REVIEW

Treatment of oral dryness related complaints (xerostomia) in Sjögren's syndrome

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Primary Sjögren's syndrome (SS) is a systemic autoimmune disorder characterised by a chronic, progressive loss of salivary and lacrimal function resulting in symptoms of oral and ocular dryness. The involvement of exocrine glands is the result of a focal, periductal mononuclear cell infiltrate and the subsequent loss of secretory epithelial cells.[1] As a consequence, major changes occur in both the salivary flow rate and salivary composition.[2–9] In the case of secondary SS a second autoimmune disease is involved, mostly rheumatoid arthritis.

The role of saliva in maintaining oral health and even quality of life is obvious in people who are lacking sufficient saliva.[10–12] The effects of the reduced salivary flow rate (xerostomia) and changed salivary composition in SS are apparent (table 1): there are problems in eating, speaking, and swallowing[12–15] and frequently disturbances in taste perception.[16] In addition, reduced clearance of food, changes in microbial ecology and a reduced buffer capacity have their effects on oral health: an increased susceptibility to dental caries and oral infections are important clinical manifestations of the oral component of SS.[17 18] When the systemic disease advances, salivary secretion declines further.[7]

A reduction of the salivary flow rate below physiological values can be induced by several other causes as well.[19] Dry mouth symptoms are known as a side effect of more than 400 drugs.[20 21] In most of these cases the level of reduction of the salivary flow is slight and can be compensated for by mechanical or gustatory stimulation. Other common causes of prolonged hyposalivation include other autoimmune disorders such as systemic lupus erythematosus,[22 23] uncontrolled diabetes mellitus[24 25] and salivary gland injury as a result of radiotherapy in the head and neck region.[26]

This review describes the current treatments with regard to xerostomia focused on patients with SS. Because the treatment of the cause of oral dryness in Sjögren patients is possible so far, treatment is focused on stimulation of the residual capacity of the salivary glands and/or substitution of saliva with mouth rinses or saliva substitutes if stimulation of residual secretory capacity produces a too small effect. In addition, these patients need special care for preservation of their dentition and protection of their susceptible oral mucosa. With the exception of systemic treatments, there are clinically no differences in the treatment approach of the oral complaints in patients with primary and secondary SS as the choice of treatment is generally related to the level of the residual salivary secretion.

Systemic treatment

Systemic treatment of SS is generally based on treatments applied in related autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In patients with secondary SS, such an approach is obvious because of the treatment of the underlying autoimmune disease. In primary Sjögren patients the use of anti-rheumatics (for example, non-steroidal anti-inflammatory drugs, NSAIDs) is to suppress inflammation.

Both prednisone and piroxicam, as examples of steroid and NSAIDs, did not significantly improve the functional or histological parameters of the salivary and lacrimal glands in SS.[27] Therefore, the use of NSAIDs in SS is only indicated for the treatment of arthralgia and myalgia and for arthritis.[28] Besides analgesics, other anti-rheumatics that may be useful are (hydroxy)chloroquine and methotrexate (table 2). Administration of hydroxychloroquine resulted in a significant decrease of immunoglobulin serum concentrations.[37 38] In two small prospective trials the observed subjective improvement was not convincing,[37 38] while in a larger retrospective trial by the same authors about 55 per cent of the patients noted improvement in ocular symptoms (pain and dryness).[39] The same trial showed improvement of corneal integrity and lacrimal gland function in 50 per cent of the patients, improvement of subjective oral symptoms (pain and dryness) in about 60 per cent of the patients and a significantly

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Table 1   Consequences of xerostomia

Dryness of the mouth*	Burning sensation
Thirst sensation	Mucus accumulation
Difficulties in oral functioning	Changes in soft tissues
Difficulties in wearing dentures	Shift in oral microbial flora
Nocturnal oral discomfort	Xerostomia induced caries
Fatigue	Taste disturbances

*A good correlation between subjective oral dryness and measured salivary flow rates is observed in about 70% of the patients.[12] The other patients complain about oral dryness notwithstanding a normal salivary flow or the opposite.

