The efficacy and safety of oral ivermectin in the treatment of inflammatory rosacea: a clinical therapeutic trial

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Background: Rosacea is a chronic inflammatory disease of unknown etiology. Few studies have been published on the use of oral ivermectin in the treatment of the inflammatory subset of rosacea. The aim of the present research was to evaluate the efficacy and safety of oral ivermectin prescribed for a series of patients with inflammatory rosacea.

Methods: On a weekly basis, 29 patients with papulopustular rosacea were orally given ivermectin at a dose of 200 µg/kg before meal for three consecutive weeks. Subjects were evaluated weekly and during the follow-up period for two successive treatment-free months.

Results: After 3 doses of ivermectin, there was a significant reduction in the total count of inflammatory lesions compared to the base line (the mean was reduced from 51.6±27.4 to 21±14.7) (P<0.05). At the end of the two-month follow-up period, more reduction was observed in inflammatory lesions (mean was reduced to 9.3±7), and 62% of the patients showed excellent responses to the treatment (≥ 80% reduction in the lesions). Nausea was reported in 10%.

Conclusion: A three-week use of oral ivermectin is an effective, safe, and well-tolerated approach to treating inflammatory rosacea .

Keywords: ivermectin, rosacea, treatment

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INTRODUCTION

Rosacea is a chronic inflammatory disease characterized by frequent flushing, persistent erythema, and telangiectasia, affecting facial convexities, and interspersed by inflammatory episodes during which swelling, papules, and pustules are observed [1]. This condition is more common in fair-skinned, middle-aged individuals [2,3]. The exact pathogenesis of rosacea is unknown, but ultraviolet radiation (UVR) exposure, dysfunction of the innate immune response with the release of cytokines and antimicrobial molecules, and vascular changes with the increase in cutaneous blood flow have been considered as different pathogenic factors [4-9]. In rosacea, *Demodex* mites (*folliculorum* and *brevis*), facial skin commensals, are often present in high numbers within the pilosebaceous follicles, and play major roles in the pathogenesis. These mites have been associated with an intense perifollicular infiltrate of predominantly CD4+ helper T cells [10-12]. Furthermore, antigenic proteins produced by a bacterium (*Bacillus oleronius*) isolated from *Demodex* mites stimulate an inflammatory response and upregulate cutaneous proteases, thereby potentiating the dysregulation of the local innate immune response [13,14].

There are five major clinical subtypes of rosacea. Erythrotelangiectatic, characterized by flushing and persistent facial erythema; papulopustular (PPR) with red central face coupled with erythematous multiple papules and pustules; glandular;

phymatous, and Ocular [15,16].

The treatment of rosacea involves systemic antibiotics like tetracycline, macrolides, metronidazole, and isotretinoin which have been successfully employed with variable rates [17-19]. Ivermectin is a synthetic derivative of a broad-spectrum antiparasitic class of macrocyclic lactones, which paralyzes arthropods, nematodes, and insects by interfering with neurotransmission [20]. It is FDA approved for onchocerciasis and strongyloidiasis [21]. Topical ivermectin has been successfully employed for the treatment of rosacea [22], yet little data has been published on the use of oral ivermectin for rosacea; accordingly, the current study was designed to evaluate the efficacy and safety profile of oral ivermectin for the treatment of papulopustular rosacea (PPR).

PARTICIPANTS AND METHODS

A cohort of 35 patients with papulopustular rosacea (PPR) was enrolled in this study at the department of dermatology, Basra General Hospital, Iraq, from August 2016 to November 2017. Twenty nine patients completed the therapeutic procedures and the follow-up period, and the remaining 6 were considered as defaulters. The participants were informed about the research work and a written informed consent was taken from them. All patients were interviewed and a detailed history was obtained. Eligible patients were examined clinically for site, type of rosacea and distribution of skin lesions. The papulopustular subset of rosacea was diagnosed depending on its characteristic primary and secondary clinical features. The presence of at least two of the following primary features was regarded as diagnostic criteria: 1)transient or persistent erythema of the face, 2) papules, 3) pustules, 4) nodules, and 5) telangiectasia [23,24]. The main exclusion criteria were a history of allergy to ivermectin, pregnant or lactating women, patients on conventional treatments for the last four weeks, and other subsets of rosacea. The patients were classified into three grades according to severity, using the grading system for PPR [25]:

