When To Start Tacrolimus Ointment For Vernal Keratoconjunctivitis? A Proposed Treatment Protocol

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Abstract

Purpose

The aim of this study was to compare treatment regimens of tacrolimus and of topical steroids for VKC and suggest a treatment protocol according to our clinical experience.

Methods

This retrospective, nonrandomized case series enrolled 85 Patients with VKC. Patients were classified clinically according to severity (mild, moderate, severe) and were treated according to a suggested protocol. Analysis was made according to treatment received: tacrolimus ointment as first line treatment (tacrolimus 1st line), tacrolimus ointment after topical steroid drops treatment (tacrolimus 2nd line) and topical steroid drops or artificial tears alone (topical steroid and tears group).

Results

Significant improvements in clinical signs and symptoms were achieved under tacrolimus treatment 14 months in the moderate group and 5 months in the severe group. The longest duration of treatment was for tacrolimus 2nd line group (p=0.031) and the mean number of visits in the clinic was the highest. The mean number of topical treatments per day was higher in the topical steroid and tears group (2.6 times) than in the two tacrolimus groups (1.3 times for both). The mean time needed to achieve disease remission or relief did not differ between the tacrolimus 1st line and 2nd line groups.

Conclusion

Tacrolimus treatment is effective and safe for VKC. Tacrolimus as 1st line treatment may be preferred for severe cases, for faster disease remission compared to tacrolimus as 2nd line treatment; and with fewer topical treatments per day compared to topical steroids.

Key Messages

We suggest a treatment protocol for VKC. Mild cases: 1 month course of topical steroids twice a day combined with artificial tears. Moderate cases: 1 month of topical steroids 3-4 times a day and artificial tears. Severe cases: tacrolimus 0.03% ointment combined with artificial tears.

Introduction

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, and sometimes severe ocular allergy. VKC mainly affects young males; the average age of onset is 6–7 years.[1] The typical clinical course is characterized

by seasonal exacerbations, but up to 23% can entail perennial symptoms that can recur throughout the year.[2–4]

The diagnosis of VKC is based on the patient's clinical history and symptoms. There is no consensual grading system, and several scales have been developed with emphasis on severity of symptoms from no inflammatory changes to severe changes.[4] The most common symptoms of VKC are itching, photophobia, burning, and tearing.[5] Other symptoms are foreign body sensation and pain upon wakening.[6] Depending on the conjunctival site involved, 3 forms of VKC can be characterized: tarsal (palpebral), limbal (bulbar), and mixed.[3] The palpebral form is characterized by large tarsal papillae, ranging from 1 to 7–8 mm, which are known as cobblestone papillae. The limbal form includes conjunctival hyperemia, which are limbal nodules that appear as gray, jelly-like, elevated lumps with vascular cores. Horner-Trantas dot are characteristic, whitish centers, filled with eosinophils and epithelioid cells, which may appear in the raised lesion. The mixed type has the clinical findings of the other two forms. Corneal involvement, which is sometimes referred to as a 4th form of VKC, includes superficial punctate keratitis, epithelial macroerosions, gelatinous limbal hypertrophy, and plaque formation. Untreated cases can progress to an oval shaped corneal epithelial defect, known as shield-ulcer, in up to 11% of the cases.[1, 5, 7]

VKC can be difficult to treat. Depending on the severity of symptoms and clinical judgment, a physician can choose to treat with frequent lubrication, mast-cell stabilizers, antihistamines, corticosteroids, topical immunomodulators, and any combination of these agents. Topical steroid drops have shown efficacy but may cause complications such as cataract and glaucoma, particularly during prolonged use.[6] To minimize these complications, immunomodulators (i.e. cyclosporine A drops, topical tacrolimus ointment / drops) have been used and have shown efficacy and safety in recent years.[7–9] Tacrolimus (FK-506) is a calcineurin inhibitor that suppresses T-lymphocyte activation. It is used for preventing rejection of organ transplants, and in immune mediated dermatologic conditions. In ophthalmic diseases tacrolimus is used off-label, topically as an ointment (0.03% or 0.1%) or drops. Previous study in a mouse model has not found deference in efficacy of topical tacrolimus depending on its concentration.[10] However, to date, no treatment for VKC is considered a gold-standard and there is no consensual protocol.

