

# Therapeutic Role of Isotretinoin in the Management of Recurrent Aphthous Stomatitis (Single-Blind Controlled Therapeutic Study)

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## Abstract

**Background:** Recurrent aphthous ulcer (RAS) is a common oral disease where its etiopathogenesis is not well elucidated. There was no effective curative therapy for this disease. Isotretinoin has been recently used in the treatment of Behcet's disease. **Objectives:** To evaluate the efficacy and safety of isotretinoin in treating RAS and the long term remission of RAS. **Patients and Methods:** This single-blind controlled therapeutic study conducted in Department of Dermatology-Baghdad Teaching Hospital during February 2011-January 2012. Thirty patients with typical RAS were included in this work. Detailed history and full examination were done for all patients. They were given isotretinoin 20 mg orally once daily for three months to be seen on Day 14 firstly and then monthly to be assessed using the oral clinical manifestation index (OCMI). After isotretinoin was stopped three months later, patients were given placebo therapy for another 3 months. **Results:** The results of 30 treated patients were as follows: 17 (56.67%) males and 13 (43.33%) females with male to female ratio was 1.3:1. Their ages ranged from 12 - 60 ( $35.33 \pm 12.06$ ) years. The OCMI before isotretinoin therapy ranged from 7 - 17 ( $13.13 \pm 2.55$ ), while after therapy the mean started to decline to a lower level within the first 14 days ( $P = 0.103$ ), and continued to decline significantly until the end of the first month of therapy ( $P = 0.023$ ). Then the OCMI declined very significantly until the end of fourth month of therapy ( $P < 0.001$ ). After that the mean started to

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**increase until the end of the 5 months (with placebo) but it remained statistically significant compared with the baseline of mean of OCMI before treatment ( $P = 0.046$ ). Then it continued to increase to become not significant at the end of 6 months of therapy ( $P = 0.107$ ). Conclusion: Isotretinoin is an effective therapeutic and prophylactic promising remedy in treatment of RAS.**

## Keywords

**Recurrent Aphthous Stomatitis, Isotretinoin, Iraq**

## 1. Introduction

Recurrent aphthous stomatitis (RAS) is a common oral problem that is encountered in a round (10% - 25% of the population [1]. There are many varieties of RAS like minor, major and herpetiform. Minor ulcers (80%) are less than one centimeter in diameter, usually heal within 2 weeks, and don't leave scars. Major ulcers (10%) usually one centimeter or more in diameter, take more than minor ulcers to heal, and may leave scars, while Herpetiform ulcers (10%) are clusters of dozens of smaller ulcers [2].

The etiology of this disease is not well elucidated [3], but there are many factors which are implicated in the etiopathogenesis like infection as herpes [4], *Streptococcus sanguis* [5] and cytomegalovirus infection [6] [7]. Other factors include immunological [8]-[11] genetics nutritional deficiency like vitamin B12 and folate deficiencies [11], trauma gastrointestinal diseases [1], hematological deficiencies [12]-[14], hormonal factors and allergies to food [1].

RAS in many cases is mild that does not need therapy but still there are other cases which are severe enough to interfere with life activities and need medical interference. Accordingly, there are many topical and systemic therapies that have been used like chlorhexidine [15], lidocaine solution [16], sucralfate suspension [16], topical honey [17], 5% lactic acid [18], nigella sativa [19], novel dexamucobasemyrtle [20], myrtle [21], colchicines, pentoxifylline [22], steroids [1] [16] thalidomide [23], BCG vaccine [24], and Etanercept [25] are used to control the symptoms. Recently an Iraqi study showed that oral zinc sulfate had an effective therapeutic and prophylactic role in management of RAS [26].

Isotretinoin is a synthetic vitamin A derivative that has been widely used to treat many dermatological diseases like acne vulgaris, ichthyosis and Darier's disease [27] through its multiple effects like increasing turnover and differentiation of epithelial cells, immunomodulator action, anti-inflammatory effect [28], inhibition of Toll like receptors 2 (TLR2) [29], and antiestrogen effect [30] Most recently, Isotretinoin had been used in treatment of Behcet's disease and was found to be effective in all the mucocutaneous manifestations including pathergy test [31].

So, the aim of the present work is to evaluate the effectiveness of isotretinoin in the treatment of RAS.

