Original Article

Oral Ivermectin as a Therapeutic Agent in Patients with Scabies

Eman M.H. Méabed

Department of Parasitology, Faculty of Medicine, Fayoum University, El Fayoum, Egypt

Objective: To evaluate oral Ivermectin as a therapeutic agent to ordinary scabies.

Methodology: Random sample of 50 cases of ordinary scabies was treated with two oral doses of Ivermectin, 200 µg/kg one week apart. The effect of the drug was monitored clinically, by complete blood count, and confirmed parasitologically at the time of clinical presentation and at week 4 of starting treatment. ELISA and Immunobloting using *Sarcoptes scabiei* crude mite extract were applied to determine the levels of specific IgG and IgE in patients' sera in comparison with 50 controls.

Results: The reported cure rate was 100%. However, 8% cases continued to have persistent itching, accompanying eosionophilia and high IgE levels.

Conclusion: Ivermectin proved to be effective and promising drug for treatment of ordinary scabies. (Rawal Med J 2013; 38:127-130).

Key words: Scabies, Ivermectin, ELISA, Immunoblotting.

INTRODUCTION

Scabies is a highly contagious and pruritic parasitic infestation. It is re-emerging in the new millennium especially with HIV pandemic causing a significant health problem in developing countries affecting both sexes, all ages and all socioeconomic levels.[1] The mainstay of therapy in the present era is topical.[2-4] Ivermectin is the only available oral scabicide that selectively binds and persistently opens glutamate-gated chloride channels in nerves and muscles causing cell death.[3] The drug has been approved for treatment of scabies in France since 2001 and used off-label in other countries using 200 µg/kg in a single dose, which may be repeated after one week.[4] It has insignificant side effects as transient tachycardia, flushing, nausea, rarely fever, headache, myalgia, and or maculopapular rash.[2] There is a paucity of high-quality studies that evaluate oral Ivermectin for scabies treatment. A Cochrane review compared studies between oral Ivermectin, and other topical drugs as 5% Permethrin, Lindane and topical benzyl benzoate.[1,5,6] There are no recent reports that correlate clinical and parasitological response with the immune response of patients. The aim of this study is to evaluate oral Ivermectin as a therapeutic agent to ordinary scabies and to correlate the clinical and parasitological response of patients with their immune response.

METHODOLOGY

The study included random sample of 50 clinically diagnosed cases of ordinary scabies from Dermatology outpatient clinic, Senores General Hospital, Fayoum Governorate, Egypt from December 2011 to February 2012. It was approved by Fayoum University Ethics Committee and informed consent was obtained from each participant in the study. Their age ranged from 5-60 years of either sex. Exclusion criteria done according to.[1] Patients with other parasitic diseases were excluded from the test by stool and urine analysis. Urine was examined by sedimentation and stool by Kato thick smear technique.[7] Patients were subjected to various test items at the time of clinical presentation and at week 4 after first dose of treatment. Secondary infection if present was treated with antibiotic. Ivermectin oral tablets in a dose of 200 µg/kg were administered and repeated after one week. Patients were instructed for decontamination of bed covers, personal clothes and to avoid using any other antiscabietic or antihestaminics during the study period. Cure was reported with complete absence of lesions and negative parasitological examination at the end of week 4. The study also included 50 healthy volunteers as a control for hematological and serological tests. Participants filled questionnaire

including personal data, weight, history suggestive of scabies, other diseases and treatment history. Cases diagnosed clinically then confirmed by parasitological examination.[8] Total Leucocytic Count (TLC), with special emphasis on peripheral eosinophils measured using automatized analyzer, Sysmex S.E. 9000. From each subject, 5 ml blood was taken, serum was separated, aliquoted and kept frozen for serological tests; ELISA and Immunobloting.