VKC differs clinically according to geographical region.[11] In middle eastern countries with warm climate VKC has a higher prevalence,[4] and in Israel, we find a perennial course to be common in contrast to the seasonal characteristic in other climates.

Therefore, a major portion of our patients presenting a severe disease which is difficult to treat, need an intense and long term treatment regime with close follow up. For many of our patients topical steroids are not effective enough or not applicable for long term due to adverse effects and they need topical tacrolimus ointment for alleviation of symptoms.

Although, multiple action drugs, such as azelastine, epinastine, ketotifen and olopatadine, have recently been suggested to combine antihistaminic effect, mast cell stabilization (MCV) and anti-inflammatory

action at treatment of VKC,[12] in meta-analysis of Roumeau et al. was not found efficacy of MCV over tacrolimus,[13] thus those treatments were not part of this study.

The purpose of our study was to describe treatment regimens of tacrolimus and topical steroids for VKC in different forms of severity. We wish to assess the efficacy and safety of these common treatments for refractory and resistant VKC, and compare remission rates under tacrolimus to other topical treatments commonly used in our practice, and purpose a recommended treatment protocol.

Subjects And Methods

Data was collected from the files of patients visiting our pediatric ophthalmology outpatient clinic who were diagnosed with VKC, during the years 2014–2019.

Criteria for diagnosis were: 1. One or more characteristic symptoms (ocular irritation, itching, tearing pain, and photophobia) 2. Characteristic findings in ocular examination (two or more of the following: hyperemia, tarsal papillae, Horner-trantas dots, and corneal epithelial defects). 3. History concurrent with VKC (recurrent events, history of atopy, seasonal exacerbations, and family history). Exclusion criteria were: loss to follow up, poor adherence to treatment regime and children suffering from other ocular surface diseases. All children were examined and followed by the same two pediatric ophthalmology physicians and two pediatric optometrists.

Data collected included: information from first visit and follow up visits for up to five years after initial diagnosis.

Data collected from initial visit included: age, clinical signs and symptoms at presentation, concurrent ocular diseases, past ocular treatments (i.e. topical artificial drops, topical steroid drops, topical tacrolimus ointment, etc.). Severity at presentation was documented and assessed clinically in an independent scale:

1. Mild – Ocular irritation, mild conjunctival injection combined with small conjunctival papillae.
2. Moderate – Ocular irritation, foreign body sensation, tearing, and signs of conjunctival injection, small papillae in tarsal VKC, or one Horner-Trantas dot in limbal VKC.
3. Severe – Symptoms of photophobia, pain, in addition to the symptoms described above with signs including giant papillae in tarsal VKC, Horner-Trantas dots in limbal VKC, or both in mixed disease, corneal pannus, and corneal micro erosions.

At presentation treatment was prescribed according to severity:

Mild cases were treated with artificial tears alone, or a single 1 month course of topical steroid drops twice a day combined with artificial tears 4 times a day. Moderate cases were treated with topical steroid drops 3–4 times a day combined with artificial tears 3–4 times a day. The Steroid drops used were Lotemax ® (loteprednol etabonate ophthalmic suspension, 0.5% Bausch & Lomb Incorporated, Inc.,

Rochester, NY, USA)]. In cases where Lotemax was unavailable, FML (fluorometholone acetate 0.1%, Allergan Pharmaceuticals, Westport, Ireland)] was prescribed. Severe cases were treated with topical tacrolimus ointment (Protopic 0.03%, LEO Pharma A/S, Ballerup, Denmark) also combined with artificial tears 3–4 times a day. No other treatments were prescribed.

