LITERATURE REVIEW

Comparison of Efficacy and Safety Outcome Among Tacrolimus Ointment, Cyclosporine, and Anti Histamine in Managing Patient with Allergic Conjunctivitis

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ABSTRACT

Objective: To evaluate and compare the efficacy and safety between tacrolimus, cyclosporine ointment and anti-histamine as single therapy for allergic conjunctivitis.
Methods: A comprehensive literature search was conducted through PubMed/MEDLINE, clinicalkey.com and ophtalmologyadvance.com databases. All studies included were interventional or observational reporting the efficacy of tacrolimus, cyclosporine, and antihistamine as monotherapy for all types allergic conjunctivitis. Outcome of this review included number of resolution, duration to resolution, recurrence and complications.
Result: Eighteen studies were included in this study. Males predominated, with overall ratio ±2:1 compared to female. Most studies use objective signs and subjective symptom scoring before treatment, during follow up and after treatment for outcome measurement. In the antihistamine group, there was a decrease in itching and redness scores of about 33-75%, especially Bepostatinebesilate solution at a concentration of 1.5% Improvement in conjunctival hyperemia and complete resolution of papillary hypertrophy reported in tacrolimus and cyclosporine group, more than 50% reduction on symptoms and signs severity was found in all patients on tacrolimus and cyclosporine group.
Conclusion: Tacrolimus and cyclosporine clinically improved allergic conjunctivitis. Topical cyclosporine and tacrolimus were suggested to be an effective and safe alternative therapy for resistant allergic conjunctivitis.

Keywords : *Allergic conjunctivitis, Tacrolimus ointment, Cyclosporine, Anti-histamine*

Ocular allergy is an ocular surface inflammatory reaction caused by hypersensitivity reactions type I or IV. It is one of the most common benign external ocular conditions estimated to affect 20% of the population worldwide.[1]

Topical antihistamines, mast cell stabilizers, and multiple actions drugs (e.g., alcaftadine, olopatadine) with addition of steroids are typical first-line therapy for allergic conjunctivitis. However, because steroids are associated with treatment-related adverse effects (cataract, glaucoma, and keratitis), they should be reserved for the management of acute allergic crises and used for no more than 2 - 4 weeks.[2,3] Currently, immunomodulatory agents such as cyclosporine and tacrolimus, have

recently been used as treatment alternatives because of their potent anti-inflammatory effects, non-steroid and favorable side-effect profiles. Cyclosporine inhibits CD4+ T lymphocyte proliferation and production of interleukin-2 (IL-2). Tacrolimus decreases the production of inflammatory mediators and histamine release from mast cells, impairs prostaglandin synthesis, and suppresses histamine release from basophils.[4,5] Tacrolimus and cyclosporine ointment is an alternative option to reduce the symptoms with minimal side effect. The aim of this literature review is to evaluate and compare the efficacy and safety between tacrolimus, cyclosporine ointment and anti-histamine as single therapy for treatment of allergic conjunctivitis.

METHODS

A comprehensive literature search was conducted using following database: PubMed/MEDLINE, clinicalkey.com and ophtalmologyadvance.com. Keywords were "allergic conjunctivitis", "tacrolimus", "antihistamine", "cyclosporine", "topical therapy", and "monotherapy". English written articles published in the last 10 years were reviewed, and cross-references were performed in each study to find additional relevant articles. Inclusion criteria were all interventional or observational studies reporting the efficacy of treatment, with or without safety and recurrence rate of topical tacrolimus, cyclosporine, and antihistamine monotherapy for all types allergic conjunctivitis. Non-English studies, or with animal subject, single case reports, disease treated concomitantly with multiple medications, inaccessible journal, non-ophthalmology journal and review articles were excluded.

The data was grouped according to mean age of the patients, type of allergic conjunctivitis, and outcomes (number of resolution, duration to resolution, recurrence and complications. All of these data was presented in table. Those values were tabulated using Microsoft Excel (Microsoft Corp, Washington DC).

RESULTS

After conducting literature search through Pubmed/MEDLINE, clinicalkey.com and ophthalmologyadvance.com using the keywords previously mentioned, a total of 537 relevant articles were found. After selection process and detailed evaluation from the full paper reading for eligibility and duplication, 18 studies were included. Those studies were published between year 2008 and 2017. Two studies were about antihistamine; 10 studies about Tacrolimus; and 6 studies about cyclosporine.The characteristics of the reviewed studies were summarized in Table 1.

