Graefe's Arch Clin Exp Ophthalmol (1999)
237:109–112

CLINICAL INVESTIGATION

Thomas Reinhard
Rainer Sundmacher

Topical cyclosporin A in Thygeson's superficial punctate keratitis

Received: 17 October 1997
Revised version received: 20 February 1998
Accepted: 9 March 1998

Free paper at the 95th annual meeting of the Deutsche Ophthalmologische Gesellschaft in Berlin, 20–23 September 1997

T. Reinhard (✉) · R. Sundmacher
Eye Hospital, Heinrich Heine University,
Moorenstraße 5, D-40225 Düsseldorf,
Germany
Tel. +49-0211-811 7320,
fax: +49-0211-811 6241

Abstract ● Background: Since September 1994 we have administered topical cyclosporin A 2% (CSA) in a prospective study to patients with Thygeson's superficial punctate keratitis (TSPK). After our promising short-term results we now present medium-term data of a larger patient group. ● Patients and methods: Topical CSA was administered to 52 eyes of 28 patients with TSPK. Forty-two were adult eyes (group I), 10 children's eyes (group II). Starting with 3 drops daily during the 1st month, CSA was reduced to 1 drop every 2nd day within 4 months and stopped after 6 months. ● Results: Complete suppression of the typical epithelial and supepithelial opacities could be achieved in 71.5% of cases in group I and 40% in group II as long as therapy was administered; the other patients responded only partially or not at all. Recurrences were a problem during tapering off or shortly after cessation of therapy, but they could again be treated effectively with the initial CSA regime. Thirty-one percent of all adult eyes and 20% of all pediatric eyes seemed to have completely healed during the observation time. ● Conclusions: In more than two thirds of our adult patients topical CSA 2% suppresses the epithelial and subepithelial opacities for as long as this non-steroid therapy is administered. Definite healing seems to be achieved in almost one third of all adult patients. In another one third, long-term low-dose CSA therapy is necessary before complete healing may be expected. Children probably do not respond to therapy as well as adults. Whereas the only therapeutic alternative, i.e. steroid eye drops, have a significant potential for side effects in the long run, no side effects have been known from low-dose CSA eye drops. We regard CSA eye drops as a significant progress in the symptomatic treatment of TSPK.

Introduction

Thygeson's superficial punctate keratitis (TSPK) is a chronic corneal disease mostly occurring bilaterally [1–3, 7–14]. Spontaneous temporary or definite healing is just as common as recurrences over many years. On slit-lamp examination epithelial "frosty" opacities with some subepithelial edema are typically found. The etiology of TSPK is still unclear. Braley and Alexander's virological research [1] gave questionable results, whereas Lemp et al. [6] were able to isolate a varicella-zoster virus. Other research groups were not able to reproduce this result in virus culture or by electron microscopy, but there are indeed some items in the clinical course of TSPK that suggest a virus as the etiological agent [11]. In the absence of laboratory confirmatory tests, diagnosis of TSPK remains exclusively clinical at present.

Since Thygeson's first description of TSPK in 1950, topical corticosteroids have been known as an efficient

symptomatic therapy for as long as they are administered [12]. Recurrences are very common, however, if steroids are tapered off. Bandage contact lenses bring temporary relief in some individual cases [11]. In 1994, topical cyclosporin A (CSA), which reduces interleukin-2 production by T-lymphocytes [5], was introduced as a new therapeutic option by Holsclaw and coworkers [4]. Since September 1994 we have applied topical CSA in a prospective study to all our TSPK patients, and in 1996 we reported our first results after treatment of 31 eyes with a mean follow-up period of 8 months [9]. We are now able to present medium-term data on a larger patient group.

Patients and methods

Topical CSA was administered to 52 eyes of 17 female and 11 male patients with TSPK. In 24 patients both eyes were affected, in 4 patients only one eye. Twenty-three patients (42 eyes) were adult and 5 patients (10 eyes) were children (aged 6, 7, 8, 9 and 11 years). The mean patient age of all patients was 30.1 years (range 6–63 years) and the mean follow-up period was 17.3 months (range 3–33 months). The diagnosis of TSPK was made by the typical appearance of "frosty" punctate epithelial opacities with some subepithelial edema (Fig. 1) and the cyclic spontaneous appearance and disappearance of these efflorescences.

CSA 2% eye drops were produced in our pharmacy as a solution of Sandimmun and oleum arachidis. CSA therapy was started after informed consent had been obtained from the patients or, in the case of children, their parents. Our therapy scheme comprised CSA 2% eye drops 3 times daily in the first month, 2 times in the second month, one drop in the third month and one drop every second day from the 4th to the 6th month. Therapy then ceased. If no or only incomplete remission of opacities was observed after 4 weeks of therapy, this scheme was modified individually. Up to 5 drops were administered in such cases over 4–6 weeks. If recurrences occured when tapering CSA, the initial therapy scheme was started and followed again, but the patients were left on 1 drop daily or every 2nd day in the long run.

