Original Research Paper

Volume-9 | Issue-3 | March-2019 | PRINT ISSN - 2249-555X

Rheumatology

PREVALENCE OF ANAEMIA IN A COHORT OF RHEUMATOID ARTHRITIS PATIENTS IN INDIA

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ABSTRACT In this study, we investigated the actual prevalence of anaemia in Indian rheumatoid arthritis(RA) patients.We also looked for its impact on RA disease activity and the relation of haemoglobin levels with therapeutic strategies. This was a prospective study including 200 RA patients attending the rheumatology OPD of a tertiary care centre in North India. Demographic, clinical and laboratory data of patients were examined retrospectively and compared between anaemic and non-anaemic RA patients. The prevalence of anaemia was 33% in the study population. Majority of our patients had anaemia of chronic disease (ACD) (24.7%). Male gender and high disease activity were significantly associated with anaemia (p-value of 0.008 and <0.001 respectively). The use of DMARDs was associated with a reduced likelihood of patients being anaemic (p-value 0.012). Our study results suggested a need for proper treatment to reduce the risk of anaemia in RA patients.

KEYWORDS : Rheumatoid arthritis, anaemia, disease activity

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease which is characterized by joint destruction, autoantibody production and other systemic involvement.[1] Anaemia is one of the most frequent extra-articular manifestations of RA and its prevalence in RA patients is found to be between 30 and 60%.[2,3] Anaemia is shown to have a significant impact on the quality of life in RA patients.[4] The influence of anaemia on the RA disease course could be profound.[2] Borah D J and colleagues in a study in Northern India found a prevalence of 64 % among patients who had been on follow up with RA for a period of more than 2 years and in this cohort, 65% of the anaemia observed was anaemia of chronic disease (ACD) while iron deficiency anaemia (IDA) accounted for 33% the anaemia.[5] The ACD and IDA, alone or in combination are the most frequent forms of anaemia in RA. Changes in iron metabolism cause anaemia of chronic disease in RA patients and are mainly induced by the altered synthesis and function of hepcidin and ferroportin, which are induced by pro-inflammatory cytokines, mainly IL-6.[3]

Increase in haemoglobin level is found to be significantly associated with positive changes in quality of life for RA patients with anaemia.[6] There are not many studies which demonstrated the effect of anaemia in RA in this part of the world.[5,7] This prompted us to study the prevalence of anaemia and its association with the parameters of RA in the Indian population .

Materials and Methods

200 patients with RA, diagnosed according to the ACR-EULAR 2010 criteria, who attended the Rheumatology OPD of a tertiary care centre of Eastern India between September 2015 and March 2017 were prospectively studied.[8] Data obtained were patient characteristics, RA disease activity and laboratory measures. Treatment history including non-steroid anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids and biologics were collected from the records.

Patients were divided into 2 groups based on haemoglobin levels; into those with anaemia and without anaemia. Anaemia was defined as haemoglobin (Hb) level <13 g/dl in males and Hb level <12 g/dl in females, based on WHO criteria for anaemia.[9] Cut off of ferritin to define ACD was set at 50 ng/ml.

Baseline information was collected from questionnaires that were completed by rheumatologists during consultations. Information included patients demographics, treatment details, disease characteristics like fatigue and morning stiffness, patient/physician assessment of RA disease activity by the visual analogue scale (VAS: 0-100 mm), and the Disease Activity Score in 28 joints (DAS 28 ESR). Haemoglobin, ferritin, MCV and ESR were measured for all patients.

Statistical analysis:

Data and statistical analysis were done using the Statistical Package for Social Science (SPSS) version 22. Descriptive Statistics included the mean and Standard Deviation (SD) for quantitative variables. Comparisons of baseline characteristics by the presence or absence of anaemia were performed using a Student t-test for quantitative variables, and Pearson's Chi-square test for categorical variables. The relation of haemoglobin concentration to patients characteristics, disease characteristics and laboratory analysis, was tested using a univariate regression model. The univariate analysis was used to explore the relationship between haemoglobin status and each individual variable. Multivariate analysis was used to examine the relationship of haemoglobin status with all variables simultaneously. Odds ratio (OR) were reported with 95% confidence intervals (CI)

Results

Table 1 displays the patient characteristics of our study population. The mean age of the study population was 50.7 years with a range of 18 - 88 years. 79% of the patients had symptoms of RA for a period of longer than 1 year before a diagnosis was made, 69% of the patients under care had been diagnosed with RA in the last 5 years.