Table 1 also presented the baseline characteristics among studies. The subject age ranged from 9.8 years[18] to 40.3±12.6 years[22]. The follow-up duration ranged from 30 days[11] to 48 months[10]. All study reveals male predominance, with overall ratio ±2:1 compared to female. Table 2 and 3 showed studies reporting improvement in each subjective and objective signs before and after treatment. Ocular itching and conjunctival hyperemia score to assess the efficacy in Antihistamin group 1% and 1.5% demonstrate at least 1.2 unit score reduction for the itching and hyperemia in 1.5% concentration. Improvement in conjunctival hyperemia and complete resolution of papillary hypertrophy after treatment of tacrolimus reported reduction in the clinical scores and inflammatory cell counts (using conjunctival impression cytology) of 54 patients after three months of topical cyclosporine 0.05% therapy without side effect.

Table 1. The characteristics of reviewed articles

No	Authors	Place of Study	Years	Treatment	Level of evidence	Total Patient	Follow up	Mean age	Gender (M/F)	Type	Frequency
	Tacrolimus										
1	Fox et al[6]	Israel	2008	T	4	20	10 weeks	10.8	15/5	Allergic	2x
2	Ohashi et al[7], l[17]	Japan	2010	T	2	56	4 weeks	17.9±91.	53/3	Allergic	2x
3	Kheirkhah[8]	Iran	2011	T	3	10	40 weeks	21.3±7.4	9/1/	VKC	4x
4	Fukushima et al[9]	Japan	2014	T	4	1436	6 months	15.8±8.9	1115/321	Allergic	2x
5	Mohammed Al amri[10]	Saudi Arabia	2014	T	4	11	48 months	32.27±12.7	10/1/	AKC	1x
6	Muller et al[11]	Brazil	2014	T	2	21	4 weeks	10.4±4.1	14/7	VKC	2x
7	Al Amri et al[12]	India	2016	T	4	20	24 months	23.14±3.8	18/2	VKC	1x
8	Liendo et al[13]	Brazil	2017	T	4	33	13 months	12±3.97	23/10	Allergic	2x
9	Chatterjee et al[14]	Saudi Arabia	2016	T	4	23	12 weeks	14.7±6.4	14/9	VKC	3x
10	Muller et al[15]	Brazil	2017	T	2	16	6 weeks	11.6±2.4	8/8	VKC	3x
	Cyclosporin										
11	Tesse et al[16]	Italy	2010	C 1%	2	197	16 weeks	5-14 years old	126/71	VKC	4x
12	Ebihara et al[17]	Japan	2009	C 0.1%	3	320	24 weeks	11	215/105	VKC	3x
13	Arbab et al[18]	Pakistan	2011	C 2%	2	20	6 weeks	11.6	18/2	VKC	4x
14	Keklikci et al[19]	Turkey	2008	C 0.05%	4	54	12 weeks	9.8	43/11	VKC	4x
15	Oray et al[20]	Turkey	2013	C 0.05%	3	36	12 weeks	11.3±4.3	Not mentioned	VKC	4x
16	Yucel et al[21]	Turkey	2016	C 0.05%				12.9±3.9	19/11	VKC	3x
	Anti histamine										
17	Maceiko et al[22]	USA	2010	AH	2	130	4 months	33.8±14.3	55/75	Allergic	3x, pre-seasonal
18	Shimura et al[23]	Japan	2011	AH	4	11	6 weeks	40.3±12.6	7/4/	SAC	Not mentioned

Abbreviations: *T; Tacrolimus; AH; Anti-Histamine; MCS: Mast Cell Stabilizer; C:Cyclosporine*

Table 2. Mean Score of Subjective signs in patients before and after treatment

No	Authors	Treatment	Itching		Hyperemia		FBS		Photophobia	
			BL	End	BL	End	BL	End	BL	End
1	Kheirkhah[8]	T 0.1%	2.9± 0.31	0	2.00±0.82	0.50± 0.53	1.80± 0.79	0.20± 0.42	1.80± 0.63	0.10± 0.32
2	Mohammed Al amri[10]	T 0.1%	2.4	0.4	2.3	0.1	2	0.4	not mentioned	
3	Al Amri et al[12]	T 0.1%	2.09± 0.33	0.21± 0.3	2.12± 0.4	0.12± 0.3	2.01± 0.5	0.23± 0.4		
4a	Macejko et al[22]	AH 1%	1.4	0.8	0.6	0.4	not mentioned			
4b	Macejko et al[22]	AH 1.5%	1.5	0.8	0.4	0.1				