Table 2 Major therapeutic agents tried for Sjögren's syndrome

Drug	Trial design	Patients*	Results	Reference
Cyclosporin (systemic)	open (continuation of double blind trial)	9 primary SS	subjective xerostomia improvement in 88% (p<0.01), mean worsening immunopathology minor salivary glands of 1.2 at a labial biopsy score from 0–4), no effect on salivary and lacrimal gland function	29
Cyclophosphamide (intravenous)	case report	1 primary SS, later development of polymyositis	good response on myositis symptoms; from extensive muscle fibre necrosis to type II muscle fibre atrophy.	30
Azathioprine	double blind, randomised, placebo controlled	13 primary SS	no clinical or biochemical changes, six withdrew because of side effects	31
Prednisone	double blind, randomised, placebo controlled	8 primary SS	no objective improvement on salivary gland function; subjective improvement on xerostomia and xerophthalmia	27
Piroxicam	double blind, randomised, placebo controlled	8 primary SS	no changes	27
Interferon α₂ + prednisone minipulse	open study *v* hydroxychloroquine	10 primary SS	improvement in salivary and lacrimal function, no changes in immunopathology; in three patients transient alopecia as side effect	32
	single blinded *v* sucralfate	28 primary SS + 2 secondary SS	improvement in salivary gland function in 50% of the patients; in nine patients decrease of lymphocytic infiltration in salivary glands	33
Methotrexate	open	17 primary SS	at 0.2 mg/kg/week: improvement of subjective oral and ocular symptoms, decrease of parotid gland enlargement frequency, dry cough and purpura; no increase of salivary and lacrimal gland function	34
Sulfasalazine	open	10 primary SS	improvement in two patients in arthralgia and fatigue; in two patients no improvement; six patients dropped out by severe side effects.	35
D-penicillamine	open	4 primary SS	subjective improvement in saliva (4 patients) and tear secretion (2 patients); side effects in two patients: pruritic rash and oral ulcers, respectively.	36
Hydroxychloroquine	open	3 primary SS	subjective improvement in saliva, tear and vaginal secretion; rose bengal staining became negative in 2 patients	37
	open, controlled	10 primary SS	decreased serum immunoglobulin levels; decreased rheumatoid factor levels	37
	double blinded placebo controlled crossover	19 primary SS	decreased serum immunoglobulin levels; no clinical beneficial effects on salivary and lacrimal gland function	38
	open, retrospective	50 primary SS	decreased IgG levels; slight improvement of oral and ocular symptoms and of arthralgia/myalgia	39
Hydroxychloroquine + prednisone (mini-pulse and daily 5 mg)	open *v* interferon α₂	10 primary SS	no changes in serum immunoglobulin and rheumatoid factor levels; no changes in salivary or lacrimal gland function	32

*Only medicated patients are listed, SS = Sjögren's syndrome.

increased salivary flow rate in 82 per cent of the patients.[39] Whether the efficacy of hydroxychloroquine is related to the duration of administration needs further study, but administration of hydroxychloroquine for less than one year probably will result in less beneficial results.[38 39] Moreover, the response to hydroxychloroquine of a population of patients with SS may be influenced by the diagnostic criteria that has been used to select the patients for the study.[39] The "San Diego criteria" for diagnosing SS are mainly focused on the autoimmune parameters, which increase the chance of response to an immunomodulating drug when compared with patient selection on the "European criteria", which depend strongly on clinical dryness symptoms.[40 41] With respect to side effects such as retinopathy, a known adverse reaction of high dose antimalarial use, hydroxychloroquine can be used safely up to 6–7 mg/kg/day.[42 43] In conclusion, use of hydroxychloroquine seems to be promising in the treatment of SS, although blinded, long term prospective studies are needed before this treatment can be accepted generally.

An approach to intervene in the T cell proliferation resulting in downregulation of interferon γ with azathioprine was not successful. In a double blind, placebo controlled trial six of 13 patients of the treatment group withdrew because of side effects, such as nausea, anxiety and indigestion.[31] One patient developed nausea and abnormal liver function and one patient withdrew because of a perforated large bowel. However, there were no distinguishing characteristics between patients who withdrew the study and patients who completed it. Therapeutic benefit of azathioprine on symptoms, signs, serological and histological parameters was not observed. This in combination with the high incidence of adverse reactions makes azathioprine not indicated in the treatment of SS.

Another T cell intervening treatment is the use of low dose cyclosporin A. This agent acts by interleukin 2 inhibition and will lead to suppression of T cell proliferation. In an open trial subjective xerostomia symptoms improved in 88% (p<0.01) of the patients.[29] However, a mean worsening immunopathology of the minor salivary glands of 1.2 (at a labial biopsy score from 0–4) was observed (p<0.01) and there was no effect on salivary and lacrimal gland function.

