

COMPARISON OF EFFICACY AND SAFETY OF TOPICAL KETOTIFEN (ZADITEN) AND CROMOLYN SODIUM IN VERNAL KERATOCONJUNCTIVITIS

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SUMMARY: The purpose of this study is to compare the efficacy of Ketotifen fumarate 0.025% (Zaditen) with Cromolyn sodium 4% eye drops in prevention of itching, tearing and redness in vernal keratoconjunctivitis (VKC).

This double masked randomized single center clinical trial conducted between April and August 2004 in Yazd. One hundred eligible patients with clinical diagnosis of moderate VKC were randomly assigned to Zaditen (Group A, n=50) and Cromolyn sodium (Group B, n=50) eye drops for a 4 week period. Itching, lacrimation, redness and photophobia were scored on a 4-point severity scale.

At the follow up visits, the responder rate based on subjects assessment of global efficacy was significantly greater in Ketotifen group (71.5%) than in Cromolyn group (53%). A clear response to treatment occurred in 94.4% of Zaditen patients and 81.2% of sodium Cromoglycate patients. The investigator's assessment of responder rates also showed that Ketotifen was superior to Cromolyn sodium ($p=0.001$). Ketotifen produced a significantly better outcome than Cromolyn ($p<0.05$) for relief of signs and symptoms of VKC. Ketotifen fumarate treatment significantly reduced the total signs and symptoms score for each patient compared to day 0.

Ketotifen had a faster onset of action and provided better symptom relief than Cromolyn: the rapid onset of action and symptom control, make Zaditen a valuable treatment for VKC.

Key words : VKC, Allergic conjunctivitis, Zaditen.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a bilateral ocular allergic disease tending to occur in children during spring and summer months (1). The disease occurs in warm temperate zone and is more common in the Middle East, Mediterranean area (2), and Iran.

VKC can certainly pose a threat to vision due to corneal involvement (3).

The immunopathogenesis appears to involve both types I and IV hypersensitivity (4, 5). The treatment of VKC is quite prolonged and demands good compliance.

Presently moderate to severe cases were treated with mast-cell stabilizers such as Cromolyn sodium and topical corticosteroids (6).

However, the risks of prolonged use of corticosteroids are cataract and glaucoma, and should be reserved for treatment of severe eye symptoms. In VKC mast cell degranulation and release of histamine stimulate

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nerve endings and leading to dilation of the blood vessels causing itching and redness (7). Mast cell stabilizing by Cromolyn has an important role for treatment. More recently interest has focused on the possibility of topical application of histamine H1-antagonists.

Ketotifen a benzocycloheptathiophene derivate has been used in the treatment of asthma (8). It blocks histamine H1 receptors, stabilizes mast cells and prevents eosinophil accumulation and degranulation (9, 10).

Ketotifen fumarate 0.025% ophthalmic solution (Zaditen) has been developed recently for alleviating the ocular signs and symptoms of VKC (11). Recent clinical trials demonstrated that Zaditen 0.025% eye drop was efficacious and safe, providing a rapid onset and long duration of action (12-14).

The purpose of this study was to compare the efficacy and safety of ketotifen fumarate 0.025% ophthalmic solution (Zaditen) with Cromolyn sodium 4% in the treatment of moderate VKC.

MATERIALS AND METHODS

Subjects

This study was performed between April and August 2004 in Yazd province. One hundred subjects (68 males and 32 females) enrolled in this research.

Subjects eligible for inclusion were required to be between age of 8 and 25 years and suffering from moderate VKC, and all had papillae on the upper tarsal conjunctiva, conjunctival erythema, limbal hypertrophy and typical mucoid discharge. Subjects with history of dry eye, other form of allergic conjunctivitis, allergy to antihistamines, the ocular surgery within 2 months before study and who had systemic or ocular corticosteroids or mast cell stabilisers within 4 weeks of randomization were excluded. Patients' written informed consent was required. The trial was conducted in accordance with the declaration of Helsinki prior to enrolment as study design.

Study design

This was single center double - masked randomized comparative clinical trial, and the patients were randomly divided into two equal groups (A and B).

Group A patients (n=50) received topical Zaditen 0.025% twice a day and placebo one time a day. Topical Cromolyn sodium 4% was prescribed to Group B (n=50) three times a day. Each group contained 34 males and 16 females.

Treatment was given to each group for 4 weeks, the packaging of all trial medications was identical in appearance. The study involved three visits, a screening visit and two treatment visits. Primary analysis was at the follow up visit held between

day 7 and 15. Responder rates were also assessed at the termination visit held at day 30.

Ocular status assessment

Different symptoms (itching, tearing, burning, redness) and signs (watery, discharge increase, swelling, presence of follicles) of VKC were evaluated at their enrollment (day zero) and at different times after starting treatment (7, 15 and 30 days). Symptoms and signs were classified in four stages: 0- Absent, 1- Mild, 2- Moderate and 3- Severe. The total symptoms and signs score (TSSS) for each subject were obtained by adding the values of each symptoms and signs divided by the total number of them. Each patient was instructed to grade his or her symptoms of itching, photophobia, watering, and mucoidal discharge on a scale from 0 to 3. The patients scored their symptoms for both eyes. Clinical signs (conjunctival erythema, conjunctival chemosis, papillae, limbal hypertrophy, presence of follicles) were also collected from the right eye of each patient at the beginning, follow-up and at the end of the study. Each patient was examined and clinically scored by an ophthalmologist who did not know either clinical status in the pre or post treatment period or the groups of patients (A or B). Subjects were asked to assess the overall effect of treatment using a five point grading scale (Table 1).