Antigen*: Sarcoptes scabiei* crude mite extract (SSCME) was prepared from mites collected from an infected dog as described,[9] with modification. Total protein concentration in the extract was measured.[10] ELISA**:** was performed to determine the levels of specific anti-*S. scabiei* IgG and IgE in participants' sera.[11] Electrophoresis and Western Immunoblotting Assay (EITB): were applied to further characterize the results obtained by ELISA and to reveal the specific bands for each antibody. The antigen was fractionated,[12] then the proteins were transferred to nitrocellulose paper strips and treated with diluted patients' sera in comparison with negative control sera.[13] Conjugates used were Peroxidase conjugated mouse anti-human IgG and IgE (whole molecules, Sigma Immunechemicals).

Statistical analysis: SPSS version 14 used to determine Mean and standard deviation (SD) for values. P-values were calculated using repeated measure Anova test. P≤0.05 was considered statistically significant.

RESULTS

The main results of clinical and parasitological examination of patients are shown in Table 1. The results revealed the highly significant cure rate 100% of cases at week 4 of treatment (P≤0.05). Some side effects were reported by patients after 1st dose of treatment but they were self limiting. They were nausea, headache and muscle pain in 6%, 8% and 4% of cases respectively. Changes of blood parameters, immunoglobulin levels are shown in table2 and table3 respectively.

Table 1. Clinical and parasitological changes with treatment (n=50)**.**

Diagnostic test		Before Treatment	Post treatment
Nocturnal pruritus	+++	n=50 (100%)	n=4 (8%) = PTCI
	Nil	0%	n=46(92%) = PTRI
Papules/ patient		15 ± 5	- ve (100%)
Burrows/ patient		16 ± 7	- ve (100%)
Parasitological		+ ve (100%)	- ve (100%)

PTCI= Post treatment continued itching,
PTRI= Post treatment relieved itching,
Values are Mean ± SD

Table 2. Changes of blood parameters in comparison with healthy controls**.**

Groups	TLC ($x10^9$ /L)	Peripheral blood eosinophils (%)
Before treatment	6.89 ± 2.4	11.9 ± 0.21
PTRI	6.71 ± 2.3	5.64 ± 0.1
PTCI	6.68 ± 1.4	8.96 ± 0.2
Control	6.7 ± 3.4	3.62 ± 0.8
P-value	≤ 0.01	≤ 0.01

Values are mean ± SD

Table 3. Changes of IgG and IgE levels in comparison with healthy controls.

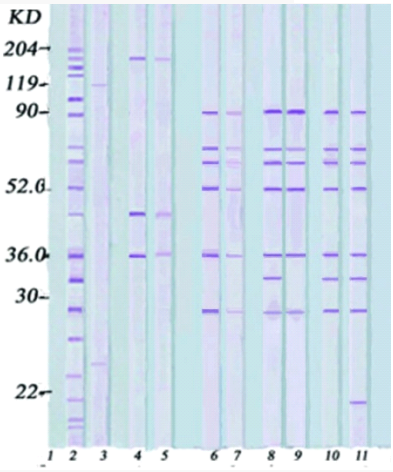
ELISA OD values	IgG	IgE
Before treatment	0.61 ± 0.35	0.47 ± 0.16
PTRI	0.38 ± 0.11	0.25 ± 0.12
PTCI	0.34 ± 0.25	0.54 ± 0.12
Control	0.2 ± 0.02	0.11± 0.09
P-value	≤ 0.01	≤ 0.01

Values are mean optical density (OD) ± SD.

The results of Fractionation of SSCME are shown in Fig1 (Lane 2) with more than 17 bands having molecular weight of ≥ 204, 180, 158, 123, 103, 89 , 69, 66, 52, 43, 36, 34, 29, 26, 24, 21, 12.5 and 11 kDa . The figure also shows that in comparison with control (Lane 3), sera of 100% of patients showed IgG binding to 3 scabies specific bands with MW; 180, 43 and 36 kDa (Lane 4), that decreased in intensity after treatment (Lane 5).