## 2. Patients and Methods

This single-blind controlled therapeutic study in which thirty patients with RAS who attended who attended Behcet's disease clinic Department of Dermatology-Baghdad Teaching Hospital, Medical City; Baghdad; Iraq; were enrolled in this work during the period February 2011-January 2012.

Detailed history was taken regarding: age, gender, occupation. History of the disease, recurrence rate, duration, symptoms associated with the ulceration, interference with the swallowing, drinking or eating and aggravating factors including food type, stress and trauma were evaluated. Also, the search about their general health, previous medical history, drug history, cigarette smoking and history of the same condition or other illness in the family were carried out. All patients were subjected to full examination detecting the shape, size, number and site of the lesions.

Investigations were done for all patients like Pathergy test using 24 gauge needle, HLA typing for HLAB51, B5 and HLAB27, complete blood picture, ESR, CRP, renal function test, liver function test to exclude Behcet's disease and other internal causes of oral ulcerations. All patients were examined by ophthalmologists in the same hospital to exclude findings suggestive for Behcet's disease.

The diagnosis of RAS was based on history, clinical examination and exclusion of other causes of oral ulceration.

Inclusion criteria were patients stopped their treatment three months before the start of the study, most cases had at least one attack per month.

Also, patients were selected only those who we trust their follow up during the course of therapy. While exclusion criteria were pregnant and nursing mothers, patients with lipid problems and cardiovascular diseases.

Formal consent was taken from each patient after full explanation about: the goal of the present study before using the remedy, the nature of the disease, course its complications, the methods of treatment, duration, cost, side effects of therapies and duration of follow up, prognosis. After full explanation regarding isotretinoin including: method of application, duration of therapy, side effects and follow up concentrating on documentation of any apparent oral ulceration, its size, location, number and associated symptoms. Patients were instructed not to stop study treatment during the study, and to consult for any cutaneous or systemic side effects that might develop. Also, the ethical approval was performed by the scientific committee of the Scientific Council of Dermatology & Venereology Iraqi Board for Medical Specializations.

Also, because of its teratogenic effect, this drug should not be used in ladies should not become pregnant for 2 months after stopping it. Patients were instructed to use isotretinoin capsules (Retane capsules from Asia Company, Syria) orally once daily for three months to be seen on day fourteen first and then on each month to be assessed by the oral clinical manifestation index (OCMI) which is the summation of multiple scoring numbers of the clinical status of the conditions of RAS (**Table 1**). Then, isotretinoin capsules were stopped and placebo therapy in a form of glucose capsules was given for further 3 months.

**Table 1.** Oral clinical manifestation index (OCMI) type score.

Type	Score
Minor ulcer	1
Major ulcer	2
Herpetiform ulcer	3
<b>Number of ulcers/attack</b>	
1 - 3	1
4 - 6	2
7 - 9	3
9 - 12	4
More than 12	5
<b>Duration of the attack</b>	
1 - 4 days	1
5 - 8 days	2
9 - 12 days	3
More than 12 days	4
<b>Frequency (attack/date)</b>	
0 - 2 weeks	5
3 - 4 weeks	4
5 - 6 weeks	3
7 - 8 weeks	2
More than 8 weeks	1
<b>Associated symptoms</b>	
Uncomfortable	1
Painful but not interfere with eating or swallowing	2
Interfere with solid feeding	3
Interfere with liquid feeding	4

The data were analyzed, and the student test was used to compare the means of OCMI before therapy and at Day 14, one month, two months, three months, four months, five months and six months of therapy.

The response was estimated by calculating the reduction in the means of OCMI at Day 14, one month, two months, three months, four months, five months and six months of therapy from the baseline of mean of OCMI before treatment. P value of less than 0.05 was considered to be statistically significant.

### 3. Results

Thirty patients were included in this study; 17 males (56.7%) and 13 females (43.3%), with male to female ratio was 1.3:1. Their ages ranged between 12 - 60 years with a mean  $\pm$  SD of  $35.4 \pm 11.97872$  years.

OCMI before treatment was ranged from 7 - 17 with mean  $\pm$  SD of  $(13.133 \pm 2.556)$ . OCMI was started to decrease after two weeks of therapy but the decrease was statistically not significant ( $P > 0.05$ ). After one month, this decrease was statistically significant ( $P = 0.023$ ) and continued to decrease. At the end of three months, the decrease was statistically highly significant ( $P < 0.001$ ). Although Isotretinoin was stopped, the effect continued till the end of fifth month and was also statistically significant ( $P = 0.046$ ). Also at the end of the six months there was a slight continued effect although was not statistically significant ( $P > 0.05$ ).