Table 1: Patient characteristics

Age, mean (SD) years	50.7(17.8) 18-88
Age groups, number(%) <30 31-49 50-69 >69	 27(13.4) 58(28.9) 82(41.2) 33(16.5)
Gender, number(%) Male Female	 27(13.4) 173(86.6)

The prevalence of anaemia was 33% in the study population. 24.7% of the patients in the study population had ACD while 8.3% had IDA. The mean haemoglobin for males was 11.8 g/dl with a median of 12.7g/dl and interquartile range(IQR)-(11.3-13.5g/dl). The mean haemoglobin for the female patients was 12.5g/dl with a median 12.9 (IQR- 11.9-13.7.) The levels of other important blood parameters are summarized in Table 2.

Table 2: Laboratory findings

Parameter	Mean(SD)	Range
ESR (mm/hr)	37.3(16.3)	1.0-75
S. Ferritin(ng/ml)	73.3(37.1)	6.9-1977.0
Hemoglobin (g/dl)	12.4(2.3)	3.0-15.7
MCV(fL)	82.8(7.9)	63.0-99.0

The DAS 28 ESR showed that most patients had moderate to high disease activity, with 59% of the patients having moderate disease activity while high disease activity was seen in 33% of the patients. Only 4% of the patients were on remission, and another 4% had low disease activity. None of the patients with low disease activity and in remission had anaemia. Out of 66 patients with anaemia 45 (68.3%) patients had high disease activity. There was a statistically significant increased chance of being anaemic as the disease activity score increased from remission to high disease activity(P<0.001). Being male was significantly associated with being anaemic with a p-value of 0.008. Males constituted only 13% of the study population and out this 20 (30.3%) patients had anaemia. There was no significant association of anaemia with the patient's age or the time since the diagnosis of RA. The study did not reveal any significant association between the duration of illness and the presence of anaemia.

Table 3: Relation of anaemia with baseline characteristics

	With anemia (N=66)	Without anemia(N=134)	P value
Age, mean (SD) years	50.6(16.8)	50.8(18.4)	0.797
Gender Male, N (%) Female, N (%)	 20(30.3) 46(69.7)	 7(5.2) 127(94.1)	 0.008
DAS28ESR Severe(>5.2)	 45(68.2)	 21(15.7)	 <0.001
Duration since diagnosis of RA <1 yr 1yr-5 yrs >5 yrs	 18(27.3) 28(42.4) 20(30.3)	 46(34.3) 41(30.6) 47(35.1)	 0.173 0.236 0.306
Patients on NSAIDs, N(%)	44(66.7)	90(67.2)	0.870
Patients on DMARDs, N(%)	54(87.1)	118(88.1)	0.012

The commonest drug used by the patients was methotrexate seen in 77% (n=154) of the study population while 67% (134) of the patients were regularly on NSAIDs. The use of corticosteroids was seen in 54.9% of the patients. 100% of the patients who were on methotrexate were on folate 5mg supplementation. The other DMARDs used in the study population were hydroxychloroquine, leflunomide and sulphasalazine. None of the patients was on biologic agents.

The study results demonstrated that the use of DMARD was associated with a reduced likelihood of patients being anaemic. The introduction of any DMARD medication was protective of anaemia (p-value of 0.012). The use of methotrexate alone or in combination was significantly associated with the reduced possibility of patients getting anaemia p-value (0.044). The study demonstrated that NSAID use over a period of more than one year was associated with an increased likelihood of a patient having anaemia. Anaemia was seen in around 40% of patients who had been on an NSAID for more than a year. Further sub-analysis of the form of anaemia in RA patients taking NSAID for more than one year showed that ACD is more than IDA as expected(ACD=72.7% ,IDA=27.3%).