Remission was defined as alleviation of symptoms (according to anamnesis at follow up) and resolution of signs on slit lamp examination (defined as mild conjunctival hyperemia alone or complete resolution). In these cases, a gradual tapering of the topical treatment was performed with a close follow-up, in addition to continued treatment of topical artificial tears until full recovery.

Refractory cases (in all groups of severity) were defined as cases with persistent signs and symptoms not improving after 1 month of prescribed treatment. In these cases treatment was changed according to the following regimen (Fig. 1):

1. Mild refractory cases with minimal improvement were redefined as moderate cases, in those cases according to clinical judgement, treatment was adjusted by increasing steroid dosage. Refractory cases with no improvement or worsening were treated with tacrolimus ointment 0.03%.
2. Moderate refractory cases were switched to tacrolimus ointment 0.03%.
3. Severe refractory cases were prescribed additional steroid treatment for 1 month. If once again no improvement was noted, tacrolimus ointment concentration was increased (Protopic 0.1%, LEO Pharma A/S, Ballerup, Denmark).

Relapse events were defined as reappearance of signs and symptoms previously stated after remission or worsening of signs after improvement and were prescribed treatment by the same protocol.

Data collected after first visit included: prescribed ocular treatment for VKC, number of visits during follow up period, duration of follow up, number of recurrences under prescribed treatment, time to achieve remission and any adverse effect of the prescribed treatment. Adverse effects were defined as one of the following: For steroid drops: Intraocular pressure (measured by using Goldman and iCare tonometers, and palpation, according to the age and cooperation level of the children) and cataract formation (examined by slit lamp). For tacrolimus ointment adverse effects were: irritation, stinging and foreign body sensation.

Documentation of refraction and pupil dilation were repeated once a year (unless clinically indicated earlier).

In order to compare treatment regimens, for the statistical analysis, patients were classified into three groups: 1. Patients treated with tacrolimus ointment as a first line treatment (tacrolimus 1st line) 2. Patients treated with tacrolimus ointment after topical steroid drops treatment (tacrolimus 2nd line) 3. Patients treated with topical steroid drops or artificial tears alone (topical steroid and tears group).

To assess the effectiveness of each treatment, the following outcome measures were compared and analyzed between the three different treatment groups: Mean follow up duration, mean number of relapses, mean number of topical treatments per day, mean total number of days in treatment. We compared additional variables between the 2 groups treated with tacrolimus: Mean time to achieve remission under tacrolimus ointment, mean total time under tacrolimus ointment and the mean number of cases needing topical steroids in addition to tacrolimus ointment.

Statistical analysis

For categorical variables, a summary table presents sample size, and absolute and relative frequencies. For continuous variables, a summary table presents arithmetic means (M) and standard deviations (SD). Pearson's chi-squared test was applied for examining correlations between the study groups for the categorical parameters. The Kruskal-Wallis or Mann-Whiney non parametric tests were applied to measure the differences between the study groups. P-value of 5% or less was considered statistically significant. The data were analyzed using the SPSS version 25 (SPSS Inc., Chicago, IL, USA).

The study and data collection were approved by the institutional IRB.

Results

A total number of 105 children were diagnosed and treated for VKC during the study period. 20 patients were excluded from the study, 4 due to low compliance and 16 due to loss to follow up. 85 patients were included. Mean age was 7.85 years (range 2–16) 16 were female (29.6%). At presentation 60 patients were defined as mild (70.5%), 9 patients were defined as moderate (10.5%) and 16 patients were severe (18.8%). The mean ages, and proportion of males did not differ significantly between these groups (Table 1).

Table 1
Means, standard deviation and differences between the study groups.