Tolerability and safety

Assessment of tolerability was based on adverse data obtained by the subject volunteering the information and by the physician. At the end of the treatment investigator provided a global assessment of safety and tolerability using the same 5-point scale as efficacy (Table 1).

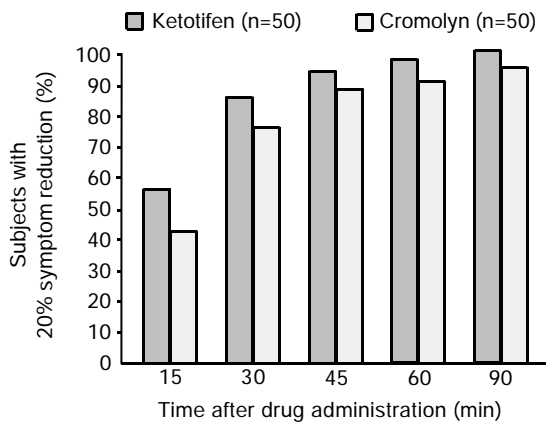
Statistical analysis

The Kaplan-Meier technique was used to describe the onset time distributions of the two treatments, with the planned observation time intervals. The onset time distributions were compared between the two treatment groups using a long-rank test and a general linear means model. The long-rank test was used to check the primary efficacy variable. This test is most sensitive to postpone the responder rate, signs and symptoms were analyzed using logistic regression for binary and ordinary data respectively.

Table 1: Subject and investigator assessment of global efficacy relative to baseline.

Score	Change from baseline	Description
0	Excellent	Complete relief of ocular symptoms
1	Good	Distinct relief of ocular symptoms
2	Fair	Some relief from ocular symptoms
3	Poor	No relief from ocular symptoms
4	Deterioration	Worsening of ocular symptoms

Figure 1: Onset of action by treatment groups.



RESULTS

One hundred subjects were screened (68 males, 32 females). The homogeneity of treatment groups was checked with regard to age, sex and baseline sum score. No significant difference was noted. Study participants were between the ages of 8 and 25 years (mean 16.3) and had a duration of disease ranging from 1 to 15 years (median duration 8.3 years).

Primary efficacy variable

The primary efficacy variables were a physicians clinical judgement scale and patients overall judgement scale of improvement from baseline.

The median time to onset of action was 15 minutes for Zaditen versus 45 minutes for Cromolyn. Onset of action was defined at first time interval in which at least a 20% decrease in composite ocular symptom score

occurred. At each post-dose time point, more subjects receiving Zaditen had 20% or more reduction in symptoms than those receiving Cromolyn. Analyses of the time to onset distribution (Figure 1) showed Zaditen to be statistically superior to Cromolyn (p=0.028).

Both primary efficacy variables showed significantly greater overall improvement of VKC from baseline with Zaditen than Cromolyn.

Responder rate

Responders were patients whose sum score of three main eye symptoms decreased by at least 3 points from a baseline score. After 7 days of treatment 59% of Zaditen treated patients and 53% of Cromolyn treated patients showed improvements of their symptoms and signs. With continued treatment through day 14 symptoms control was achieved in 81% of Group A and 63% of Group B and this difference was significant (p<0.001).

At the final visit the responder rate as judged by the subject was significantly greater with Zaditen compared to Cromolyn (p=0.01).

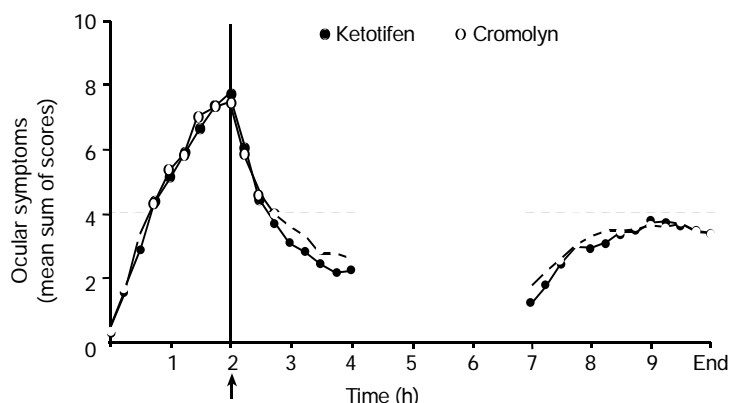
Moreover administration of Zaditen eye drop for thirty days significantly (p<0.0001) reduced the TSSS for each patient between days 0 and 30.

