Utilization Characteristics of Topical Cyclosporine and Punctal Plugs in a Managed Care Database

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Introduction

Various terms have been used to describe dry eye disease (DED) including keratoconjunctivitis sicca and, more recently, dysfunctional tear syndrome.[1] DED is a condition characterized by the inability of the tear film to function properly in lubricating and nourishing the external eye. The typical symptoms include scratchiness, itchiness, burning, and foreign body sensation.[1] Studies have demonstrated that DED appears to have an inflammatory component that is further exacerbated by various external factors.[1] Increased T-cell infiltration and cytokine production of the lacrimal gland with resulting release of these inflammatory mediators onto the ocular surface have been linked to the pathophysiology of DED. These inflammatory mediators continue to assault the external ocular surface.[1] By providing relief from the ocular inflammatory cascade, the underlying pathophysiology is addressed.

The prevalence of DED seems to increase with age. DED is estimated to affect more than 3.2 million women 50 years of age or older and 1.7 million men 50 years of age or older in the United States alone.[2,3]

Until the release of cyclosporine ophthalmic emulsion, approved by the US Food and Drug Administration (FDA) late in 2002,[4] very few treatment options existed. In fact, generally the treatment consisted of artificial tears, gels, and nighttime ointments. The sheer number and variety of artificial tear solutions (the most common treatment for DED) available over the counter (OTC) illustrates that very few treatments provide the DED patient with more than palliative relief. In many cases the signs and symptoms continue to intensify with the patients administering more frequent eye drops, gels, or nighttime ointments to obtain relief. Topical cyclosporine is the first nonsteroidal prescription product for the treatment of DED that provides pharmacologic treatment for the inflammatory component of DED. Topical ocular steroids have been known to have some benefit in DED, but are limited to short-term use because of their ocular side-effect profile, which includes glaucoma, secondary infections, and cataract formation, as noted by Lemp in an accompanying article in this supplement.[5]

Another treatment option is to insert punctal plugs. Punctal plugs are small collagen or silicone devices that are inserted into the puncta of the lower eyelids to provide conservation of tears. However, based on what is known today about the pathophysiology of DED, punctal plugs may not provide full DED relief because the inflamma-

Abstract

A retrospective administrative claims analysis of treatment options for dry eye disease (DED) evaluated treatment patterns and utilization characteristics of patients receiving cyclosporine, punctal plugs, or a combination of cyclosporine and punctal plugs, and examined differences in health plan costs with the 2 treatments. A total of 23,821 commercial health plan enrollees that initiated treatment with cyclosporine or punctal plugs between January 1, 2004, and December 31, 2005, were reviewed. There were 9065 subjects in the cyclosporine group, with a mean of 3.93 (median of 3) prescription fills reported in the 365-day follow-up period per subject. The mean health plan cost per patient was $336 (median $228), with total health plan costs of $3.05 million. In the punctal plugs cohort of 8758 subjects, there was a mean of 2.85 punctal plugs procedures per patient in the follow-up period. Total health plan costs for punctal plugs procedures were $3.28 million (mean cost per patient $375). During the follow-up period, 21.1% of punctal plugs patients subsequently received cyclosporine, whereas only 11.4% of topical cyclosporine patients subsequently received punctal plugs. Our results suggest that use of topical cyclosporine before punctal plugs insertion may be of benefit to patients with DED and could result in a savings in overall treatment costs.

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For author information and disclosures, see end of text.

Severity Level*	Signs and Symptoms	Recommended Treatment
1	Mild to moderate symptoms and no signs Mild to moderate conjunctival signs	Patient counseling, preserved tears, environmental management, allergy eye drops, water intake, hypoallergenic products. *If no improvement, add level 2.*
2	Moderate to severe symptoms Tear film signs Mild corneal punctate staining Conjunctival staining Visual signs	Unpreserved tears, gels, ointments, topical cyclosporine, secretagogues, topical steroids, nutritional support. *If no improvement, add level 3.*
3	Severe symptoms Marked corneal punctate staining Central corneal staining Filamentary keratitis	Tetracycline, punctal plugs after control of inflammation. *If no improvement, add level 4.*
4	Severe symptoms Severe corneal staining, erosions Conjunctival scarring	Systemic anti-inflammatory therapy, oral cyclosporine, moisture goggles, acetylcysteine, punctate cautery, surgery.