Abbreviations; *T: Tacrolimus; AH: Antihistamine; FBS: Foreign Body Sensation; BL: Baseline*

Table 3. Mean Score of Objective signs in patients before and after treatment

No	Authors	Treatment	Corneal Involvement		Giant papillae	
			Baseline	End	Baseline	End
1	Kheirkhah[8]	T 0.1%	0.50±1.10	0.40±0.84	2.70±0.48	0.60±0.52
2	Mohammed Al amri[10]	T 0.1%	2	0	2	0.3
3	Al Amri et al[12]	T 0.1%	2.00±0.62	0.10±0.09	2.07±0.54	0.16±0.31

Abbrevations; *T: Tacrolimus; AH: Antihistamine*

The dosage of tacrolimus given to allergic conjunctivitis patient in this review were 0.03%, 0.005% and 0.1%. Two studies[17,18] assessed efficacy of antihistamine in allergic conjunctivitis while cyclosporine were 0.05%, 0.1%, 1% and 2%. No serious side effect was found in these review. All complications were tolerable to the patients and mostly healed in early follow up time.

DISCUSSION

Allergic keratoconjunctivitis is an chronic bilateral allergic inflammation of the ocular surface involving tarsal and bulbar conjunctiva. The symptoms include severe itching, redness, photophobia, tearing, foreign body sensation and discharge. The disease is more common among males, with ratio reported among male to female in literature were ±2:1[11] consistent to this review finding. Treatment are determined based on the severity and chronicity of the disease in each patient. First line treatment includes antihistamines, mast cell-stabilizer agents, non-steroidal anti-inflammatory agents (NSAID's) and steroid. Previous studies have suggested that tacrolimus, cyclosporine and antihistamine pre-seasonal may be effective in the management of Allergic conjunctivitis.[1,4]

Tacrolimus is a topical immuno modulatory agent that appears to control allergic conjunctivitis by inhibiting T-cell activation by calcineurin inhibition furthermore reducing inflammatory cytokine production (i.e IL-4 and IL-5) and following inflammatory cytokine production without rebound effects following discontinuation of the drugs. All symptoms significantly improved after treatment with Tacrolimus eye drop. A study had reported that itching was the first symptom to show dramatically relief, while another suggested that Tacrolimus might be an alternative treatment for VKC or AKC that does not impose the risk of developing glaucoma.[8,10] No serious adverse effects of these treatments was found in this study. Side effect of topical tacrolimus was burning sensation and tend to improve with time. Cyclosporine, an immunomodulatory agent, inhibits antigen-dependent T-cell activation, an important component in inflammatory ocular surface disease.

Previous studies reported the use of topical cyclosporine was effective to control the symptoms and signs of allergic conjunctivitis.[20] Early administration of topical cyclosporine had more significant ocular improvements than later.[16]

Histamine (H_1 receptor-specific) antagonists can be used for intermittent, acute allergic reactions from a limited exposure to the antigen. It suppress the clinical symptom of conjunctival itching, foreign body sensation, lacrimation and injection. A study suggested that it took about four weeks to suppress the clinical allergy symptoms with Olopatadine, while another reported bepotastinebesilate ophthalmic solution reduce ocular itching in four weeks during therapy.[22,23] Limitation from this studies was relatively small sample size, wide dose range and unstandardized grouping of treatment modality. Another limitation was the duration of symptoms and subject age before initial treatment was not homogen. In addition, the unavailability of tacrolimus and cyclosporine eye ointment in Indonesia limited the use of this agents. Tacrolimus has been approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe atopic dermatitis in topical preparations with a dose of 0.03% dan 0.1% to reduce symptom like pruritus, erythema, edema, excoriation, oozing, scaling, and lichenification.[4,5]

CONCLUSION

It can be concluded that tacrolimus and cyclosporine clinically improved allergic conjunctivitis. Topical cyclosporine and tacrolimus was suggested to be an effective and safe alternative therapy for resistant allergic conjunctivitis.

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