A clear response to treatment (an improvement of sum scores of ≥ 3 points compared to base line) occurred in 94.4% of Zaditen treated patients and 81.2% of Cromolyn patients. Based on subject daily records the superiority of Zaditen in relieving signs and symptoms including redness and tearing was observed from the beginning of the treatment and was most marked during

Table 2: Mean ocular sign and symptoms at day 5-8 visit.

Signs and symptoms	Mean Score		P value Zaditen V Cromolyn
	Zaditen (n=50)	Cromolyn (n=50)	
Redness	0.68	0.90	0.03
Itching	1.25	1.44	0.27
Tearing	0.53	0.88	0.01
Lid swelling	0.40	0.43	0.85
Discharge	0.12	0.24	0.82
Composite score	2.98	3.89	0.02

Figure 2: Change in mean composite ocular symptom scores over time.



the first day. Zaditen was superior to Cromolyn in preventing itching ($p < 0.001$) and redness ($p < 0.005$) at most assessments. Mean scores for eyelid swelling and mucous discharge were generally low for Zaditen Group (Table 2).

At the termination visit the analysis showed significantly better relief of signs and symptoms with Zaditen than Cromolyn ($p = 0.0$), with mean composite sign and symptom score of 2.98 and 3.89, respectively (Table 2). Analysis of the mean composite ocular symptoms scores versus time showed Zaditen to have a faster onset of action in the relief of ocular symptoms (2 hours post-dose) than Cromolyn sodium (Figure 2). At the end of treatment global assessment of efficacy by the investigator was considered at least 91.4% for Zaditen and 78% for Cromolyn sodium.

Safety

Both treatments were generally well tolerated and majority of adverse events were of mild transient irritation and burning. However, the dropout rate due to adverse events was lower in the Zaditen Group ($n = 2.4\%$) compared to Cromolyn ($n = 4.8\%$).

Investigator global assessment of tolerability gave an opinion of at least satisfactory in 95.6% of Zaditen -and 86.3% of Cromolyn sodium, treated patients.

DISCUSSION

VKC is a common, prevalent and clinically significant IgE mediated hypersensitivity response. VKC is an immunopathological disease in which the number of mast cells in substantia propria increase (15-16). Activation of

mast cells by IgE bound receptor crosslinking by allergen promotes the release of several mediators such as histamine, prostaglandins and cytokinase, all of which contribute to the symptoms of VKC (17,18). The mast cell is considered to play a pivotal role in producing symptoms and signs of VKC (19). Current therapy of VKC focuses on modulation of the immune system and pharmacologic inhibition of the chemical mediators involved in the immune response. Mast cell stabilizers and antihistamines are two of the most commonly used groups of therapeutic agents. They stabilize the mast cell membranes by preventing calcium influx across the mast cell membranes, thereby preventing mast cell degranulation and mediator release. The new antihistamines have been demonstrated to be capable of affecting several phenomena of the allergic inflammation including mediator release (20,21).

Among these drugs, new multiple - action agents like Ketotifen fumarate (Zaditen) is histamine H1- receptor antagonist, as well as mast cell stabilizer.

In addition, *in vitro* and animal studies (22) have shown that Zaditen inhibits the activation and chemotaxis of eosinophils into the conjunctiva, (23) which is an important step in the late phase of the immune response.

Cromolyn sodium as a mast cell stabilizer is effective and safe in the treatment of VKC, but topical steroids are often required which increase the chance of bacterial keratitis, cataract and glaucoma, so we decided to perform a randomized double blind study in order to investigate and compare the effect of the topical Ketotifen with Cromolyn sodium in moderate VKC.

In the present study main VKC symptoms decreased significantly by day 3 with sustained improvement on days 7 and 14.

The results of this study showed that Zaditen 0.025% applied topically twice a day was superior to Cromolyn QID ($p=0.001$). Zaditen produced a significantly better outcome than Cromolyn ($p < 0.05$) for relief of signs and symptoms of VKC. Leonardi's study (24) showed investigators assessment of responder rates for Zaditen was superior to Cromolyn that is similar to our study. A recent study by Andrea (25) reported a clear response of 91.2% for Zaditen and 83.5% for Cromolyn treatment groups that was similar to our study.

In the current study as Friedrich Horak's (12) report Zaditen was found to have a faster onset of action than Cromolyn. In term of efficacy, Zaditen was numerically superior to Cromolyn for the majority of the individual symptoms score (26).

We can conclude that at 15 minute and 4-hour Zaditen was superior to Cromolyn in preventing itching and redness which was the same as Greiner's results (27).

In this study the responder after 7 days of treatment was 59% for Zaditen and 53% for Cromolyn treated patients, however, in Kidd's report (28) these were 56.5% and 49.3% respectively. In this study at the follow up visit the responder rate based on subject's assessment global efficacy was significantly greater in Zaditen group (71.5%) than in Cromolyn group (51%). That was not comparable with Kidd's study with responder rate of 49.5% and 33% respectively.

CONCLUSION

Zaditen 2 times a day was significantly more effective than sodium Cromolyn four times a day in alleviating symptoms and signs of moderate VKC. The faster onset action (within 15 minutes) and better symptoms relief observed with Ketotifen during the initial 2 hours, along with favourable safety and tolerability profile make Zaditen a new valuable treatment option for patients with moderate VKC.

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