British Journal of Medicine & Medical Research
4(17): 3248-3254, 2014

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A Controlled Trial of Oral Rifampin in Chronic Plaque Psoriasis

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Authors' contributions

This work was carried out in collaboration between all authors. Author VNS designed the study, wrote the Protocol. Authors LD, JD and NK wrote the draft of the manuscript managed the analyses of the study and literature searches. All authors read and approved the final manuscript.

Original Research Article

Received 4th February 2014
Accepted 7th March2014
Published 20th March 2014

ABSTRACT

Group A Streptococcal infection in the throat is responsible for causing initial and recurrent attacks of acute guttate psoriasis (AGP). Up to 70% of these AGP patients go on to develop chronic plaque psoriasis (CPP). We hypothesized that chronic sub-clinical, on-going streptococcal infection might solely be responsible for CPP in a genetically predisposed individual.

Rifampin, a useful drug for several types of bacterial infections including Group A Streptococci (GAS) because of its broad spectrum, excellent tissue penetration, low side-effect profile and its salivary concentrations after oral administration greatly exceeds the minimum inhibitory concentration for most GAS, thus helpful in eradicating pharyngeal carriage of GAS, was considered for long term use in CPP.

Fifty patients with moderate to severe CPP were enrolled. Of these 25 were randomly selected to receive rifampin for 36 weeks as a single oral morning dose of 10 mg/kg body weight (approx. patient weighing <50 kg received 450mg per day and patients >50 kg received 600mg per day). Remaining 25 patients received placebo. Rifampin group was further followed-up to one more year.

Significant improvement in PASI score was noted from 12 weeks in majority of patients in

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Rifampin group. Relevant investigations and clinical assessment was done at regular intervals to observe any side effects and check progress of the disease. Data were analyzed statistically using the t-test.
As psoriasis is a chronic disorder that waxes and wanes over time, withdrawal of treatments usually is accompanied by relapse of skin manifestations so a follow-up with one year drug-free period was added to verify treatment consistency. Patients tolerated the therapy well.

Keywords: Chronic plaque psoriasis; rifampin; group A streptococci; extended dosage.

1. INTRODUCTION

Streptococci as a major factor of importance in causation of chronic plaque psoriasis (CPP) may revolutionize the therapeutic approach to this disease. Psoriasis with the hallmark of waxing and waning course can be more effectively prevented or treated by an extended course of anti microbial treatment that probably eradicates streptococcal sub-clinical infection than by continuous suppression of cell-division by immune-suppressive agents.

Four lines of evidence support the hypothesis that persistent streptococcal infection is a major factor in causing CPP:

First, Group A Streptococci (GAS) infection in the throat is responsible for causing initial and recurrent attacks of acute guttate psoriasis (AGP) [1,2]. Of these AGP cases approx. 33 to 68 percent go on to develop typical plaque psoriasis [3,4].

Second, induction of psoriatic lesions following inoculation of killed streptococcal material has been observed and such inoculate has provoked exacerbation of psoriasis at distant sites [5].

Third, the blood levels of IgG antibodies reactive to secreted Streptococcus pyogenes proteins had been shown to be increased in CPP (when compared to age- and sex-matched controls). Further, blood from the psoriasis and control groups had similar titers of IgG for various other bacteria tested [6].

And finally, the observation of the beneficial effects of antimicrobial like benzathine penicillin [7] and azithromycin [8] in extended dosage schedule in such patients. Thus, we hypothesized that sustained sub-clinical streptococcal infection might solely be responsible for CPP.

Rifampin, a useful drug for several types of bacterial infections including GAS because of its broad spectrum, excellent tissue penetration, low side-effect profile and its salivary concentrations after oral administration greatly exceeds the minimum inhibitory concentrations for most GAS, [9] thus helpful in eradicating pharyngeal carriage of GAS was carefully considered for long term use in CPP. Previous Bulgarian experience with rifampin in the treatment of psoriasis yielded encouraging results however, their therapeutic approach in psoriasis was attributed primarily to its immunosuppressive properties. [10]

2. MATERIALS AND METHODS

Fifty patients with moderate-to-severe CPP were enrolled. Disease duration was 5 months to 29 years. Age ranged from 19 to 66 years. Of these 25 were randomly selected to receive rifampin for 36 weeks as a single oral morning dose of 10 mg/kg body weight-either 450mg/day (<50 Kg) or 600mg/day (>50 Kg). Remaining 25 patients received placebo as per this schedule.

