: Variation in C-reactive values after drug.

Name of drugs	Total no. of patients	Decrease in CRP values with graded					
		A. >3 mg/dl decrease		B. 1-3m g/dl decrease		C. <1 mg/dl decrease	
		No.	%	No.	%	No.	%
Indomethacin	12	04	33.33	05	41.70	03	50.00
Naproxen	12	02	16.70	03	25.00	07	58.30
Etoricoxib	12	03	25.00	04	33.33	05	41.70
Etodolac	12	03	25.00	04	33.33	05	41.70
NSAID + hydroxychloroquine	16	08	53.33	05	33.33	02	13.34
NSAID +sulfasalazine	15	13	86.67	02	13.33	-	-
NSAID + methotrexate	15	03	75.00	01	25.00	-	-
NSAID + prednisolone	04	08	50.00	05	31.25	03	18.75
NSAID + hydroxychloroquine + sulfasalazine	16	12	75.00	03	18.75	01	06.25
NSAID + hydroxychloroquine + sulfasalazine + methotrexate	22	20	90.90	02	09.10	-	-
NSAID + leflunomide	14	11	78.57	02	14.29	01	07.14

Table 3 shows that C-reactive values decreased maximally by Combination therapy if NSAID + hydroxychloroquine + sulfasalazine + methotrexate in 20 (90.9%) patients, followed by NSAID + methotrexate in 13 (86.67%) patients. There was minimal decrease in C-reactive protein value by NSAIDs used alone.

Table 4: Radiological changes after drug therapy.

Name of drugs	Total no. of patients	Radiological change					
		A. Regression		B. No change		C. Progression	
		No.	%	No.	%	No.	%
Indomethacin	12	-	-	06	50.00	06	50.00
Naproxen	12	-	-	04	33.33	08	66.67
Etoricoxib	12	-	-	03	25.00	09	75.00
Etodolac	12	-	-	03	25.00	09	75.00
NSAID + hydroxychloroquine	16	04	26.67	09	60.00	02	13.33
NSAID +sulfasalazine	15	06	40.00	07	46.67	02	13.33
NSAID + methotrexate	15	-	-	03	75.00	01	25.00
NSAID + prednisolone	04	02	12.50	09	56.25	05	31.25
NSAID + hydroxychloroquine + sulfasalazine	16	06	37.50	08	50.00	02	12.50
NSAID + hydroxychloroquine + sulfasalazine + methotrexate	22	14	63.63	05	22.73	03	13.33
NSAID + leflunomide	14	06	42.86	06	42.86	02	14.28

Table 4 shows that maximum radiological improvement was Occurred by the treatment with combination therapy of NSAID +Hydroxychloroquine + Sulfasalazine + Methotrexate in 14 out of 22 (63.63%). Patients, followed

by with NSAID + leflunomide in 6 out of 14 (42.86%) Patients, with NSAID + methotrexate 6 out of 15 (40.0%) patients. There was no radiological improvement by treatment with NSAIDs when used alone.

Table 5: DAS (Disease Activity Score) among patients.

Name of drugs	Total no. of patients	Response to drug (DAS 20)					
		DAS 28<2.6 (remission)		DAS 28 <3.2 (low disease activity)		DAS 28 >5.1 (High disease activity)	
		No.	%	No.	%	No.	%
Indomethacin	12	02	16.67	06	50.00	04	33.33
Naproxen	12	02	16.67	07	58.33	03	25.00
Etoricoxib	12	01	08.33	03	25.00	08	66.67
Etodolac	12	01	08.33	04	33.33	07	58.34
NSAID + hydroxychloroquine	16	06	40.00	07	46.67	02	13.33
NSAID +sulfasalazine	15	08	53.33	04	26.67	03	20.00
NSAID + methotrexate	15	01	25.00	02	50.00	01	25.00
NSAID + prednisolone	04	06	37.50	07	43.75	03	18.75
NSAID + hydroxychloroquine + sulfasalazine	16	09	56.25	05	31.25	02	12.50
NSAID + hydroxychloroquine + sulfasalazine + methotrexate	22	15	68.20	05	22.70	02	09.10
NSAID + leflunomide	14	09	64.28	03	21.43	02	14.29

Table 5 shows that patients on combination therapy of NSAID + hydroxychloroquine + sulfasalazine + methotrexate therapy of NSAID +(DAS < 2.6) in 15 out 22 (68.2%) patients, followed by in therapy with NSAID + leflunomide in 9 out 14 (64.28%) patients, in NSAID + hydroxychloroquine + sulfasalazine in 9 out of 16 (56.25%) patients. Minimal remission caused by the NSAIDs when used alone.

DISCUSSION

In the present series majority of patients 96 (64.0%) did not show any radiological changes at the time of examination or show only increase in soft tissue shadow. Most common radiological finding was osteopenia present in 44 (29.33%) patients. Joint narrowing was seen in 28 (18.67%) patients and bony erosion in 14 (9.33%) patients.

Radiological changes were present mostly in whom, the disease duration was >12 months or above, indicating chronicity of disease which is linked to radiological changes. Caruso et al in their series reported that 37% of patients had some radiological changes by 1 year and 66% had them by 36 months.[3]

Maximum correction in ESR following drug therapy was seen with combination therapy of NSAID + hydroxychloroquine + sulfasalazine + methotrexate in 18 (81.82%) patients, followed by NSAID + leflunomide in 9 (60.0%) patients, by NSAID + hydroxyl-chloroquine + sulfasalazine in 7 (46.67%) patients, and by NSAID + hydroxychloroquine in 7 (43.75%) patients.