Grade 1 was described as having few papules and/or papulopustules, and mild persistent centrofacial erythema. Grade 2 was persistence of several papules and/or papulopustules, and moderate persistent centrofacial erythema. Grade 3 was extensive papules and/or papulopustules, and pronounced persistent centrofacial erythema, inflammatory plaques or edema. On a weekly basis, ivermectin was orally administered at a dose of 200 µg/kg before meal for three consecutive weeks, and patients were followed up monthly for two successive treatment-free months. A photograph was taken at the baseline and at the end of the trial, using a camera of 20.7 megapixel from a fixed distance. The treatment outcome was assessed by the following parameters:

1- Counting the number of inflammatory lesions (papules, pustules, nodules) at the baseline and in each subsequent visit (first and second week, first and second month of the follow-up period).
2- Measuring the percentage of reduction in the number of inflammatory lesions in each visit, and comparing it with the baseline values.
3- Grading the response to treatment according to the percentage of total reduction in inflammatory lesion counts is as follows: ≥80% reduction =excellent response, 60-79%=good, 40-59%=moderate, and <40% = poor response.
4- Patient satisfaction toward the response to treatment was assessed using the following scale: 0 = not satisfied, 1 =partially satisfied, 2 = fully satisfied.

Adverse effects of the treatment were recorded in each visit.

Data analysis was done using SPSS version 22, IBM corporation, and descriptive data were presented in mean and SD (standard deviation). So as to specify the statistical significance among different variables, chi square test and z-test were made use of.

RESULTS

The patients demographic criteria are shown in Table 1.

After 3 doses of ivermectin, a significant reduction was seen in the total count of inflammatory lesions, compared to the baseline (the mean was reduced from 51.6±27.4 at baseline to 21±14.7) (P<0.05), the papules were reduced from 38.6 ±27.2 to18.7±15.7; similarly, the pustules and nodules were also reduced from 11.4±9.8 and 1.6 ±3.7 to 1.9±2.4 and 0.4±1.1, respectively (Table 2).

At the end of the treatment-free follow up

Table 1. The demographic data of the patients (n=29)

Category	Subcategory	Number and percentage
Age	25-63years	mean 40±11 years
Sex	Male	3 (10.3%)
	female	26 (89.7%)
History of Treatment Before	Treated before	19 (65.5%)
	Not treated before	10 (34.5%)
Severity	Grade I	3 (10.3 %)
	Grade II	18 (62 %)
	Grade III	8 (27.6 %)

period, a further reduction was observed in all inflammatory lesions (mean was reduced to 9.3±7); the papules, pustules and nodules were reduced to 8.7±7.8, 0.5±1.6 and 0.1±0.3, respectively. By scoring the response to treatment, there was 82.6% reduction in the total number of inflammatory lesions compared to the baseline (papules, pustules and nodules were reduced by 77.7%, 96.9% and 94.8%) (Table 2, Figure 1).

Table 3 showed that excellent response to treatment was observed in18 (62.1%) patients, 11(37.9%) were with good response and none had moderate or poor scores.

The response to treatment was not influenced by the severity of rosacea, and there was no significant difference among different grades of rosacea concerning the reduction in the number of inflammatory lesions, although grade III showed higher response rates than others (Table 4).

Regarding patient satisfaction, 25 (86.2%) patients were fully satisfied with the results, and four (13.8%) patients were partially satisfied.

Adverse responses to ivermectin were reported in three patients (10.3%) only in the form of mild nausea which did not necessitate stopping the treatment.

Table 3. The scoring system according to percentage of total reduction of the inflammatory lesions .

Scoring the response	Number and percentage
(excellent) ≥ 80%reduction	18 (62.1%)
(good) 60%-79% reduction	11 (37.9%)
(moderate) 40%-59% reduction	0 (0%)
(poor) < 40% reduction	0 (0%)

Table 4. The mean number of inflammatory lesions ±SD and percentage of reduction according to the grades of rosacea at base line and at the end of 8th week follow-up period.