Discussion

The prevalence of anaemia in the study was 33% of the study population. Borah DJ et al studied RA patients in the past 2 years in a rural Northern India outpatient clinic at Kashmir and found the prevalence of anaemia to be 64% while Aggarwal et al. in Lucknow found a prevalence of 70.6% when he did a 2 year prospective follow up of 214 patients with RA.[5,7] Possible reasons for the differences can be due to the study design and difference in study populations. The likely reasons considered for high anaemia burden among Indians were insufficient dietary intake, being a predominant vegetarian society with limited nutritional iron sources, and chronic blood loss from hookworm infestations in rural areas. Another reason which can account for the significant disparity in the prevalence is the difference in the number of patients on DMARDs in the two populations. Also, the study in India by Aggarwal was carried out around 9 years ago.[7] There has been a great improvement in knowledge of the subject which may translate to better care now. Lastly, our study was done in a highly preselected population, being followed up in a tertiary setting and hence had improved care and ability to access quality health care.

Our study showed that 75% of the cases of anaemia were ACD while IDA accounted for 25%. The findings were similar to studies done in other centres. Borah DJ et al. study in India found a prevalence of 65% and 33% respectively for ACD and IDA in RA patients while Davis D et al. in the United Kingdom found a prevalence of ACD in RA to be 67%.[5,11] The high prevalence of ACD may be explained by inadequate control of the disease as it was found that ACD was the common form of anaemia in those patients with moderate and high disease activity. Delayed diagnosis is also a possible major contributing factor to the high ACD burden.

The study did not demonstrate any significant association between IDA and the use of NSAIDs/steroids (P-value 0.870). However, the patients who had been on NSAIDs for more than one year were likely to have anaemia (P-value 0.033). But the predominant anaemia was still ACD as opposed to IDA which would have been the expected finding. In our study 73% of the RA patients on NSAID had ACD, and 27% had IDA. This could possibly be explained due to the regular prescription of proton pump inhibitors among the patients on long term NSAID prescriptions. This also reflects the failure of clinicians to adequately adjust treatment once the resolution of the severe pain had occurred. ACD in these patients is due to inadequate control of mild chronic inflammation.

There was a statistically significant relationship between high disease activity and the occurrence of anaemia. Multivariate analysis also found that disease activity was independently associated with anaemia. Similar findings have been reported by other authors; Aggarwal et al. found anaemic patients had severe disease activity with a mean DAS of 5.3 compared to non-anaemic patients who had moderate disease activity (3.3-5.1) with mean disease activity of 3.83.[7] Borah DJ and Aggarwal et al. demonstrated that there was an inverse correlation between haemoglobin level and the disease activity score.[5,7]

Anemia tended to be commoner among males with 45% of them being anaemic (P <0.008). This finding in our study has been less reported in literature elsewhere. The finding could be by chance due to the small number of patients studied although multivariate analysis showed this variable to be independently associated with anaemia. Other possible explanation for this finding could be poor health-seeking behaviour in males and delay in diagnosis of RA. A literature search did not yield any study which has correlated anaemia with gender in patients with RA.

The initiation of any DMARD reduced the likelihood of anaemia (P-value 0.012). Subgroup analysis of drugs showed that methotrexate reduced the chance of a patient being anaemic (P-value 0.044). The introduction of DMARDs/methotrexate leads to control of the inflammatory process hence this protects the patients from being anaemic due to ACD.[12]

Conclusion

Our study shows that the burden of anaemia in our RA patients was lower compared to studies from other regions. Anaemia correlates very well with disease activity, and those patients with anaemia tend to have high disease activity scores. The commonest anaemia type is ACD, which means disease control is still not adequate. The screening of anaemia should be a part of the RA management program, and appropriate treatment should be instituted. The initiation of DMARDs is protective of anaemia. Men form a small percentage of patients with RA, but when they present, they have more severe disease and severe anaemia. Additional large-scale studies on the prevalence and anaemia-related outcomes and the influence of gender on anaemia in RA should be done in developing countries like India, to establish the importance of anaemia screening and treatment in RA.

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