NSAIDs when used alone cause minimal improvement in ESR. Indomethacin and Naproxen both cause Grade-A improvement in ESR value in 1 patient (8.4%). Etoricoxib and Etodolac cause no Grade-A improvement in ESR value.

In another study from Iran, fifty-two rheumatoid arthritis patients randomly received methotrexate, chloroquine, prednisolone (MCP) or azathioprine, chloroquine, prednisolone (ACP) and all were followed up for 34 weeks. Chloroquine and azathioprine were given, 150 mg/d and 2 mg/kg/d, respectively. Methotrexate was given, 0.2 mg/kg/week and simultaneously increased 2.5 mg monthly if no clinical response was seen. Prednisolone was started, 0.3 mg/kg/d and tapered after one week. ESR at baseline and during follow-up were checked. The data were collected and analyzed. The percentages of obtaining normal ESR after 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 18^{th}, 34^{th} weeks of follow up were 42.4%, 53.9%, 57.7%, 65.4%, 88.5%, 96.2% in the MCP group and 47.9%, 65.3%, 74%, 78.3%, 82.7%, 87% in the ACP group. The mean time of obtaining normal ESR was 9.15 (95%CI, 5.58 to 12.73) weeks in MCP group and 9.04 (4.04 to 14.05) weeks in the ACP group (p>0.05). Their results are comparable to present results.[4] A large prospective study of long-term MTX treatment also demonstrated sustained clinical response and improvement in the Westergren ESR and functional assessment scores, with an acceptable toxicity profile.[5]

In this series Grade-A decrease in C-reactive protein values following drug therapy was maximum with combination therapy of NSAID + hydroxychloroquine + sulfasalazine + methotrexate in 20 (90.9%) patients,

followed by NSAID + methotrexate in 13 (86.67%) patients, by NSAID + leflunomide in 14 (78.57) patients, NSAID + sulfasalazine + hydroxychloroquine in 12 (75%) patients, by NSAID + sulfasalazine in 8 (53.33%) patients, followed by NSAID + hydroxyl- chloroquine 8 (50%) patients. NSAIDs cause minimal decrease in CRP values. Present results are comparable to those reported by Gossen et al who conducted a study among 1,695 patients with a diagnosis of either rheumatoid arthritis with an initial biologic drug (etanercept, infliximab, adalimumab, golimumab) prescription and documented CRP levels within one year. CRP levels significantly decreased from a mean of 17.7 mg/L before the index date to 11.7 mg/L after the index date (33.9% reduction, P< 0.001).[6]

In present series, regression of radiological changes after drug therapy was maximum by treatment with combination therapy with NSAID + hydroxychloroquine + sulfasalazine + methotrexate in 14 (63.63%) patients, followed by treatment with NSAID + leflunomide in 6 (42.86%) patients, by NSAID + methotrexate in 6 (40%) patients, followed by NSAID + sulfasalazine in 4 (26.67%) patients, and by NSAID + hydroxychloroquine in 2 (12.5%) patients. There was no radiological improvement seen when NSAIDs were used alone.

Radiological progression was present when NSAIDs used alone. Maximum radiological progression was seen with the treatment with Etoricoxib and Etodolac in 9 (75%) patients. Similarly, Radiographic progression was observed in up to 36.6% of Spanish patients with early RA after 1 year of DMARD therapy in spite of a significant reduction in disease activity.[7]

In present series DAS score shows that maximum remission is caused by the combination therapy with NSAID + methotrexate in 15 (68.2%) patients followed by treatment with NSAID + leflunomide in 9 (64.28%) patients with NSAID + hydroxychloroquine + sulfasalazine in 9 (56.25%) patients, with NSAID + methotrexate in 8 (53.33%) patients, with NSAID + hydroxychloroquine in 6 (37.50%) patients NSAIDs when used alone cause remission in very less patients.

In a study by Silva et al the significant correlation between DAS-ESR and DAS-CRP, indicated that it will not be necessary to perform both evaluations. DAS-CRP yielded a better activity score more often than DAS-ESR, but with 84,7% of concordance in the disease activity status, indicating that both measures are useful for assessing disease activity in RA.[8]

Disease Activity Score in 28 joints (DAS28) is being used as a measurement for assessing disease activity in patients with RA for the past several years.[9]

The DAS28 requires measurement of acute phase reactants, and a complex formula requiring a calculator, computer or access to an internet-based online calculator for computing it. Newer tools such as Clinical Disease Activity Index (CDAI) 10, are scoring systems that do not need any of the above tools for calculation. These can be easily employed in the evaluation of patients with RA, consistently at a greater frequency and without complex mathematical calculations. The CDAI, DAS28 (ESR or CRP), PAS, PAS-II, RAPID-3, and SDAI all accurately reflect disease activity; are sensitive to change; discriminate between low, moderate, and high disease activity states; are feasible to perform at the point of care; and are acceptable to most practicing rheumatologists.[11] Quantitative assessment of rheumatoid arthritis in standard clinical care is valuable to improve the quality of visits for patients and health professionals. Quantitative monitoring improves the physician's capacity to assess and document a patient's clinical status and changes over time, which leads to greater accuracy in the underlying rationale for clinical decisions.[12]

CONCLUSION

All NSAIDs produced poor fall in values of acute phase reactants and radiological progression continued in majority of patients when a DMARD or combination of DMARDs were used with NSAIDs response was much better and relief was obtained earlier, and remission was sustained for longer duration. Radiological progression was seen in comparatively lesser number of patients. Combination therapy of two three DMARDs gave better response in comparison when single DMARD used.

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