Sulfasalazine has been applied to suppress hyperactive B lymphocyte activity in acute RA and primary SS.[44] The clinical effects of sulfasalazine in primary Sjögren patients were disappointing: six of 10 patients stopped the study early because of side effects such as allergic reactions and agranulocytosis. Improvement of fatigue and arthralgia was observed in two patients only. It is concluded that the use of sulfasalazine in SS is not indicated.[35]

The use of methotrexate is indicated in patients with RA. With regard to Sjögren patients some improvement of dryness of the mouth and eyes has been reported from administration of 0.2 mg/kg/week methotrexate, but the objective parameters remained

Table 3 Pilocarpine trials in Sjögren's syndrome for alleviating oral dryness

Trial design	Treatment regime	Patients	Results	Reference
double blind, placebo controlled, crossover	single dose, 5 mg capsule	2 primary SS + 4 chronic non-specific sialadenitis	subjective dryness decreased in all patients (interview score). In all patients the salivary flow was at least 10-fold after pilocarpine use compared to the placebo.	49
single blind, placebo controlled	three times daily oral administration of an ophthalmic 2% pilocarpine solution (eq. 5 mg)	3 primary SS + 6 secondary SS	no changes in salivary flow in primary SS; whole salivary flow increase of 0.18 ml/min (p<0.05), stimulated parotid salivary flow increase of 0.34 ml/min (p<0.01)	52
double blind, placebo controlled, crossover	three times daily, 5 mg capsule	18 primary SS + 3 secondary SS + 18 others with hyposalivation	26 of 39 reported an increase of parotid and sublingual/submandibular saliva. Seven patients withdrew from the study because of adverse effects.	50
multicentre, double blind, placebo controlled	unknown	11 SS★	improvement in 9 patients on xerostomia and in 8 patients on oral discomfort using a 20 point XOS scale. Mean stimulated salivary flow rate increased about threefold (p<0.08)	53
open	single dose, 5 mg tablet	9 primary SS + 9 secondary SS	twofold increase of mean whole salivary output	54
double blind, placebo controlled	5 mg four times daily (7.5 mg after 6 weeks if tolerated by the patient)	60 SS★	64.3 % of the treatment group v 25.0% of the placebo group indicated improvement in a global dry mouth assessment on a VAS scale (p<0.005). Mean salivary flow increase was 0.14 ml/min v zero of the placebo group.	51

★Discrimination between primary or secondary Sjögren's syndrome was not reported.

unchanged.[34] As with sulfasalazine, no double blind studies have been performed to justify the use of methotrexate in SS.

Summarising, the use of systemic drugs in primary SS is not successful yet. Cyclosporin A, azathioprine, and sulfasalazine are not indicated. More insight into the pathogenesis of primary SS is needed before new systemic treatments can be developed.

Stimulation of the residual capacity of the salivary glands

Salivary secretion is increased by non-specific mechanical and gustatory stimulants. For example, gustatory stimulation can be achieved by administration of citric acid, while chewing gum induces both mechanical and gustatory stimulation. In edentate patients acidulous stimulants can be applied ad libitum, but its use is restricted by mucosal irritation. In dry mouth patients having their own dentition, these stimulants are discouraged because the harmful effect on the teeth (demineralisation). The absence of saliva and concomitant salivary proteins and minerals makes the teeth extremely susceptible to dental erosion. Sugar free chewing gum, however, can be applied in patients with a rather high residual secretory potency of the salivary glands. In some patients, chewing gum is too sticky to dentures, although low tack chewing gums (for example, Freedent) are available. Another problem is that gustatory and mechanical stimulants only can be used during daytime as the patient has to suck or to chew. Many early Sjögren patients, however, particularly suffer from oral dryness when being at rest or during the night. This particular pattern of complaints is caused by the fact that in early Sjögren patients the salivary secretion from the mucous salivary glands (submandibular and sublingual glands), which are the major contributors to whole saliva during night time is diminished.[5 7] When eating or being subject to any other gustatory or mechanical stimulation, the contribution of (serous) parotid saliva to whole saliva increases, resulting only a transiently reduction of a dry mouth sensation in these patients. As the disease proceeds the secretion of the parotid glands reduces as well and the effect of

stimulants becomes insufficient.[7] Humidification of the patient's bedroom and lubrication of the oral mucosa by a vegetable oil are widely used household medicines.

