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Comparison of the discontinuation rates and side-effect profiles of pilocarpine and cevimeline for xerostomia in Primary Sjögren's syndrome

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ABSTRACT

Objective. *There are currently no head-to-head comparisons of sialagogues for Primary Sjögren's syndrome (pSS). We compared the tolerability and side effect profile of pilocarpine and cevimeline in patients with pSS and determined clinical, laboratory and pathological variables associated with therapeutic failure.*

Methods. *We retrospectively reviewed the use of pilocarpine and cevimeline in 118 patients with pSS who fulfilled the 2002 American European Consensus Group criteria in a University-based setting. Clinical, laboratory and pathological baseline variables were collected. Failure of therapy was defined as the clinician or patient's decision to stop treatment either due to lack of efficacy or side effects.*

Results. *Cevimeline was associated with lower failure rates compared to pilocarpine among first-time users: 27% vs. 47% (p=0.02), and all users: 32% vs. 61% (p<0.001). Severe sweating was the most frequent side effect leading to cessation of therapy and occurred more frequently in pilocarpine (25%) than cevimeline (11%) users (p=0.02). Patients who previously failed one secretagogue were less likely to discontinue treatment with the other agent, 52% of first-time users vs. 27% of second-time users (p=0.004). Only ANA positivity was associated with failure: [59% vs. 38%] (p=0.03).*

Conclusion. *pSS patients were more likely to continue cevimeline than pilocarpine long-term due to fewer reported side effects with cevimeline. Therapeutic failure of one secretagogue did not predict similar results with the other since second time users were more likely to continue long-term treatment.*

Introduction

Secretagogues, or sialagogues, are a group of medications that bind to M3 muscarinic receptors on the salivary glands and increase saliva production in patients with xerostomia (1). In clinical trials, secretagogues have been shown to enhance saliva production in patients with pSS, provide symptomatic relief of xerostomia and other oral symptoms (2, 3) and demonstrate subjective and objective improvement of dry eyes (4).

Two agents are available in the US, pilocarpine and cevimeline. Both exhibit side effect profiles mostly related to their activity as cholinergic agonists; these include sweating, nausea, vomiting, diarrhea, abdominal cramps, blurred vision, headache, dizziness, urinary frequency, dyspepsia, myalgias and hot flashes (5-7).

Unfortunately, many patients fail to respond to therapy (8) or develop side effects that necessitate discontinuation. No previous head-to-head studies have evaluated efficacy and side-effect profiles of cevimeline and pilocarpine. Furthermore, little is known about the clinical or laboratory variables that predict side effects or therapeutic response. We compared the discontinuation rates and side effect profiles of pilocarpine and cevimeline in patients with pSS and investigated clinical, laboratory and pathological variables associated with their discontinuation.

Materials and methods

We retrospectively reviewed the use of secretagogues in all treated patients with pSS who fulfilled the 2002 American European Consensus Group criteria (9) and were seen at least twice from January 2002 to June 2012 at our institution.

Patients underwent a standard evaluation: complete history and physical examination, Schirmer's test, 15-minute measurement of unstimulated salivary flow (sialometry), laboratory testing and technetium-99 salivary scintigraphy (10). Labial salivary gland biopsy was performed in patients who initially failed to meet classification criteria. All patients were treatment naïve and assessed by one provider (FBV). Individuals with inadequate follow-up (less than two visits) were excluded. The protocol was approved by the local Institutional Review Board.

The decision to start secretagogues was based on severity of symptoms, history of oral complications (*e.g.* accelerated caries) and/or an abnormally low whole mouth unstimulated salivary flow rate (<0.3 cc/minute). The decision to choose pilocarpine *vs.* ce-

vimeline was made by the treating physician. Patients were started on a once daily dose and advanced as tolerated to minimise the chance of adverse effects. Patients who developed persistent side effects were advised to decrease the dose and continue treatment as long as they reported clinical benefit. We defined failure of therapy as the clinician or patient's decision to stop treatment either due to subjective lack of efficacy or side effects as documented in the medical record. Patients who failed one agent were offered the other agent. Baseline variables included age, sex, duration of xerostomia prior to therapy, unstimulated salivary flow rate, and the presence or absence of abnormalities of the following tests: SSA/SSB antibodies, rheumatoid factor (RF), antinuclear antibodies (ANA), complement levels, beta 2 microglobulin, serum protein electrophoresis (SPEP) (presence or absence of polyclonal gammopathy), salivary scintigraphy (normal or abnormal), focus score on lip biopsy ≥1/4 mm^2, and previous use of hydroxychloroquine (at least 3 months prior to starting a secretagogue).

Statistical analysis included the use of two-sided *t*-tests and Chi-square tests for group comparisons. A *p*-value of 0.05 or less was considered statistically significant. The proportion of subjects considered treatment failures was compared between pilocarpine and cevimeline among all treatment attempts as well as first time users only.