During and after CSA therapy, tear film substitution already applied before topical immunomodulation was continued.

Fig. 1 Typical epithelial opacities with slight subepithelial edema in Thygeson's superficial punctate keratitis

Results

Complete suppression of the typical epithelial and subepithelial opacities could be achieved in 71.5% of cases in the adult group and 40% in the pediatric group, mostly during the first 2–4 weeks of therapy (Figs. 2, 3). Some 40.5% of the adult group and 40% of the children group did not experience recurrences during tapering off or after cessation of therapy, with follow-up periods of up to 17 months after the last CSA drop. Recurrences occurred at 2 drops daily (2 eyes), 1 drop daily (2 eyes), 1 drop every second day (3 eyes) and within 6 weeks after cessation of therapy (6 eyes) only in adult eyes. The recurrences were again treated effectively with the initial CSA regime and the patients receive 1 drop daily or every 2nd day in the long term.

Nineteen percent of patients in the adult group and 20% in the children's group responded only with incomplete suppression of the opacities (Figs. 2, 3). Higher CSA doses with up to 5 drops daily were not able to bring

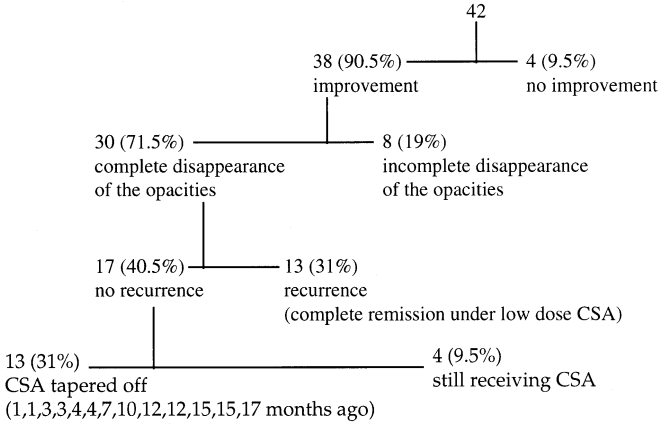

Fig. 2 Response of 42 adult TSPK eyes to topical CSA

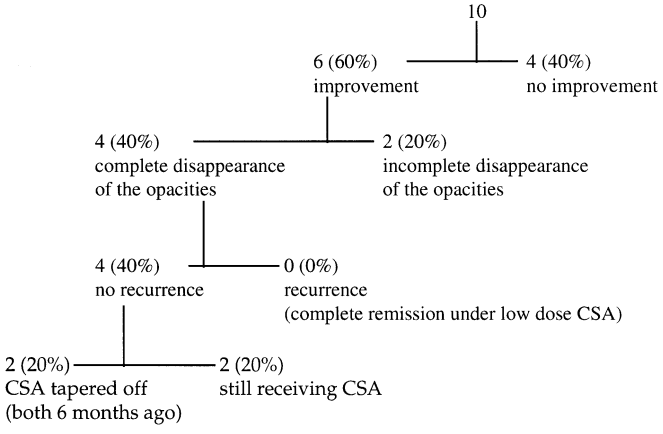

Fig. 3 Response of 10 pediatric TSPK eyes to topical CSA

about further improvement. Some 9.5% of patients in the adult group and 40% in the children group did not respond at all to therapy, although higher CSA doses with up to 5 drops daily were tried (Fig. 2, 3). The difference between the adults and the children was not statistically significant (Fisher test, P=0.18). In neither group, adults or children, could a correlation between extent of disease and response to topical CSA be observed.

A burning sensation after topical application of CSA was noted by all patients. No further side effects occurred.

Discussion

In 1994 Holsclaw and coworkers [4] described for the first time the beneficial effect of topical CSA in TSPK. Their experience was limited to the very small number of 5 eyes. Since September 1994 we have administered – after obtaining informed consent – topical CSA to all our patients with TSPK. In 1996 we presented the short-term results in a group of 31 eyes with a mean follow-up of 8 months. We have now treated 52 eyes with a mean follow-up of 17 months. The data confirm and extend our findings from 1996.

In the adult group, 71.5% of eyes with clinically classified signs of TSPK responded with complete disappearance of the opacities. Almost one third of all adult eyes can be regarded as cured. In another one third, recurrences occurred. These were treated effectively with the initial CSA scheme and in such cases long-term low-dose CSA therapy seems necessary. Some 28.5% of the adult group had incomplete or no response and were therapeutic failures. Possible reasons are: (1) In these TSPK eyes topical CSA may be an excessively weak immunosuppressive agent. This possibility is supported by the fact that no (further) improvement was brought about by higher CSA doses (up to 5 drops daily). 2. Diagnosis of TSPK is exclusively clinical and based on a typical patient history and typical epithelial opacities with some subepithelial edema. It is possible, therefore, that the clinical appearance of TSPK includes two or more entities which are not equally sensitive to CSA therapy.

