MILTEFOSINE IN TREATMENT OF OLD WORLD CUTANEOUS LEISHMANIASIS IN PAKISTAN

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ABSTRACT

Objective: To evaluate the efficacy of miltefosine in the treatment of cutaneous leishmaniasis

Study Design: Uncontrolled, open label, quasi-experimental study

Place and Duration of Study: The study was carried out in Military Hospital Rawalpindi and five other Army Hospitals from Jan 2006 to Aug 2006.

Patients and Methods: This study was dome to investigate the efficacy of treatment of cutaneous leishmaniasis patients with oral miltefosine in doses of 2.5 mg/kg/day at 6 centers in Pakistan. The study was conducted among 90 hospitalized adult cutaneous leishmaniasis patients. All patients completed the full 28-days treatment course.

Results: The study revealed excellent response in 32(28.8%), good in 38(34.4%), fair in 17(15.3%) and poor in 3(2.7%) patients. Treatment-related adverse events were transient rise in ALT (95%), followed by myalgia (33%), arthralgia (15%), nausea vomiting (12%), bad oral taste (2%), testicular pain (4%), cough (2%), conjunctivitis (2%) and fever (1%). All theses side effects were transient and settled on discontinuation of medication. Compliance was good

Conclusion: The use of oral miltefosine in doses of 2.5 mg/kg/day is effective & well tolerated in old world cutaneous leishmaniasis.

Keywords: Cutaneous leishmaniasis, Miltefosine, treatment trail

INTRODUCTION

Reduced efficacy, difficulties of administration, increasing frequency of adverse events and development of resistance to pentavalent antimony have stimulated the quest for new anti-leishmanial drugs. Several clinical studies testing injectable, oral and topical anti-leishmanial drugs have yielded inconsistent results. Oral hexadecylphosph-ocoline (Miltefosine) originally an anti neoplastic drug has been found to have a potent leishmanicidal activity as consequence of its interference in parasite metabolic pathways and the induction of apoptosis. It has demonstrated efficacy in old world L. donovani visceral disease and in new world L. panamensis cutaneous disease[1]. Studies regarding the use of this drug in treatment of old world cutaneous leishmaniasis are very scarce and have limitation of lesser number of patients been tested. Cutaneous leishmaniasis is a major public health problem in western and south western parts of Pakistan and both wet and dry type of leishmaniasis is seen caused by L major and L tropica. We conducted this study in a relatively larger number of patients to evaluate the effectiveness of oral miltefosine in treating Old world cutaneous leishmaniasis in Pakistan.

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MATERIALS AND METHODS

A multi centric uncontrolled, open label, quasi-experimental study was conducted from Jan 2006 to August 2006, to see the efficacy of oral miltefosine in treating old world cutaneous leishmaniasis. It was conducted in six military medical centers (Rawalpindi, Bahawalpur, Peshawar, Quetta, Malir and Multan) simultaneously. Miltefosine was donated by the kind courtesy of representatives of Nimral Pharma, Pakistan and Zentaris GmbH Frankfurt Germany. Approval to conduct this study was taken from the surgeon general and the ethics committee in the medical directorate. Informed written consent was taken from the patients. Same treatment protocol was followed in parallel in all medical centers. The history clinical features and laboratory findings were recorded on a specially prepared proforma in all cases. Patients included were both civilian

and soldiers who acquired infections mostly in the endemic areas. They were of either gender, aged 12 years or older, had parasitologically confirmed cutaneous leishmaniasis and did not have any other significant concomitant disease. They had normal blood counts, liver enzymes and renal function tests before the onset of therapy. Children less than 12 years of age, females of childbearing age and patients who were pregnant or lactating were excluded.

Ninety patients fulfilling the inclusion criteria were enrolled in the six centers. Each patient was started on oral miltefosine in a dose of 2.5mg/kg body weight which was continued for 28 days. Pre-treatment complete physical examination was done along with necessary laboratory investigations in all cases. Patients received medicine with meals in 2 divided doses. All patients were hospitalized during treatment and were daily interviewed for subjective adverse events. Blood samples were obtained for blood cell counts, liver function tests, renal function tests at two weeks and then at the end of treatment. Clinical evaluation for parameters of healing was done at day 0, day 15 and day 28. Clinical photographs were taken at that time. Parasitology was done before the onset and at the end of treatment period. Response was graded as excellent, good, fair or poor according to the criteria shown in table-1. The patients were advised to report back after three months for follow up if the lesions did not heal completely or there was a relapse of the lesion. Data had been analyzed using SPSS Version 10. Descriptive statistics were used to describe the data.

RESULTS

A total of 90 patients were included in the study belonging to a large variety of ethnic groups / castes. The duration of disease ranges from 5 - 15 weeks and all the patients were newly diagnosed cases of cutaneous leishmaniasis. The demographic characteristics of the patients are shown in Table-2. All patients completed the 28 days course of miltefosine showing good complia nce with medicine. Response was graded according to the grades of response to treatment as shown in table-2 and it was excellent in 32(28.8%), good in 38(34.4%), fair in 17(15.3%) and poor in 3(2.7%) patients. Only ten patients reported for follow up at three months interval all of which showed no evidence of relapse or untoward effect of medication. Most common treatment related adverse events were transient rise in ALT seen in 95% of cases. On day 1 average level of ALT was 38U/L, at day 15 average level rose to 57 U/L and fell down to an average of 52 U/L at day 28. Out of these 95% of patients 37.7% showed ALT with in normal range and rest had shown the decline in ALT at the end of treatment. This was followed by myalgia (33%), arthralgia (15%), nausea vomiting (12%), bad oral taste (2%), testicular pain (4%), cough (2%), conjunctivitis (2%) and fever (1%). All these side effects were transient and settled on discontinuation of medication.