Results

One hundred and eighteen patients met inclusion criteria, of whom, 109 were females (92.4%). The mean age was 61.4 years. Baseline characteristics were similar for all the variables studied among first-time users of cevimeline and pilocarpine and also among first and second-time users of secretagogues overall (Table I).

Initial Therapy

Pilocarpine was used as a first line therapy in 59 patients (50%), of whom, 28 patients (47%) discontinued treatment due to adverse effects. Eleven patients (19%) discontinued therapy due to lack of efficacy. Side effects included sweating (n=15), nausea, dyspepsia or vomiting (6), flushing/hot flashes (3), paresthesias (1), myalgias (1), headaches (1), and rash (1).

Cevimeline was used as initial therapy in 59 patients (50%); of whom, 16 patients (27%) discontinued medication due to side effects and 6 patient's (10%) due to lack of efficacy. Side effects included: sweating (n=8), nausea, dyspepsia and vomiting (5), flushing/hot flashes (1) headaches (1), and breast swelling (1).

Subjects switching to another agent

Thirty two patients who failed pilocarpine as first-line therapy switched to cevimeline as a second line agent. Seven (22%) developed side effects requiring discontinuation including sweating (n=2), dyspepsia (1), flushing/ hot flashes (1), diarrhoea (1), parotid swelling (1) and postnasal drip (1). None of these patients stopped treatment due to lack of efficacy.

Thirteen patients who failed cevimeline opted to try pilocarpine. Three patients (23%) developed side effects requiring discontinuation including sweating (n=1), dyspepsia (1), and flushing/hot flashes (1). Two patients stopped treatment due to lack of efficacy.

Compared to pilocarpine, cevimeline was associated with lower overall failure rate among first-time users: 22/59 (37%) *vs*. 39/59 (66%) (p=0.002) and all users (29/91, 32%) *vs*. (44/72, 61%) (p<0.001) (Table II).

Among first-time users, cevimeline was also associated with significantly lower failure rates due to reported adverse effects (16/59, 27%) *versus* pilocar-

Table I. Patient baseline characteristics within treatment category.

Variable	1st time users pilocarpine* n=59	1st time users cevimeline* n=59	1st time users† (all patients) n=118	2nd time users† n= 45
Duration of therapy (year)#	3.06 (3.49) (n=55)	2.87 (2.60) (n=57)	2.96 (3.04) (n=112)	2.52 (2.62) (n=44)
USFR#	0.15 (0.14) (n=46)	0.13 (0.16) (n=49)	0.14 (0.15) (n=95)	0.12 (0.10) (n=36)
SSA and /or SSB	62.1% (36/58)	72.4% (42/58)	67.2% (78/116)	65.1% (28/43)
ANA	67.8% (40/59)	63.2% (36/57)	65.5% (76/116)	70.4% (31/44)
Focus score# (when biopsy is positive for FLS)	1.84 (1.16) (n=24)	2.42 (1.75) (n=14)	2.05 (1.39) (n=38)	1.87 (0.87) (n=15)

*all p>0.05; †all p>0.05; # Mean value (standard deviation).
USFR: Unstimulated Salivary Flow Rate; ANA: Anti-Nuclear Antibody; FLS: Focal lymphocytic sialadenitis.

Table II. Failure rates among pilocarpine *vs*. cevimeline users.

	1st time users(n)	Failure due to side effects (1st time users)	All failures (1st time users)	2nd time users (n)	All failures (1st and 2nd time users)	Sweating (All users)
Pilocarpine	59	28/59 (47.4%)	39/59 (66.1%)	13	44/72 (61.1%)	18/72 (25%)
Cevimeline	59	16/59 (27.1%)	22/59 (37.2%)	32	29/91 (31.9%)	10/91 (11%)
p-value		0.02	0.002		<0.001	0.02

Table III. Failure rates among first *vs*. second time secretagogue users.

	1st time users*	2nd time users*
Total number of subjects	118	45
Number of subjects who failed therapy	61 (51.7%)	12 (26.7%)
p-value	0.004	

*For both pilocarpine and cevimeline.

pine (28/59, 47%). (p=0.02) (Table II).
Among all users, the proportion of subjects stopping medication for any documented side effect tended to be higher in the pilocarpine group (31/72, 43%) than cevimeline group (23/91, 25%) (p=0.09).
Severe sweating was the most frequent side effect leading to cessation of therapy and occurred more frequently among patients using pilocarpine (18/72, 25%) compared to cevimeline (10/91, 11%) (p=0.02) (Table II).
Patients who previously failed one secretagogue were less likely to discontinue treatment with the other agent: *i.e.* 61/118 (52%) of first-time users compared to 12/45 (27%) of second-time users (p=0.004) (Table III).
Among the various clinical and laboratory parameters studied, only ANA positivity was significantly associated with therapeutic failure: 45/76 (59%) of ANA-positive patients *vs.* 15/40 (38%) of ANA-negative patients. (p=0.03). Therapeutic failure did not correlate with the duration of xerostomia or baseline unstimulated salivary flow rate. There was no association between the focus score (representing the grade of sialadenitis) and treatment discontinuation (OR 0.55 (0.045–6.7) p=0.6)