	Tacrolimus as 1st line (n = 16)	Tacrolimus as 2nd line (n = 15)	Topical steroids (n = 54)	p
Age at enrolment (M ± SD)	8.2 ± 2.0	6.8 ± 2.8	7.9 ± 3.4	0.502
Gender, Male (n, %)	14, 87.5	11, 73.3	44, 81.5	0.619
Follow up, months (M ± SD)	19.4 ± 17.2	26.6 ± 17.4	17.1 ± 15.2	0.194
Number of visits (M ± SD)	7.4ab ± 5.0	10.9a ± 6.5	4.9b ± 2.9	0.001
Number of relapse (M ± SD)	1.2a ± 1.1	0.9a ± 1.2	0.5b ± 0.7	0.050
Number treatments per day (M ± SD)	1.3b ± 0.6	1.3b ± 0.5	2.6a ± 1.4	< 0.001
Days in treatment (M ± SD)	250b ± 210	419a ± 294	248b ± 288	0.031
Steroids in addition to tacrolimus (M ± SD)	0.4 ± 0.5	0.3 ± 0.5	-	0.526
Time for control after tacrolimus (M ± SD)	5.1 ± 6.7	11.1 ± 12.6	-	0.105
Tacrolimus time (M ± SD)	8.2 ± 7.3	12.0 ± 12.1	-	0.513
M - Mean, SD - Standard deviation				
a-b: different letters in each row represent significant differences between the means.				

12 patients in the mild group were refractory to treatment. In that group 2 were given a higher dose of steroid drops and 10 were given tacrolimus. 13 of the mild patients improved but did not completely resolve after one month and treatment was prolonged or tapered at a slower pace for one or two more months. All patients in this group did not relapse during the study period (Fig. 2).

In the moderate group 5 patients were refractory – and were prescribed protopic. In the severe group 7 were refractory. Treatment was adjusted according to protocol

The mean number of relapses was 0.64, 0.62 and 1.18 in the mild, moderate and severe groups, respectively. Besides occasional complaints of itching and foreign body sensation after tacrolimus use, no adverse events were recorded during the study period. After 1 year of follow up, no additional adverse effects were reported. No complications of VKC (shield ulcer, corneal melting, or keratoconus) presented during the study period.

Mean time to remission under tacrolimus treatment was 14 months in the moderate group and 5 months in the severe group. Concurrent ocular and systemic diseases included myopia, astigmatism, amblyopia,

accommodative esotropia, congenital cataract, neurofibromatosis type 1, conjunctival nevus, and prematurity. Differences between the groups in the distribution of these conditions were not significant.

In the severe group, 4 children who were refractory to treatment were known to have an emotional stressful environment.

Classified by treatment regimen – 16 patients received tacrolimus as a 1st line treatment. 15 patients received tacrolimus as a 2nd line treatment, and 54 patients received artificial tears alone or a single 1 month course of topical steroid drops combined with artificial tears 4 times a day with no switching to tacrolimus ointment.

Comparing all three groups, total treatment duration was significantly longer ($p = 0.031$) for the tacrolimus 2nd line (419 ± 294) than the tacrolimus 1st line group and the steroid and tears group (250 ± 210, 248 ± 288 respectively) see Table 1.

The mean number of topical treatments per day for those receiving topical steroids with artificial tears only (2.6 ± 1.4) was double than the mean number of treatments for both the topical tacrolimus groups (1.3 ± 0.6 as 1st line, 1.3 ± 0.5 as 2nd line). This difference was statistically significant ($p < 0.001$).

A lower proportion of relapses was observed for the topical steroid and tears group (0.5 ± 0.7) than for the other two groups ($p = 0.05$). The highest proportion of relapses was observed for the tacrolimus 1st line group (1.2 ± 1.1), but the difference from the tacrolimus 2nd line group (0.9 ± 1.2) was not statistically significant.

The total follow up period was longer for the tacrolimus 2nd line than the tacrolimus 1st line group, and longer than for the topical steroid and tears group (mean 26.6 ± 17.4, 19.4 ± 17.2, and 17.1 ± 15.2 months, respectively). This difference was not statistically significant ($p = 0.194$).