Grade	Mean±SD (baseline)	Mean±SD (8th week follow up, *P* value)	% of reduction
I	21±9.64	3.33±0.58, 0.0001*	84
II	41.63±9.77	6.74±3.59 , 0.0001*	83.4
III	91.71±22.67	18.71±10.26, 0.0001*	98

**P* <0.05 as compared with base line

DISCUSSION

Oral ivermectin in the scheduled three weekly doses was an effective and safe treatment for inflammatory papulopustular rosacea with remarkable improvement in all types of inflammatory lesions. The significant improvement was durable and continued for further two months following the termination of the drug. Ivermectin has anti-inflammatory properties as it reduces the recruitment of inflammatory cells and the release of cytokines [26], and has a direct antiparasitic action on *Demodex Folliculorum* [20] mites .On reviewing the literatures, there are few published clinical trials on the use of oral ivermectin to treat PPR; these studies are either a case report or a clinical trial utilizing a combination therapy, whose results are variable and lack specific clinical parameters for assessing drug effectiveness. Salem DA et al. demonstrated a complete remission of PPR and significant reduction in mite population in

Table 2. The mean of inflammatory lesions at baseline & follow up (mean ± SD) and percentage of reduction.

Time	Papules (*P* value)	% of reduction	Pustules (*P* value)	% of reduction	Nodules (*P* value)	% of reduction	Total number (*P* value)	% of reduction
Base line	38.6±27	0%	11.4±9	0%	1.6±3	0%	51.6±27	0%
1st week	23.3±1 0.0001*	38.1%	4.7±4 0.0001*	59.7%	0.6±1 0.0001*	57.7%	28.6±1 0.04*	44%
2nd week	18.7±1 0.0001*	51.1%	1.9±2 0.0001*	83.3%	0.4±1 0.0001*	68.5%	21±14 0.04*	59.6%
4th week	13.4±1 0.0001*	65.3%	1.2±2 0.0001*	90.9%	0.2±0.6 0.0001*	85.7%	14.9±1 0.032*	71.4%
8th week	8.7±7 0.0001*	77.67%	0.5±1 0.0001*	96.9%	0.1±0.3 0.0001*	94.8%	9.3±7 0.032*	82.6%