Discussion

To our knowledge, this is the first study to compare discontinuation rates and side effect profiles of pilocarpine and cevimeline. Our data suggest that patients with pSS who use secretagogues for xerostomia are more likely to continue cevimeline than pilocarpine long-term, primarily due to fewer reported side-effects (primarily sweating) among cevimeline users. This has important implications to clinical practice, since access to cevimeline is expected to increase as it comes off patent.
Interestingly, therapeutic failure of one secretagogue did not necessarily predict similar results with the other. In fact, second time users seemed more likely to continue long-term treatment compared to initial users. Thus, pSS patients should not be denied treatment with the other agent simply based on an adverse experience with a previous therapy. While this finding may reflect a lack of effective therapeutic alternatives or altered patient expectations or perceptions regarding side effects, we believe this observation is reassuring and suggests that use of a second agent after initial treatment failure is reasonable and will not necessarily lead to the same result.
Among the various clinical and laboratory features of pSS, only ANA positivity was associated with a higher likelihood of treatment failure. ANA positive subjects may have a different disease phenotype that is less likely to respond to secretagogue therapy. This is hypothesis generating only and needs to be confirmed in other cohorts. In our institution, the cutoff for positive ANA is 1:160, which may explain the low prevalence of ANA in our cohort.
Our retrospective cohort study also has some limitations. Firstly, this study was observational and involved patients at a single site. Physician bias may have resulted in over or under reporting of side effects and affected the decision to stop therapy based on personal perception of efficacy. Secondly, the results of this single site study may not be fully generalisable to other groups and therefore needs to be confirmed in other SS patient populations. Sicca symptoms are frequently associated with fibromyalgia syndrome and use of certain medications among patients with pSS. Our study was limited in ability to study these associations, in part due to small sample size resulting in insufficient statistical power to study the independent effects of specific medications. Finally, issues such as compliance to secretagogue therapy, which could potentially affect the validity of the result, were not addressed. Interestingly, a recent report suggests low compliance rate to antimalarial drugs in these patients (11).
In conclusion, subjects taking cevimeline are less likely to discontinue therapy than those taking pilocarpine due to a lower incidence of sweating. Previous use of another secretagogue and a negative ANA were associated with a lower likelihood of discontinuation of therapy. Treatment failure with one secretagogue due to lack of efficacy or side effects did not predict treatment failure with the second line treatment.

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References

1. BRAGA MA,TARZIA O, BERGAMASCHI CC *et al*.: Comparison of the effects of pilocarpine and cevimeline on salivary flow. *Int J Dent Hyg* 2009; 7: 126-30.
2. VIVINO FB, AL-HASHIMI I, KHAN Z *et al*.: Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. *Arch Intern Med* 1999; 159: 174-81.
3. PAPAS AS, SHERRER YS, CHARNEY M *et al*.: Successful treatment of dry mouth and dry eye symptoms in Sjögren's syndrome patients with oral pilocarpine: a randomized, placebo-controlled, dose-adjustment study. *J Clin Rheumatol* 2004; 10: 169-77.
4. AKPEK EK, LINDSLEY KB, ADYANTHAYA RS *et al*.: Treatment of Sjögren's syndrome-associated dry eye an evidence-based review. *Ophthalmology* 2011; 118: 1242-52.
5. CHAINANI-WU N, GORSKY M, MAYER P *et al*.: Assessment of the use of sialogogues in the clinical management of patients with xerostomia. *Spec Care Dentist* 2006; 26: 164-70.
6. VIVINO FB: The treatment of Sjögren's syndrome patients with pilocarpine-tablets. *Scand J Rheumatol* 2001; 115 (Suppl.): 1-13.
7. PETRONE D, CONDEMI JJ, FIFE R *et al*.: A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum* 2002; 46: 748-54.
8. JORKJEND L, BERGENHOLTZ A, JOHANSSON AK *et al*.: Effect of Pilocarpine on impaired salivary secretion in patients with Sjögren's syndrome. *Swed Dent J* 2008; 32: 49-56.
9. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
10. HERMANN GA, VIVINO FB, GOIN JE: Scintigraphic features of chronic sialadenitis and Sjögren's syndrome: a comparison. *Nucl Med Commun* 1999; 20: 1123-32.
11. BALDINI C, NOTARSTEFANO C, PEPE P *et al*.: Discontinuation rates and timing of antimalarial drugs in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2013; 31: 160.