Compared to the tacrolimus 1st line group, for the tacrolimus 2nd line group, the mean time lapsed until disease remission or relief, and the mean time of tacrolimus use were longer. However, these differences were not statistically significant ($p = 0.105$, $p = 0.513$, respectively). The proportion of patients needing topical steroids in addition to tacrolimus treatment (defined as severe refractory patients) was similar between the two tacrolimus treatment groups ($p = 0.526$).

Discussion

To date, numerous clinical scores are available for VKC according to clinical signs and symptoms that are assessed in the clinic by taking patients' history and physical examinations.[14] No scoring system has been shown to be superior or more credible than others.[4] The variability of treatment choices and the lack of a standardized treatment protocol leads to prolonged treatment periods, various attempts of different medications, relapse episodes and added emotional and physical stress on the child and parents. Patients were divided by severity and treated according to our treatment protocol based on clinical judgment as discussed earlier.

The mean number of days under treatment was significantly higher in the tacrolimus as 2nd line group than the tacrolimus 1st line group. We also show a trend towards a longer follow up duration when using tacrolimus as 2nd line treatment compared to 1st line treatment.

Chatterjee et al described tacrolimus ointment as effective and safe for patients diagnosed with VKC who are refractory to topical steroids.[15] Our results suggest early treatment with tacrolimus in moderate to severe patients will shorten the duration of treatment and the follow up period.

Our series also shows that treating with steroids alone doubles the mean number of treatments per day compared to both tacrolimus groups. It has been shown in adults that longer duration and a higher frequency of treatments per day lower the compliance.[16] Treating children, compliance issues are even more significant and more treatments per day can be even more challenging for parents for many reasons, such as children's reluctance to cooperate, the need for parent availability during the day, and fatigue over a long treatment period. These may lead to lower compliance and eventually treatment ineffectiveness. Therefore treating with tacrolimus poses a benefit of needing less treatments per day thus improving compliance. In addition, treating with tacrolimus as a 1st line shortens the total duration of treatment and the need for long term follow up.

The need for additional topical steroid treatment for patients refractory to tacrolimus ointment has also been described.[15] In our series, there was a similar number of refractory patients requiring topical supplemental steroid treatment in both tacrolimus groups which shows similarity of severity between the groups, making the groups more comparable. Therefore, we suggest that patients originally classified as moderate would benefit an early tacrolimus treatment rather than initial treating with steroids.

The mean number of visits was significantly higher in the tacrolimus 2nd line group compared to the two other groups. Even though this data is incomparable between the groups due to different follow up periods, it can be an indicator of uncontrollable disease which needs more attention. Therefore it supports tacrolimus as 1st line of treatment to achieve fewer visits.

Our analysis revealed that those treated with topical steroids or artificial tears alone were considered mild cases. We observed that this group showed a lower number of relapses ($p = 0.05$), fewer visits in the clinic ($p = 0.001$), and shorter follow-up time ($p = 0.194$) than the two groups treated with tacrolimus. The patients who did not receive tacrolimus ointment represented the mildest cases in this series; therefore, these results are evidently attributed to the severity at presentation and not to the effectiveness of treatment.

On the other hand, our analysis revealed that the children treated with tacrolimus ointment as 1st line treatment had a higher number of relapses. Due to higher severity level at baseline in this group, we do not think this should be attributed to treatment.

The four children with the most severe and refractory disease, with the longest treatment duration, were all subjected to environmental stress factors, both socially and psychologically. The association of

psychological stress with other atopic diseases, such as atopic dermatitis, have been described. However, a specific association of such stress with VKC remains unknown.[6, 17]

Our series showed a variability in time to achieve remission according to treatment received. We see a trend towards a shorter time to achieve remission and shorter duration of tacrolimus treatment time for patients receiving tacrolimus as a 1st line treatment compared to patients who received tacrolimus as 2nd line treatment. Although these differences were not statistically significant ($p = 0.105$ and $p = 0.513$, respectively), this data supports our hypothesis that early tacrolimus treatment is beneficial.