**P* value < 0.05 when compared with base line

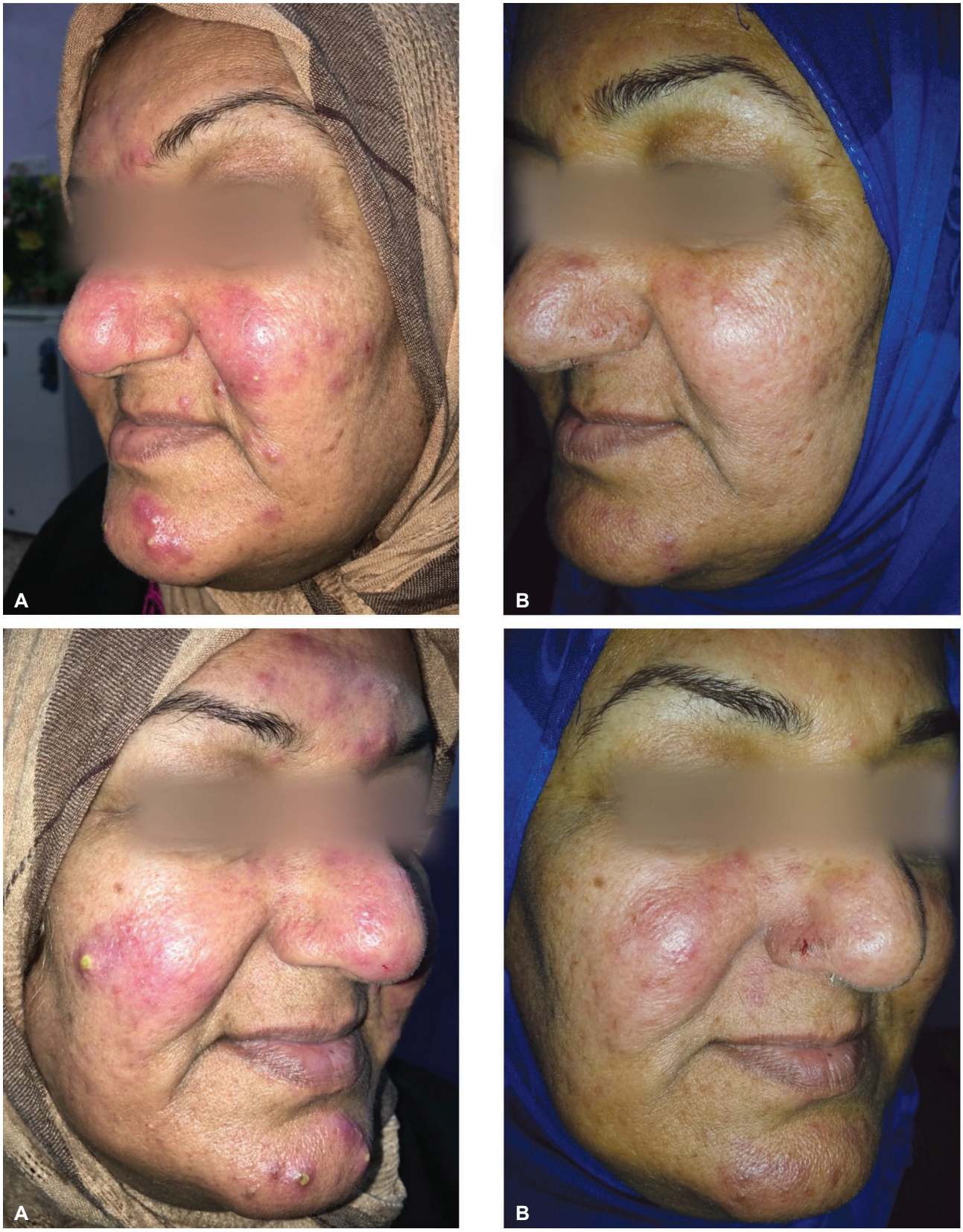

Figure 1. A 46 year old lady with inflammatory rosacea, A: at baseline & B: at the end of the trial showing remarkable improvement.

71.6% patients after two doses of oral ivermectin if combined with metronidazole [28]. Brawn M et al. reported that a single oral dose of ivermectin was efficacious in a reported case with severe oculocutaneous rosacea [29]. More recently, in a case series study including children with PPR, complete clearance was achieved in 93% of patients [30]. Our study showed comparable results and 62 % of the patients had complete or nearly complete ($\geq$ 80%) clearance of all inflammatory lesions. In 2014, FDA approved 1% ivermectin cream for the treatment of rosacea in adults [31]; nevertheless, topical treatment, more often than not, requires long term daily application and may cause skin irritation and pruritus [32]. To avoid this and depending on patient preference, the oral intake of ivermectin would be more convenient and facile to administer than the topical approach. The treatment consensus of American Acne and Rosacea Society recommends using oral sub microbial doses of doxycycline or isotretinoin for all grades of inflammatory rosacea [33]. Research has shown that doxycycline causes 80-100% clearance [34] and isotretinoin results in 75% reduction in the inflammatory lesions [27]; however, patient selectivity, long term administration and the risk of adverse events are major concerns related to such treatments. In our results, though preliminary, the efficacy of oral ivermectin was comparable to other conventional oral therapies with few side effects. Although there were no statistically significant differences in response to treatment among various grades of inflammatory rosacea, a high percentage of reduction was noticed in grade III (98%) than in other grades, suggesting that ivermectin is more effective in severe types of inflammatory rosacea.

In conclusion, oral ivermectin is effective, safe and a well-tolerated drug, and may be included in the armamentarium against inflammatory subsets of rosacea. These findings have to be confirmed in a comparative, controlled clinical trial.

Conflict of Interest: None declared.

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