Sera of 100% of patients showed IgE binding with 6 bands with MW; 89, 69, 64, 52, 36 and 29 kDa (Lane 6) that became faint in PTRI (Lane7) and continued to be intense in PTCI (Lanes 8-11) with appearance of one or two additional bands with MW (34 & 21 kDa).

Fig 1: Results of EITB reaction.



Lane 1: low molecular weight protein standard. Lane 2: SSCME antigenic fractions. Lane 3: reaction with negative control serum.
Lanes 4-5 (IgG) and 6-11 (IgE) specific reactive bands respectively

DISCUSSION

Topical scabicidal drugs have many limitations, they may be poorly tolerated or need to be repeated several times. Patients' contacts need to be treated also leading to increasing cost. This justifies the search for an easy administered treatment involving a single dose and with minimal adverse effects.[2,6] The present study showed that oral Ivermectin 200 µg/kg in two repeated doses one week apart is effective scabicidal agent since it showed highly significant cure rate 100% that agreed with several studies.[3,6,14,15] Sule & Thacher[16] reported no more than 95% cure rate using the same regimen. Goldust et al.[17] reported 100% cure rate with only one single oral dose of Ivermectin 200µg/kg. However, Ivermectin has not been proved to be ovicidal,[2,4] and a single dose may be inadequate to kill the newly hatched mites, and a higher or a second dose may be required within one or two weeks for 100% cure rate.

The only mild, self-limited side effects reported in this study, ensure that the drug is safe and well tolerated and agrees with previous studies.[2,3,4] However, lack of data about drug safety in pregnant women and children younger than 5 years whom were excluded from this study limits its wide scale use despite its high cure rate. Additional drawback that oral Ivermectin is not very effective in relieving pruritus. This comes with Bachewar et al.[6] and may cause a major clinical problem that face physicians since the underlying cause may be reinfection, drug resistance or drug failure that may require changing the treatment regimen or repeated treatment.[8] Another possible cause is stimulation of allergic reaction by dead mites' antigens and their products which are still present in the stratum corneum and aren't removed from skin except after a long time.[18] In this situation studying the immune response of the patients helps to differentiate allergic from other causes of continued itching. The results of this study showed that allergy was reported in the cases with continued itching (PTCI) as indicated by the significantly continued increase of peripheral eosinophilia and IgE values in ELISA and EITB and agreed with Arlian &Morgan.[19]

An antigen from dog mite was used in this study due to difficulty in obtaining human mites since they are few in ordinary scabies. Also, due to proved cross reactivity between human and dogs' mite antigens.[20] The MW of bands detected by Fractionation of SSCM antigen was in range with Arlian et al.[21] In addition, the MW of IgE and IgG binding bands detected by EITB technique was in range with the same study.

The higher number of bands identified by IgE more than those by IgG antibodies may indicate the importance of IgE antibodies in the immune response to invasive parasitic infections through immediate hyper sensitivity reaction.[22] The continued intensity of IgE binding in PTCI patients than in patients with relieved itching PTRI with appearance of new bands confirmed the results obtained by ELISA and agreed with an earlier study by Tarigan,[23]

CONCLUSION

Oral Ivermectin is effective, well tolerated and simpler to use for treatment of scabies. However, the drug is not fully effective in relieving pruritis.

ACKNOWLEDGEMENT

To Professor Dr. Mohamed M. El Bahy, Professor of Parasitology Vet. Medicine Cairo University for help in the serological study. Also to the staff of Dermatology Clinic, Senores General Hospital, Fayoum Governorate, for their much help in clinical diagnosis and sampling and For Dr. Wafaa, Y. Abed Elwahed Lecturer for Community Medicine Fayoum University for revising the statistical part.