*At least 1 sign and 1 symptom of each category should be present to qualify for corresponding level assignment.
ITF indicates International Task Force.
Source: Reference 1.

tory component of the disease is not addressed.

A Delphi panel was conducted to determine treatment recommendations for DED.[1] Because evidence-based treatment guidelines are not available to address all the considerations for DED, international experts convened to provide a simplified approach to treatment for the clinician incorporating the most updated evidence-based trials available. A full description of these recommendations is beyond the scope of this paper; however, treatment-specific guidelines by this International Task Force (ITF) included topical cyclosporine or steroid therapy at level 2 severity whereas punctal plugs insertion was included as an option at level 3 severity, after control of the inflammatory component of the disease (Table 1).

The purpose of this study was to investigate DED patients who are treated with topical cyclosporine and/or punctal plugs by evaluating treatment patterns of topical cyclosporine prescription fills, assessing utilization characteristics of punctal plugs patients, and examining the combination use of topical cyclosporine and punctal plugs. The study also investigated health plan costs for topical cyclosporine and punctal plugs among the topical cyclosporine and punctal plugs cohorts. An assessment of the overall clinical outcomes of topical cyclosporine relative to punctal plugs in DED patients was not conducted because the claims data analyses performed were retrospective in nature. Rather, our focus was on evaluating the utilization characteristics and costs associated with use of these treatments in patients with DED.

Methods

Claims data were gathered from a proprietary research database containing health plan enrollment, medical claims, and pharmacy claims data from 1993 until the current date. The claims submitted by providers and pharmacies to obtain payment for healthcare services rendered were collected. Enrollment data to track plan membership were procured in addition to health plan provider data to track physicians providing services. For 2004, data for approximately 13 million individuals with pharmacy and medical coverage were mined. Data are updated regularly with about 95% of medical claims complete within 6 months. The full study period was July 4, 2003, through December 31, 2006. The period for identification of study subjects was January 1, 2004, through December 31, 2005. The proprietary research database used enrollment data, pharmacy claims, and medical claims to capture a longitudinal record of medical services, irrespective of treatment site.

The study population consisted of 23,821 commercial health plan members with both medical and pharmacy benefits initiating treatment with topical cyclosporine or punctal plugs during the identification period.

Inclusion criteria:

1. More than 1 prescription filled for topical cy-

closporine or 1 physician or facility claim for a punctal plugs procedure between January 1, 2004, and December 31, 2005. The service date on the first claim for either topical cyclosporine or punctal plugs was assigned as the *index date*.
2. Continuously enrolled in health plan for 180 days prior to the index date with no prescription for topical cyclosporine or claim for punctal plugs insertion and at least 365 days of follow-up.
3. Aged 18 years or older as of the year of the index date.
4. Patients were assigned to either the topical cyclosporine cohort or the punctal plugs cohort based on the treatment used on the index date. Patients initially treated with topical cyclosporine and punctal plugs on the same date were identified, but were not analyzed further (n = 133). Cohorts were analyzed separately according to their treatment regimen in the follow-up period (includes the index date).

The first objective was to evaluate treatment patterns for topical cyclosporine. A descriptive analysis of the topical cyclosporine cohort was conducted to assess basic utilization characteristics, including the number of unique prescription fills in the 365-day follow-up period, days supplied per prescription, quantity supplied per prescription, average days between filled prescriptions, and plan cost per filled prescription. Cyclosporine ophthalmic emulsion 0.05% is commercially available as a unit-dose vial with 32 vials per tray.