Besides oral and ocular sicca symptoms in SS, fatigue is a manifestation that affects the quality of life very seriously. It has been suggested that nocturnal oral dryness is a factor that contributes to the fatigue complaints.[45] Nocturnal dryness can occur in a very early stage in SS when the submandibular glands, which are the main contributors to whole saliva during night time, are affected. In this context, studies on treatment of oral dryness in SS, reported benefits of the applied treatments during the night.[46–48]

Pharmacological stimulants may act throughout the day. Most studies dealing with application of pharmacological stimulants in SS have been focused on pilocarpine (for example, Salagen, Chiron, Middlesex, United Kingdom) (table 3). Pilocarpine is a muscarinergic cholinergic agonist that stimulates salivary secretion in both normal subjects and in patients suffering from impaired salivary gland function. Salivary flow rate increases within 15 minutes after oral pilocarpine administration and peak flow rates maintains for at least one hour in patients with xerostomia.[49 50] The efficacy of pilocarpine administration, however, varies by study. Unfortunately, reports of large (multicentre) studies are lacking and study designs are sometimes unclear or incomparable by poor definition of the patient population,[51] or by unusual administration forms[52] (table 3). A clinical problem of the use of pilocarpine is its broad spectrum of pharmacological (side)effects, for example, it increases secretion of all exocrine glands, including the sweat, lacrimal, gastric, pancreatic and intestinal glands, and the mucous cells of the respiratory tract.[53 56] When applied as 5 or 10 mg tablets, three times per day, adverse effects such as sweating, chills, nausea, dizziness, rhinitis and asthenia in patients suffering from irradiation induced xerostomia or chronic graft versus host disease has been observed.[57 58] Administration of pilocarpine in patients with primary SS showed a similar reduction of the sensation of oral dryness, but with less adverse effects.[49 50]

Because of a better peak concentration control, less side effects and a prolonged effect of pilocarpine on oral dryness probably can be expected from the use of slow release preparations.[59 60]

Another potential drug for treatment of xerostomia in Sjögren patients is anethole trithione. The exact mechanism of action of this drug is still unknown, but it has been reported to induce less side effects than pilocarpine.[61] In Sjögren patients a beneficial effect on oral dryness has been reported by 25 mg anethole trithione, three times per day.[62] A combination of pilocarpine and anethole trithione showed a synergistic effect on salivary secretion.[63] Beneficial effects within the first five days of administration, were not observed in patients whose hyposalivation was attributable to anti-psychotic drug use.[64]

Besides pilocarpine and anethole trithione, many other drugs can stimulate the salivary glands, including carbamylcholine, yohimbine, neostigmine, and pyridostigmine, but their use is limited. In patients with a drug induced oral dryness, administration of the α_2 adrenergic antagonist yohimbine resulted in more success than the use of anethole trithione.[64] Besides pharmacological stimuli, acupuncture and electrostimulation have been used in the treatment of xerostomia with varying success. Both treatments seemed to be helpful for some patients, but a large individual variation in response has been reported.[65 66]

Saliva substitutes

Replacement of saliva by a fluid other than saliva has been proposed as a possible treatment in relieving subjective complaints of xerostomia for more than three decades. Water can be used as a saliva replacement, but it is known that water does not moisten and lubricate the oral mucosa and teeth adequately.[67] Therefore, saliva substitutes containing thickening agents for longer relief and increased moistening and lubrication of the oral surfaces have been developed. Particularly saliva substitutes based on carboxymethyl-cellulose[68] or mucin[69] have been applied world wide. In numerous clinical trials with different experimental designs the efficacy of carboxymethylcellulose and mucin based saliva substitutes in patients with SS have been evaluated.[12 46 70–76] Mucin preparations were also developed as a lozenge and as a chewing gum and may be used as "saliva additives".[47 75] In general, most of these studies report a beneficial effect of the substitutes tested. However, there is a discrepancy between the author's opinion in review papers concerning management of xerostomia and those of original articles. Opinions about the benefit of saliva substitutes gained in patients with dry mouth in review papers are in general more reserved than the reported clinical data.[76 77] Two major reasons may, at least in part, count for this discrepancy. Firstly, the efficacy of a saliva substitute is dependent on the instruction given and expectations of that patient.[78] Without proper instruction, a beneficial effect of a saliva substitute is generally not to be expected. Secondly,

the composition of the commercially available saliva substitutes often differs from the composition of the substitutes tested in the clinical trial. For example, the mucin ingredient in the saliva substitute Saliva Orthana was primarily a mixture of bovine submandibular mucin and porcine gastric mucin, but was changed later to porcine gastric mucin only, resulting in essentially different rheological and lubricating properties.[67 79 80]