Informed consent was obtained from all patients enrolled in this controlled trial. A history of psoriasis in other family members was recorded. Criteria for exclusion included pustular psoriasis, a history of complete spontaneous remission of the disease, pregnancy and other associated systemic diseases, specifically with hepatic involvement. Patients taking any prior medication were advised to discontinue the same for two weeks before they were enrolled in this trial.

In all the patients, routine blood counts, Anti-Strepto-lysin-O (ASLO) titer, C-reactive proteins, blood sugar, blood urea, serum creatinine and liver function tests were done. No local treatment except mineral oil was applied. No corticosteroid, coal tar preparations or any other therapeutic preparation in the form of cream, ointment or lotion was advised.

The disease severity was evaluated every 4 weeks using a clinical scoring system- the Psoriasis Area and Severity Index (PASI).

The total duration of on-drug period was 36 weeks but those in rifampin group were followed up for another one year to precisely confirm that the results were not attributable to spontaneous remission of the disease and whether or not withdrawal of treatment was accompanied by a relapse of skin manifestation.

Data were analyzed statistically using Student t-test.

3. RESULTS

41 patients (out of total 50 enrolled initially) completed the 36 week trial period. 17 patients had a positive ASLO titer (>200IU/ml) of which 9 were in the study group. At the end of 36 weeks titer became negative in all patients in study group. C-reactive protein was initially positive in 10 patients in study group, which became negative in all, at 36 weeks.

Statistically significant data is tabulated in Tables 1-4. Table-1 shows Mean $\pm$ S.D of PASI Score at various interval of Case and Control group subjects, just to show the effect of treatment. Here t-test is not applied. Significant improvement in PASI score was noted from 12 weeks in majority of patients in rifampin group (Table-2). Table-4 shows Mean change ($\pm$ S.D) in PASI Score from the point of induction to various interval of Case and Control group subjects which is highly significant (HS) at all intervals ($p<0.001$).

At the end of 36 weeks, 20 patients (80%) showed excellent improvement, while 2 patients (8%) showed good improvement and 2 patients (8%) showed mild improvement. 8 patients (32%) in the control group and 1 patient (4%) in study group did not complete the prescribed duration of study. Figure shows the comparative Mean PASI score of psoriasis patients taking treatment and controls at various time intervals.

Drop out participants from a study, have a special significance in situation like psoriasis, with no hard end point, as this strongly reflects dissatisfaction with treatment results.

At the end of one year follow-up an exacerbation in lesions (relapse) was reported in 5 cases (20%).

Patients tolerated the therapy well except for complaints of nausea in 7 cases and abdominal discomfort in 3 cases in the study group while 'on-drug' but did not require discontinuation of treatment.

Table 1. Mean ± S.D of PASI Score at various interval of case and control group subjects

Group	Basal	At 12 weeks	At 24 weeks	At 36 weeks
Case (n=24)	17.41±3.86	9.67±2.98	2.02±1.50	2.78±3.39
Control (n=14)	15.16±2.29	15.16±2.29	14.96±2.09	14.98±2.11