The most concerning adverse effect related to topical tacrolimus use is the risk of T-cell lymphoma. A debate in the current literature revolves around the possible correlation between topical use of tacrolimus for skin treatment and non-ophthalmic use. A multicenter cohort study found an increased risk of lymphoma in children and cutaneous T-cell lymphoma in adults who initiated treatment with tacrolimus for atopic dermatitis. However, the increased risk was small and the authors mentioned that cutaneous T-cell lymphoma may be misdiagnosed as atopic dermatitis, and that this may have caused an overestimation of the results.[18] On the other hand, in a meta-analysis that assessed the correlation between lymphoma risk and topical calcineurin inhibitors (e.g. tacrolimus), only one article reported this association in regard to topical skin use for atopic dermatitis.[19] A Cochrane review did not find evidence associating a risk of malignancies with the use of topical tacrolimus.[20] Moreover, many have questioned such correlation due to the possible association between atopic dermatitis and the increased risk of malignancy and lymphoma, which would render the topical treatment a confounding factor.[21–23] A long term follow up for topical ophthalmic use of tacrolimus 0.1% ointment found it to be an effective and safe treatment for atopic keratoconjunctivitis.[24]

Adverse effects of topical steroid drops include elevated intraocular pressure and increased risk for posterior subcapsular cataract.[25] Some topical steroid agents are considered to have a low risk of elevating intraocular pressure. However, manufacturers still list this as a possible adverse effect. In our study, no cases of cataract formation or elevated intraocular pressure were observed. Beside itching and foreign body sensation, there were no side effects of tacrolimus ointment use.

Therefore we believe tacrolimus to be a safe and efficacious treatment for VKC also as a 1st line treatment.

Based on our results, we suggest a treatment protocol for an effective treatment for VKC patients, stratified according to the severity grade at presentation (Fig. 2).

According to our treatment protocol, Mild cases should be treated with a 1 month course of topical steroids twice a day combined with artificial tears. In cases that are partially resolved, treatment should be adjusted by increasing steroid dosage. Initiation of tacrolimus ointment should be reserved for cases with no improvement.

Moderate cases should be treated initially with 1 month of topical steroid drops 3–4 times a day with artificial tears 4 times a day. If not improved, we suggest to switch treatment to tacrolimus ointment 0.03% and classify them as severe cases.

Severe cases should be treated directly with tacrolimus 0.03% ointment once a day combined with artificial tears 4 times a day. Assessment is suggested after 1 month and remised cases should be gradually tapered and switched only to artificial tears. Refractory cases should be treated with a higher dose (tacrolimus 0.1% once a day or 0.03% twice a day) or addition of topical steroids.

This study has a number of limitations. After exclusion of patients who did not meet eligibility criteria, the total number of patients was small.

The history collected in the clinic has inherent difficulties. Data is based on parents' reports of home treatment which sometimes may be incorrect. Each patient has their own timeline which is not congruent to other patients. In order to bypass this challenge and make a correct statistical analysis we used objective measurements as discussed earlier. Patients were assessed according to their own timelines; and their own number, interval, and frequency of clinical visits, and duration of follow up period. However, this bias cannot be fully corrected. We believe that a large randomized prospective cohort trial can fully evaluate this protocol.

Conclusion

VKC may need long and intensive care. There are many choices for treatment with no standard protocol and no evidence for the optimal timing for using tacrolimus. We have built a treatment protocol combining common treatments and suggest it as a toolbox for the ophthalmologists.

Tacrolimus as 1st line treatment may be preferred for severe cases and for some moderate cases, for faster disease remission compared to tacrolimus as 2nd line treatment, and with fewer topical treatments per day compared to topical steroids alone. When a physician opts to start with topical steroids, we suggest considering only a one-month trial before switching to tacrolimus. This is to shorten the treatment duration and the number of visits in the clinic. We hereby suggest a treatment protocol based on these results and our team's experience.