Conflict of Interest: None declared

Corresponding author email:emeabed@gmail.com
Rec. Date: Nov 16, 2012 Accept Date: Jan 12, 2013

REFRENCES

1. Sharma R, Singal A. Topical Permethrin and oral Ivermectin in the management of scabies: A prospective, randomized, double blind, controlled study. IJDVL.2O11; 77(5): 581-586.
2. Saqib M, Afridi IU, Ali A, Jahangir M. Scabies saftey of permetherin and ivermectin. Professional Med J. Feb 2012; 19(1):086-092.
3. Khan I, Yasmin R. Ivermectin in the treatment of Scabies. Journal of Pakistan Association of Dermatologists. 2007; 17:78-83.
4. Currie BJ, McCarthy JS. Permethrin and Ivermectin for scabies. New Eng J Med. 2010;362:717-25.
5. Strong M, Johnstone PW. Intervention for treating scabies. Cochrane Database Syst Rev. 2007; 3: CD000320.
6. Bachewar NP, Thawani VR, Mali SN, Gharpure KJ, Shingade VP, Dakhale GN. Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and ivermectin in patients of scabies. Indian J Pharmacol. 2009; 41:9-14.
7. Katz N, Chaves A, Pellegrino J.A simple device for quantitative stool thick-smear technique in *Schistosomiasis mansoni*. Rev Inst Med Trop Sao Paulo. 1972; 14: 397-400.
8. Michigan Department of Community Health: MDCH. Scabeies prevention and control manual. 2005; Version 1.0 online PDF document.
9. Elder BL , Arlian LG , Morgan MS. *Sarcoptes scabiei* (Acari: Sarcoptidae) Mite Extract Modulates Expression of Cytokines and Adhesion Molecules by Human Dermal Microvascular Endothelial Cells. J Med Entomol. 2006; 43(5): 910–915.
10. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem. 1976; 72:248–254
11. Voller A, Bidwell D, Bartlett A .Enzyme immunoassays in diagnostic medicine. Theory and Practice. Bulletin of the World Health Organization, 1976; 53: 55-65.
12. Laemmli UK. Cleavage of structural proteins during the assembly of the head of Bacteriophage T_4. Nature. 1970; 227:680-687.
13. Towbin H, Staehelin T, Gordon J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. Proc. Natl. Acad. Sci. U. S. A 1979;76:4350-4.
14. Worth C, Heukelbach J, Fengler G, Walter B, Liesenfeld O, Hengge U, et al. Acute Morbidity Associated with Scabies and Other Ectoparasitoses Rapidly Improves After Treatment with Ivermectin. Pediatr Dermatol 2012;29:430-6.
15. Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. IJVDL 2012;78:605-10.
16. Sule HM, Thacher TD. Comparison of Ivermectin and Benzyl benzoate lotion for scabies in Nigerian patients. Am J Trop Med Hyg 2007;76:392-5.
17. Goldust M, Rezaee E, Hemayat S. Treatment of scabies: Comparison of permethrin 5% versus ivermectin. J Dermatol 2012;39:545-7.
18. Arlian LG, Morgan MS. Serum antibody to Sarcoptes scabiei and house dust mite prior to and during infestation with S. scabiei. Vet Parasitol 2000;90:315-26.
19. Walton SF, Beroukas D, Roberts-TP, Currie BJ. New insights into disease pathogenesis in crusted (Norwegian) scabies: the skin immune response in crusted scabies. Br J Dermatol 2008;158:1247-55.
20. Arlian LG, Morgan MS, Arends JJ. Immunologic cross-reactivity among various strains of Sarcoptes scabiei. J Parasitol 1996;82:66-72.
21. Arlian LG, Morgan MS, Estes SA, Walton SF, Kemp DJ, Currie BJ. Circulating IgE in patients with ordinary and crusted scabies. J Med Entomol 2004;41:74-7.
22. Walton SF. The immunology of susceptibility and resistance to scabies. Parasite Immunol 2010;32:532-40.
23. Tarigan S. Antibody responses in naïve and sensitized goats infested by Sarcoptes scabiei. JITV 2004;9:258-65.