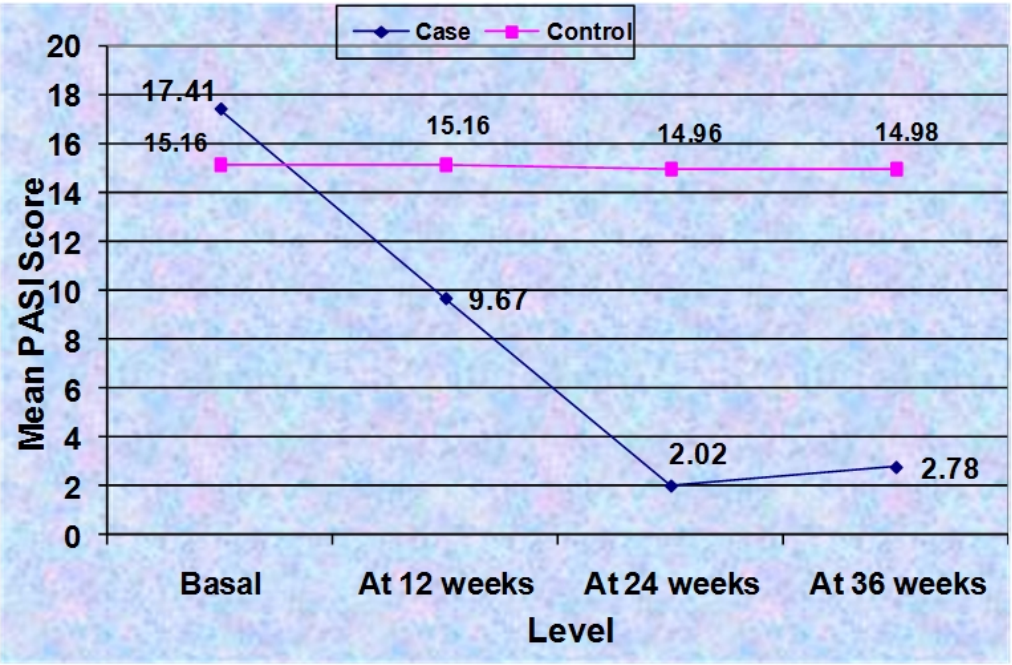

Figure showing mean PASI score in both Case/Control groups at various time interval

Table. 2 Mean change (± S.D) in PASI Score from basal to various intervals of Case group subjects

	At 12 weeks	At 24 weeks	At 36 weeks
Mean change ± S.D	7.74 ± 3.00	15.39 ± 4.04	14.63 ± 3.64
p- value	< .001	< .001	< .001
Significance	HS	HS	HS

Table. 3 Mean change (± S.D) in PASI Score from basal to various intervals of Control group subjects

	At 12 weeks	At 24 weeks	At 36 weeks
Mean change ± S.D	0	0.19±0.38	0.17±0.37
p- value	-	> .05	>.05
Significance	-	NS	NS

Table. 4 Mean change (± S.D) in PASI Score from basal to various intervals of Case and Control group subjects

	At 12 weeks	At 24 weeks	At 36 weeks
Case	7.74±3.00	15.39±4.04	14.63±3.64
Control	0±0.00	0.19±0.38	0.17±0.37
p- value	< .001	< .001	< .001
Significance	HS	HS	HS

4. DISCUSSION

Psoriasis is not a dermatologic illness alone, but is linked to obesity, metabolic syndrome, PCOS [11] and also probably shares an infective etiological component via C pneumonia with coronary artery disease (CAD) [12].

Our understanding of complex mechanisms of induction and maintenance of psoriatic lesions is evolving [13]. The reason for failure to demonstrate streptococcal organisms by throat swab is because of the organisms ability to become intracellular and thus undetectable by routine throat swab examination [7,8]. And once intracellular in tonsillar epithelial cells, they are not eradicated by routine dosage of penicillin and require extended dosing schedules.

Regardless of the extended dose antimicrobial regimen used, successful eradication of Streptococcal infection markedly reduces the risk of recurrence. GAS can survive up to 7 days intracellular in immortalized human respiratory epithelial cells grown in an antibiotic supplemented medium. Whenever the extra cellular antibiotic was withdrawn viable GAS externalized and established as extra cellular infection [14].

Tonsillectomy as an approach of eradicating GAS carrier status, has been advocated by some authors, although this approach fails to consider that many children and young adults who are believed to have had multiple episodes of GAS pharyngitis are instead GAS carrier with inter-current non-streptococcal illness [15].

In any particular patient it is impossible to predict whether or when a relapse or remission will occur, [16] therefore rifampin was considered for use, predicting its antibacterial activity against intracellular GAS reservoir [14] and its promising results when used over an extended period [10].

Previous Bulgarian experience with rifampin in the treatment of psoriasis indicated towards its therapeutic efficacy via its immunosuppressive property [10] however, considering the clearing of plaque lesions with long term benzathine penicillin in earlier trial [7], improvement of psoriasis after tonsillectomy [17] and research work at Leicester University, UK [6] its

antibacterial role against Streptococci seems more plausible. Also, had the initial improvement with rifampin been due to its immunosuppressive action alone, a decreased relapse rate during the 1-year follow up period (as witnessed in our study), cannot be explained. Further, considering chronic sub clinical infection in disease causation, immune-suppressants are unethical as the primary pathology remains unattended. Hence, the authors strongly predict that the primary role of Rifampin in psoriasis may be attributed to its anti bacterial action, albeit immunosuppressive properties may have a synergistic effect manifesting as faster lesion clearing and improvement in PASI scores.