After placebo treatment, patients showed no improvement but the effect of Isotretinoin continued with gradual increase in the mean of OCMI until reached a level which was almost comparable to baseline data (**Table 2**).

### 4. Discussion

RAS is a major health problem but its etiopathogenesis is not well elucidated [3].

There are many therapies have been used to treat RAS but none of them is curable [29] and there is a high relapse rate when these therapies are stopped. Still some patients might get remission either as a result of therapy or spontaneously [26].

Dapsone and oral zinc sulfate have been used successfully in treatment of RAS through double blind therapeutic study and both of them showed effective therapeutic and prophylactic actions in controlling the disease [26].

The present work using oral Isotretinoin showed a new effective therapy in controlling RAS. The effect of this drug started after 14 days and became statistically significant after one month ( $P = 0.023$ ) then the OCMI continued to decrease and became highly significant at the end of three months of therapy ( $P < 0.001$ ). When the treatment was stopped and placebo started at the end of three months, the effectiveness of Isotretinoin continued and remained highly significant ( $P < 0.001$ ) at the end of four months and significant at the end of fifth month ( $P = 0.046$ ).

This could be explained as retinoids in general are stored in fatty tissue for longer time after stopping the therapy [32]-[34]. Acitretin could be also tried in treatment of oral aphthosis and probably might has a similar effect to isotretinoin and preferably might have longer prophylactic effect as it may stay in the body for about 2 years after stopping therapy [35].

These results are closely similar and comparable to the effectiveness of isotretinoin in controlling the oral manifestations in patient with Behcet's disease [31].

Accordingly, Isotretinoin had a prophylactic action in addition to its therapeutic effect. These results are very comparable to the results of dapsone and oral zinc sulfate although isotretinoin was less effective than zinc sulfate and dapsone (**Table 3**).

**Table 2.** Effects of the drug on OCMI.

	Before therapy	Isotretinoin therapy				Placebo therapy		
		Day 14	One month	Two months	Three months	Four months	Five months	Six months
Mean	13.133	10.567	7.6	5.5667	4.0667	5.9333	8.2	10.667
SD	2.556	3.9277	4.9522	5.3219	4.2421	4.7119	4.3263	3.8714
P-value		0.103 NS	0.023 S	$P < 0.001$ HS	$P < 0.001$ HS	$P < 0.001$ HS	0.046 S	0.107 NS

**Table 3.** Comparison between effects of zinc sulfate, dapsone and isotretinoin OCMI score.

OCMI score	Zinc sulfate	Reduction in mean	Dapsone	Reduction in mean	Isotretinoin	Reduction in mean	P-value
At day 0	11.93		10.87		13.133		
At 2 weeks	6.07	5.86	3.73	7.14	10.567	2.566	0.034 S
At one month	1.73	10.2	4.40	6.47	7.6	5.533	0.039 S
At 2 months	2.80	9.13	4.27	6.6	5.5667	7.566	0.089 NS
At 3 months	0.93	11	2.80	8.07	4.0667	9.066	0.048

The mechanism of action of isotretinoin in controlling RAS is difficult to be explained but it might work through its multiple actions like increasing differentiation of epithelial cells, antiinflammatory effect, immunomodulator effect [28], Tolllike receptors 2 (TLR2) [29] and antiestrogenic effect [30].

The present study showed that isotretinoin is an effective therapy but unfortunately it might be associated with side effects like dryness of the lip, mucosa, skin and eye [32]. Also because of its teratogenic effect [32], this drug should not be used in pregnant and ladies should not become pregnant for 2 months after stopping it. But when the patient gets better, the dose of therapy could be minimized to reduce these side effects. Hence isotretinoin could be used either alone in cases failed to respond to other therapies or as a combined therapy with others like dapsone and zinc sulfate especially in difficult refractory cases.

## 5. Conclusion

To the best of our knowledge, this is the first study that has been carried out using isotretinoin in treatment of RAS. Isotretinoin is an effective new therapy for RAS either alone in cases failed to respond to other therapies or as a combined therapy with other drugs. Other retinoids like acitretin will be tried in management of oral aphthosis and Behcet disease by further studies which will be published.

## Disclosure

This study was an independent study and not funded by any drug companies.

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