Declarations

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Conflict of interest: The authors have no conflicts of interest to disclose

Availability of data and material: The data that support the findings of this study may be available from the corresponding author upon reasonable request.

Ethics approval: Ethical approval was received by Helsinki committee of Assuta-Samson Medical Center.

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Figures

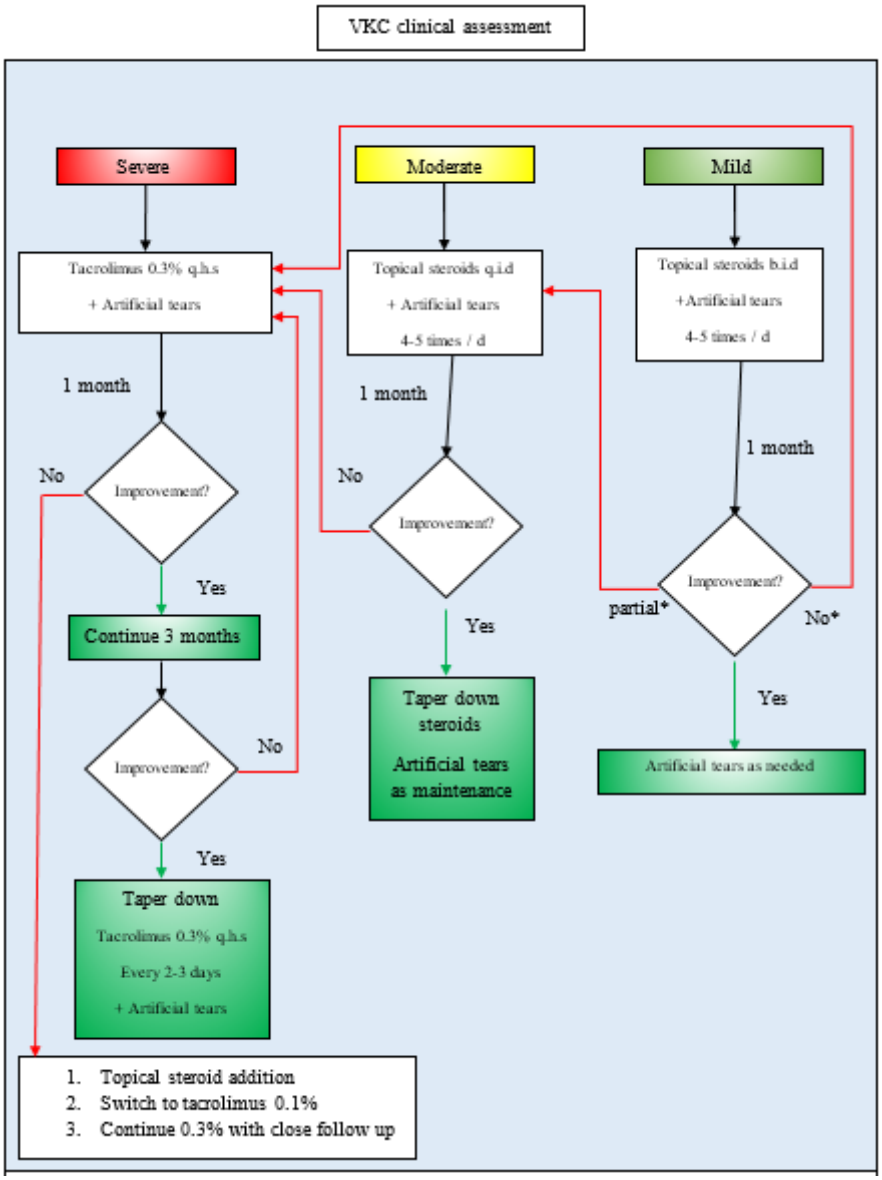

Figure 1

Suggested Algorithm for treating VKC according to severity at presentation * According to clinical judgement, history, previous treatments, and individual clinical evaluation. Some children may benefit from a second course of lubrication and others may be graded as having moderate VKC and as needing topical steroid drops.