5. CONCLUSION

Thus, we conclude that with the use of oral rifampin in CPP, majority of the patients witnessed excellent long-term clearing of their lesions with no major adverse effects. Rifampin may provide a scientific baseline for further research to help identify potential anti-streptococcal interventions in CPP.

6. PREVIOUS PRESENTATION

This article was presented at 22nd World Congress of Dermatology, Seoul, 2011.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

ACKNOWLEDGEMENTS

Authors acknowledge the help of Mr. M.C.Vyas, Statistical Assistant, Central Bureau of Health Intelligence, Jaipur of Statistical analysis of our data.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Baker BS, Bokth S, Powles A, Garioch JJ, Lewis H, Valdimarsson H, et al. Group A Streptococcal antigen-specific T lymphocytes in guttate psoriatic lesions. Br J Dermatol. 1993;128:493-9.
2. Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. Arch Dermatol. 1992;128:39-42.
3. Williams RC, Mckenzie AW, Roger JH, et al. HLA antigen in patients with guttate psoriasis. Br J Dermatol. 1976;95:163-7.

4. Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of guttate psoriasis? Arch Dermatol. 1996;132:717-8.
5. Rosenberg EW, Noah PW. The koebner phenomenon and the microbial basis of psoriasis. J Am Acad Dermatol. 1988;18:151-2
6. El-Rachkidy RG, Hales JM, Freestone PPE, Young HS, Griffiths EM, Camp RDR. Increased blood levels of IgG reactive with secreted streptococcus pyogenes protein in chronic plaque psoriasis. J Invest Dermatol. 2007;127:1337-42.
7. Saxena VN, Dogra J. Long term use of penicillin for the treatment of chronic plaque psoriasis. Eur J Dermatol. 2005;15:359-62.
8. Saxena VN, Dogra J. Long term oral azithromycin in chronic plaque psoriasis: a controlled trial. Eur J Dermatol. 2010;20(3):329-33.
9. Mc Cracken GH Jr, Ginsburg CM, Zwieghaft TC, Clansen J. Pharmaco-kinetics of rifampin in infants and children: Relevance to prophylaxis against Haemophilus influenza type-b disease. Pediatrics. 1980;66:17.
10. Tsankov N, Grozdev I, Kazandjieva J. Eruptive psoriasis and treatment with rifampicin. Trakia J Scien. 2005;3(4):21-6.
11. Savastano S, Balato N, Gaudiello F, Di Somma C, Brancato V, Colao A, et al. Insulin-like growth factor-1, psoriasis and inflammation: A ménage a trios? Eur J Inflam. 2011;9:277-83.
12. Dogra J. Oral azithromycin in extended dosage schedule for chronic, sub-clinical Chlamydia pneumonia infection causing coronary artery disease: a probable cure at sight? Results of a controlled preliminary trial. Int J Gen Med. 2012;5:505-9.
13. Wardrop P, Weller R, Marias J, Kavanagh G. Tonsillitis and chronic plaque psoriasis. Clin Otolaryngol. 1998;23:67-8.
14. Osterlund A, Popa R, Nikkila T, Scheynius A, Engstrand L. Intracellular reservoir of streptococcus pyogenes in-vivo: A possible explanation for recurrent pharyngo-tonsillitis. Laryngoscope. 1997;107:640-7.
15. Tanz RR, Shulman ST, Barthel MJ, Willert C, Yogev R. Penicillin plus rifampin eradicate pharyngeal carriage of group A streptococci. J Paediatr. 1985;106:876-80.
16. Hone SW, Donnelly MJ, Powell F, Blaney AW. Clearance of recalcitrant psoriasis after tonsillectomy. Clin Otolaryngol. 1996;21:546-7.
17. Thorleifsdottir RH, Sigurdardottir SL, Sigurgeirsson B, Olafsson JH, Sigurdsson MI, Petersen H et al. Improvement of psoriasis after tonsillectomy is associated with a decrease in frequency of circulating T cells that recognize streptococcal determinants and homologous skin determinants. The Journal of Immunology. 2012;188:5160-5.

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