Although the difference between the groups of adults and of children was not statistically significant, we may conclude that children seem to respond less effectively to topical CSA treatment than adults. Besides the possibility that at different ages different entities may be encountered, age-related immunological peculiarities may be responsible for this observation. Furthermore, the possibility that some of the young patients refused the "burning" drops cannot be excluded, although all parents stated that the drops were administered strictly according to our therapy scheme.

How does topical CSA work in patients with TSPK? CSA interferes with interleukin-2 production by T-lymphocytes, leading to inhibition of T-cell proliferation. Regarding the virus hypothesis of TSPK, we assume that CSA suppresses the immunological response to virus replication only to some extent, bringing about a reduction of symptoms (i.e. the opacities disappear), but leaving enough immunological competence to minimize virus replication or even to eliminate the virus in the long run. If corticosteroids are administered, symptoms also disappear, but due to a much larger extent of immunological suppression. Therefore, virus replication probably cannot be controlled effectively any longer, resulting in recurrences in most patients after tapering off.

The great advantage of topical CSA over topical corticosteroids is the lack of severe side effects such as development of cataract, glaucoma and surface disorders, including infections. In view of the fact that therapy for TSPK is sometimes necessary for months or years, these corticosteroid side effects cannot be neglected. The only side effect of topical CSA of which we have become aware is a burning sensation lasting some minutes after administration of the drops. This burning sensation, however, was so inconvenient that one patient (two eyes) with incomplete remission of opacities refused to continue therapy after 6 months. Systemic side effects have not yet been observed, and in view of the very small amount of CSA administered they do not seem very probably. One drop of our preparation contains about 1 mg CSA. Even if 5 drops are applied daily, this dose is far below that with systemic formulas, e.g. 3–5 mg/kg body weight after allogeneic penetrating high-risk keratoplasty. Furthermore, we were unable to detect CSA blood levels in 49 healthy patients after topical administration of 1 or 2 drops of CSA 2%, even using very sensitive detection methods (high-performance liquid chromatography–electrospray mass spectrometry; unpublished data). However, in our TSPK patients CSA blood levels were not examined routinely.

In summary, topical CSA is a safe and recommendable therapy in patients with TSPK, leading to complete remission in more than two thirds of all adult eyes as long as they are treated. In the medium term, about one third of patients are free of significant symptoms after tapering off. Those who need to continue topical CSA as a low-dose therapy, seem to run a very low risk of side effects. The only side effect of topical CSA therapy which we observed was a burning sensation lasting for some minutes after application. We hope this problem may be reduced or eliminated if CSA drops are produced and distributed commercially in the future.

References

1. Braley AE, Alexander RC (1953) Superficial punctate keratitis. Isolation of a virus. Arch Ophthalmol 50:147–154
2. Brini A, Payeur G (1966) Kératite ponctueé superficielle de Thygeson (rappel clinique et thérapeutique à propos de deux cas). Bull Soc Ophthalmol Fr 66:1282
3. Duke-Elder S (1965) Thygeson's superficial punctate keratitis. In: Duke-Elder S (ed) System of ophthalmology. Kimpton, London, pp 743–746
4. Holsclaw DS, Wong IG, Sherman M (1994) Masked trial of topical Ciclosporine A in the treatment of refractory Thygeson's punctate keratitis. Invest Ophthalmol Vis Sci 35:1302
5. Kahan BD (1989) Cyclosporine. N Engl J Med 321:1725–1738
6. Lemp MA, Chambers RW, Lundy J (1974) Viral isolate in superficial punctate keratitis. Arch Ophthalmol 91:8–10
7. Quéré M, Diallo J, Rogez JP (1968) La kératite de Thygeson. Arch Ophthalmol 28:497
8. Quéré MA, Delplace MP, Rossazza C, Moulene C, Combé J (1973) Fréquence et étiopathogénie de la kératite de Thygeson. Bull Soc Ophthalmol Fr 73:535
9. Reinhard T, Sundmacher R (1996) Lokale Cicloporin A Therapie bei Keratitis superficialis punctata Thygeson – eine Pilotstudie. Klin Monatsbl Augenheilkd 209:224–227
10. Sundmacher R, Neumann-Haefelin D, Bettge F (1976) Keratitis superficialis punctata Thygeson. Klin Monatsbl Augenheilkd 168:868–869
11. Sundmacher R, Press M, Neumann-Haefelin D, Riede U (1977) Keratitis superficialis punctate Thygeson. Klin Monatsbl Augenheilkd 170:908–916
12. Thygeson P (1950) Superficial punctate keratitis. J Am Med Assoc 144:1544
13. Thygeson P (1961) Further observations on superficial punctate keratitis. Arch Ophthalmol 66:158–162
14. Thygeson P (1966) Clinical and laboratory investigations on superficial punctate keratitis. Am J Ophthalmol 61:1344–1349