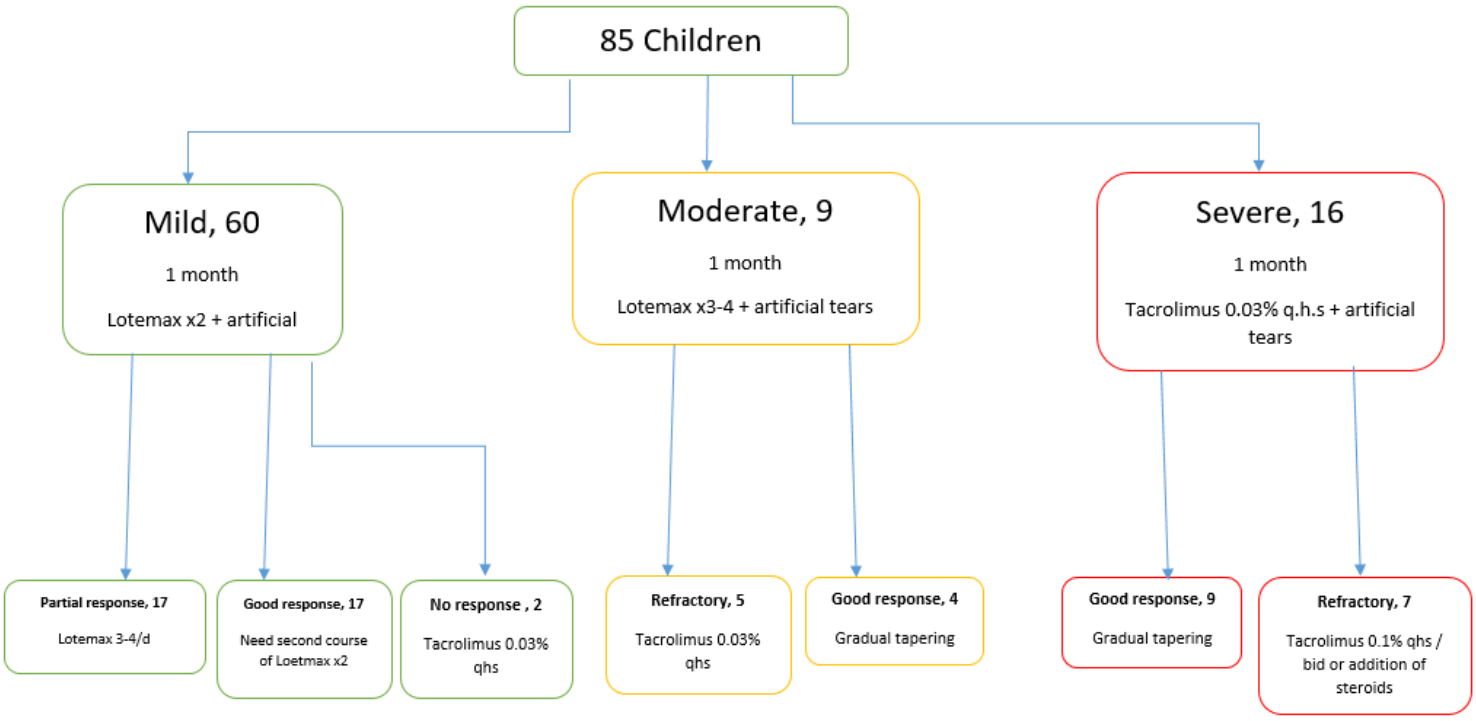

Figure 2

Based on our results, we suggest a treatment protocol for an effective treatment for VKC patients, stratified according to the severity grade at presentation