The utilization characteristics of patients with punctal plugs were also assessed. This consisted of a descriptive analysis of the punctal plugs cohort, identified as treated with a punctal plugs procedure on the index date. The outcomes measured included the number of unique procedures in the follow-up period and associated plan costs. The type of procedure was also analyzed based on appearance of Healthcare Commom Procedure Coding System (HCPCS) code A4262 (collagen) and/or A4263 (silicone) with the procedure code. In cases where an HCPCS was not reported, the procedure type was classified as "unknown." In cases where both HCPCS designations were reported, the procedure type was classified as "both." Collagen plugs are often inserted as initial therapy to determine if punctal plugs provide any therapeutic value for a particular DED patient. These plugs are not permanent, are absorbed over a period of days to months,[6] and may be replaced with nonabsorbable silicone plugs. The average number of days between procedures, the total plan cost for the first punctal plugs procedure, and the total plan cost for subsequent punctal plugs procedures in the 365-day follow-up period were also reviewed.

The examination of the combination use of topical cyclosporine and punctal plugs included descriptive analysis of combination treatment by the topical cyclosporine and punctal plugs cohorts. These analyses focused on describing the supplemental use of topical cyclosporine or punctal plugs in patients during the follow-up period of the study. Outcomes measured for the topical cyclosporine cohort included treatment with punctal plugs in the follow-up period and time from index date to treatment with punctal plugs. The outcomes measured for the punctal plugs cohort included treatment with topical cyclosporine in the follow-up period and time from the index date to treatment with topical cyclosporine.

Patient characteristics assessed were age, sex, and length of time following the index date during which a patient was continuously enrolled. The descriptive analysis included the numbers and percents for dichotomous and polychotomous variables, and the means, medians, and standard deviations for continuous variables.

Results

Among the commercial health plan enrollees who met all inclusion criteria, there were 9065 subjects in the topical cyclosporine group, while the punctal plugs cohort had 8758 members. The overall topical cyclosporine and punctal plugs cohorts are similarly distributed across age, sex, and length of study follow-up. The majority of the study population was aged 45 years or older including 76.6% of the topical cyclosporine cohort and 65.8% of the punctal plugs cohort. The patients were predominantly female (80% in the topical cyclosporine group and 76% in the punctal plugs group).

Topical cyclosporine cohort analyses

Topical cyclosporine utilization varied during the follow-up period, with 58.4% (5294) having 2 to 4 prescriptions filled during the follow-up period, while 41.6% (3771) of topical cyclosporine patients had 5 or more prescription fills for topical cyclosporine during the follow-up period. There were

Utilization Measure	Result
Unique prescription fills in follow-up period	
Total number	35,591
Mean	3.93
Standard deviation	2.68
Median	3.00
Days and Quantity Shipped	
Mean (median) days supplied per prescription	31.51 (30)
Mean (median) quantity supplied per prescription	55.02 (32)
Mean (median) days between prescription fills	128.29 (92.44)

Source: Allergan, Inc, unpublished data, 2008.

35,591 unique topical cyclosporine prescription fills reported in the 365-day follow-up period (includes the index date), with a mean of 3.93 (median of 3) per subject (Table 2). The mean days supply per topical cyclosporine prescription was 31.51. The mean quantity per prescription was 55.02 vials for the topical cyclosporine cohort. There was a mean of 128.29 (median of 92.44) days between prescription fills for the topical cyclosporine cohort.

The mean health plan cost per patient (prescription cost paid by the plan) in the 365-day follow-up period was $336 (median $228) for the topical cyclosporine cohort. The health plan cost per topical cyclosporine prescription for the average patient was $98. Total health plan costs for the topical cyclosporine cohort in the follow-up period were $3.05 million.