Table-2: Patient's demographic data.

Age	**Range**	**19-42 years**
	Average	**30.1 years**
Sex	Male	86.6%
	Female	13.3%
Weight	Range	57-73 kg
	Average	65.3kg
No of lesions	Single	43%
	Multiple	57%
Site of lesions	Feet and legs	58%
	Hands and arms	27%
	Face	14.4%
	Trunk	1.1%

Table-1: grades of response to treatment.

Grade	Clinical	Parasitological
Excellent	Complete healing	no parasites
Good	Healed with residual swelling and redness	Parasite -ve
Fair	Partially healed	Parasite -ve
Poor	No change in the lesion	Parasite +ve

DISCUSSION

Antimonials are the mainstay of treatment in cases of cutaneous leishmaniasis. These compounds have the disadvantage of both toxicity and clinical resistance in certain regions where they have been in use for long time[2,3]. The other well-known problems with

pentavalent antimony are difficulties of administration and increasing frequency and severity of adverse events. Common adverse effects are myalgias, arthralgias, increase in liver enzymes, arrhythmias and repeated parenteral injections[3,6]. These limitations have stimulated the search for new agents which are more potent, convenient and have better safety profile. In the past decade, there have been several advances with the introduction of new therapies like liposomal amphotericin, paromomycin and oral miltefosine[3-7]. Miltefosine has recently been claimed of being effective in patients, who had not responded to the standard antimony compounds. It was initially tried in patients with visceral leishmaniasis in India beginning in 1998 and was found very effective[3]. In 1999, clinical studies were also initiated in Colombia for cutaneous disease. More than 2500 patients were treated, including patients with diffuse cutaneous leishmaniasis, mucosal disease and patients co-infected with HIV. Cure rates between 91 and 100% were seen with a dose of 2.5 mg/kg/day for 28 days. It was also found tolerable except for few mild gastrointestinal events and mild transaminase and creatinine elevations[3,7,8]. After several clinical trials, it is now established as first line oral treatment in visceral leishmaniasis and its efficacy in case of cutaneous and mucocutaneous forms of the disease is still being evaluated both in New World as well as in Old World[3,7-9]. The present trial in immune-o-competent patients shows that oral miltefosine in a dose of 2.5 mg/kg body weight is an effective and safe treatment for cutaneous leishmaniasis. 96.67% of the patients showed improvement at the end of 28 days with complete re-epithelialization and no residual swelling or redness in 28.8%, complete re-epithelialization but with residual swelling and redness in 34.4% and partial re-epithelialization in15.3%. Only 3.34% of patients failed to improve at all. Ten patients reported for follow up at the end of three months and were free of the disease. The follow up of the patients was difficult in the scenario and the patients were asked to report back after three months only if there lesions failed to heal or relapse. The patients who did not report back for follow up were considered to be cured. The over all cure rate was 96.67%. Cure rate seen in our trial was higher when compared with trials in New World, where the cure rate was 91% (40 of 44 patients) in cutaneous leishmaniasis due to L. v. panamensis in Colombia and was 53% in Guatemala where L. v. braziliensis and L. mexicana mexicana are common[7,10]. Very few clinical trials have been published so far describing clinical efficacy of the agent in Old World disease. Mohebali et al reported a cure rate of 92.2% (total patients 32) in old world zoonotic cutaneous leishmaniasis from Iran[11], 67% for L. tropica from Afghanistan and 86% (total patients 15) from Pakistan[12]. Our study had a substantially larger population as compared to the published studies and the results of our study seem promising.

The most common clinical side effect was myalgias seen in about one third of the patients followed by arthralgias, nausea vomiting, bad oral taste, testicular pain, cough, conjunctivitis and fever. Bad oral taste and testicular pain have never been reported before. All these side effects were transient and settled on discontinuation of medication. The most frequent biochemical abnormality was a transient rise in liver transaminases seen in 95% of the cases but it also settled on discontinuation of medication in 37.7% of cases and showed reversion trend to normalization in rest of the patients.

The limitations of our study were physical follow up and breakdown of the patients according to the age and type of lesions. The follow up at three months was difficult as they were mostly from armed forces coming from different areas of duty so only a few could be followed up. However they were advised to report back if lesion failed to heal or relapse. We further recommend the double blind randomized controlled trial to evaluate the efficacy of the drug as well as comparison with conventional anti leishmanial therapies giving due consideration to the type of cutaneous leishmaniasis, causative organism, age of the patient and duration of the disease.

CONCLUSION

Our study has generally proved that oral miltefosine appears to be a safe and effective therapy for old world cutaneous leishmaniasis. Its major advantage over conventional antimonial is oral administration. Miltefosine may be helpful in cases where currently available conventional anti leishmanial agents are not feasible and is a good addition to the therapeutic armamentarium against cutaneous leishmaniasis.

A more specified clinical trial including the response of miltefosine with regards to the causative organism, clinical type of lesion, size of the lesions, duration of the disease and age of the patients is recommended for future studies.

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