Punctal plugs cohort analyses

In the punctal plugs patients there were 24,981 unique procedures reported in the 365-day follow-up period (includes the index date) with a mean of 2.85 procedures per subject. Punctal plugs procedures were also analyzed separately by type (ie, collagen, silicone, unknown and both) (Table 3). Punctal plugs procedures of unknown type were most common in the follow-up period, followed by silicone, collagen, and both. There was a mean of 1.72 unknown-type procedure per subject in the follow-up period. There was a mean of 0.93 silicone procedures per subject in the follow-up period. The total health plan cost for punctal plugs procedures across all patients was $3.28 million ($375 mean cost per patient) in the 365-day follow-up period (includes index date). Total costs for the initial punctal plugs procedure were $2.24 million and an additional $1.04 million in costs for subsequent punctal plugs procedures during the follow-up. The mean cost per subject for the initial punctal plugs procedure was $256 and increased to $307 per procedure in the remaining 365-day follow-up period for patients with multiple plug procedures. Approximately 39% of the punctal plugs cohort had an additional plugs procedure in the 365-day follow-up period. Of the punctal plugs cohort that had follow-up procedures, there was an average of 65.7 (median of 23.3) days between punctal plugs procedures.

Combined topical cyclosporine and punctal plugs use analyses

An additional objective of this work was to evaluate how frequently patients with DED received both topical cyclosporine and punctal plugs treatment during the follow-up period. Analysis showed that 21.1% (n = 1848) of punctal plugs patients subsequently received topical cyclosporine during the follow-up period; 11.4% (n = 1033) of topical cyclosporine patients subsequently received punctal plugs during that same time period. The combined topical cyclosporine and punctal plugs cohorts were similarly distributed across age, sex, and length of

	Result				
Utilization Measure	**Total Plugs**	**Collagen Plugs**	**Silicone Plugs**	**Unknown Type Plugs**	**Both Type Plugs**
Total number of procedures	24,981	1507	8173	15,049	252
Mean	2.85	0.17	0.93	1.72	0.03
Standard deviation	2.16	0.74	1.53	2.01	0.33
Median	2.00	0.00	0.00	1.00	0.00

Source: Allergan, Inc, unpublished data, 2008.

Topical Cyclosporine Subjects Treated With Punctal Plugs in Follow-up Period	
Number of procedures	1535.01
Mean	0.17
Standard deviation	0.60
Median	0.00
Punctal Plugs Subjects Treated With Topical Cyclosporine in Follow-up Period	
Number of prescriptions	3554.77
Mean	0.41
Standard deviation	1.21
Median	0.00

Source: Allergan, Inc, unpublished data, 2008.

study follow-up as noted for each individual group. No correlation could be made with severity of disease in the combined group because this information was not available from the data source.

In the topical cyclosporine cohort, there were 1535 total punctal plugs procedures in the follow-up period, with a mean of 0.17 per subject (**Table 4**). The topical cyclosporine cohort had a mean of 253.3 days from treatment on the index date with topical cyclosporine to the first punctal plugs procedure. In the follow-up period, the topical cyclosporine subjects had a punctal plugs procedure at a rate of 61.45 per 1000 person-years (**Figure**).

For the punctal plugs cohort there were 3555 prescription fills in the follow-up period, with a mean of 0.41 per subject (Table 4). The punctal plugs cohort had a mean of 203.9 days from treatment on the index date with punctal plugs to the first topical cyclosporine prescription fill. In the follow-up period, punctal plugs subjects filled a topical cyclosporine prescription at a rate of 113.02 per 1000 person-years (Figure).

Discussion

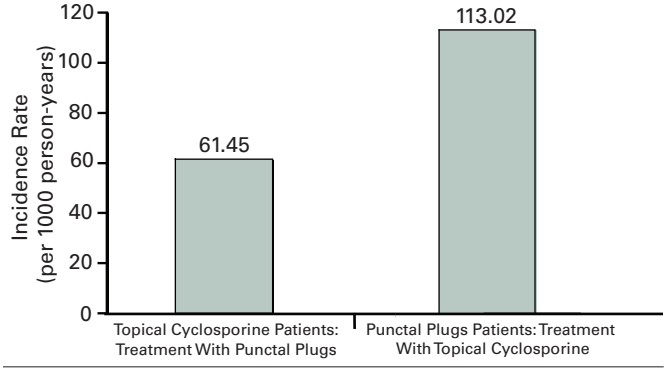
The ITF recommendations are that anti-inflammatories such as topical cyclosporine be initiated at level 2 severity and that inflammation be controlled before punctal plug insertion at level 3 severity in patients with DED (Table 1). This study sought to determine if real-world usage reflects ITF recommendations by evaluating treatment patterns and utilization characteristics of patients receiving cyclosporine ophthalmic emulsion 0.05%, punctal plugs, or a combination of topical cyclosporine and punctal plugs. This study was not designed to support or refute the ITF recommendations, but to analyze utilization patterns of topical cyclosporine versus punctal plugs in DED patients.

There was combination use of treatments among cohorts, suggesting that providers are prescribing both punctal plugs and topical cyclosporine to better address symptoms of DED and associated diagnoses. Punctal plugs subjects used topical cyclosporine at a higher rate than topical cyclosporine subjects used punctal plugs in the follow-up period. Total punctal plugs costs were highest on the index date and dropped in the follow-up period, as a result of fewer subjects having additional punctal plugs procedures. However, the mean cost per subject (of those who had follow-up punctal plugs procedures) increased for subsequent procedures.

There are limitations that are inherent with analysis of the data that are collected for the purpose of payment and not research. The presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. OTC medications or medications provided as samples by the physician could not be accounted for in the claims data. The presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Some information that could have an effect on study outcomes, such as certain clinical or disease-specific parameters, is not readily available in claims data.

The utilization and cost results appear congruous with ITF recommendations that topical cyclosporine

Figure. Combination Treatment by Topical Cyclosporine and Punctal Plugs Cohorts in the Follow-up Period



Source: Allergan, Inc, unpublished data, 2008.

be initiated at level 2 severity, with punctal plug insertion used at level 3 severity, after control of inflammation. In a recent study that implemented ITF guidelines,[7] punctal plugs were inserted in only 2 of 183 subjects. For 2 other subjects who would have received punctal plugs from their physician, topical cyclosporine was used, per ITF guidelines, to avoid having inflammatory factors remain on the ocular surface.[7] By following the guidelines, when artificial tears and patient education did not resolve a level 1 complaint, physicians were more likely to use topical cyclosporine to interrupt the inflammatory cycles, possibly helping prevent disease progression. In the topical cyclosporine cohort in our study, patients were treated with punctal plugs at an incidence of 61.45 per 1000 person-years versus an incidence of 113.02 per 1000 person-years for punctal plugs cohort patients prescribed topical cyclosporine. Comparison of these utilization and cost analysis data suggests that patients initially treated with punctal plugs were more likely to require additional treatments than patients initially treated with topical cyclosporine. It appears that, when using combination treatment of topical cyclosporine and punctal plugs, patients may benefit from initial treatment with topical cyclosporine before punctal plugs insertion.

Conclusions

A significant percentage of DED patients are receiving punctal plugs prior to topical cyclosporine, which does not reflect published ITF guidelines. Combination use of topical cyclosporine and punctal plugs suggests that both are being used to provide relief of symptoms of DED. Punctal plugs subjects used topical cyclosporine at a significantly higher rate than topical cyclosporine subjects used punctal plugs in the follow-up period. The lack of clinical data such as severity ratings limits what conclusions can be drawn from this study. However, the lower incidence of a second intervention, that is, punctal plugs, following topical cyclosporine supports the ITF recommendations that topical cyclosporine be initiated at level 2 severity and that inflammation be controlled before punctal plugs insertion at level 3 severity and this connection merits further study. Based on this utilization and cost analysis, the adoption of the ITF recommendations could result in a savings in overall treatment costs.

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