Besides saliva substitutes based on carboxymethylcellulose and animal mucins, a number of saliva substitutes based on other thickening agents have been developed such as polyethylenoxide based substitutes[76] and linseed polysaccharide extracts.[81] Polyethylenoxide formulations seem to give more relief in xerostomic patients than a methylcellulose based saliva substitute.[76] The linseed polysaccharide based substitute has been reported to reduce the complaints of hyposalivation in about 75% of the patients.[81] More recently, saliva substitutes based on polyacrylic acid and xanthan gum have been developed and evaluated in Sjögren patients.[48] The latter study showed that the total population of Sjögren patients can be subdivided into subpopulations in which a particular saliva substitute is the most effective. Use of highly mucoadhesive polymers (polyacrylic acid) is recommended in saliva substitutes for patients with extremely low salivary flow rates. Patients who still are able to secrete some saliva may experience more benefit with saliva substitutes with moderate mucoadhesive and high elastic properties (xanthan gum) as these polymers can increase the "physico-chemical quality" of their residual saliva: moistening and lubrication. A similar correlation between residual salivary flow rate and efficacy of a particular saliva substitute is mentioned in the mucin containing lozenge study of 's-Gravenmade and Vissink[47] and the polyglycerylmethacrylate study of Regelink and coworkers.[82]

Treatment of oral infections

In several studies the relation between reduction of salivary flow and increase of risk on oral infections has been demonstrated. The main oral infections observed in patients with hyposalivation are oral candidiasis, dental caries and periodontitis.[83]

Clinical manifestations of candidiasis have been reported to occur in up to 80% of patients with SS, mostly characterised by angular cheilitis (19–35%) and acute erythematous candidiasis (38–65%) rather than a whitish coat on the oral mucosa.[84–87] The predominant predisposing factors of oral candidiasis in SS are the reduced salivary flow and the concomitant reduced mechanical cleansing (washing effect) of the oral surfaces.[88] The removal of aggregated or adhered fungal cells is hampered, resulting in overgrowth and colonization of *Candida* species.[89 90] The risk on development of candidiasis is higher in patients wearing removable dentures.[91 92]

Adequate oral hygiene is needed to prevent erythematous candidiasis and angular cheilitis. Denture wearing during the night is

Table 4   Recommended guidelines in the prevention of xerostomia related dental decay. (Modified after Newbrun[95] [101])

1   *Personal dental plaque measures*
Twice daily cleaning of the teeth by use of a toothbrush (if an electric toothbrush is used, professional instruction is needed), dental floss, or interdental brush, and fluoride containing dentifrice.

2   *Dietary instruction*
Limit the use of between meals intake of sugary foods, candies, and sugar containing beverages. Encouraging the use of non-cariogenic sweeteners such as aspartame, saccharin, acesulfam K, sorbitol or xylitol. The last two sugars are not separately available as sweeteners.

3   *Office fluoride therapy*
At the initial visit at the dental office application of a high concentration fluoride agent, either a neutral fluoride gel for 4 minutes in a tray or a fluoride varnish directly onto the dentition. Varnishes can be applied simply by a small handbrush. As the application frequency is an important factor in determining efficacy, a four times per year application frequency is recommended.

4   *Office chlorhexidine therapy (optional)*
At the initial visit a 1% chlorhexidine gel for 5 minutes or a high concentration chlorhexidine varnish can be applied.

5   *Home use fluoride therapy*
A weekly to daily application of a neutral fluoride gel in a custom fitted tray. The application frequency depends on the severity of caries susceptibility. For patients who cannot tolerate a gel, a daily 0.05% sodium fluoride rinse for one minute is an alternative. The use of acidulated phosphate fluoride gels in patients with (severe) oral dryness is not recommended because of the dental erosive effects of these gels.

6   *Home use chlorhexidine therapy (optional)*
As complementing therapy, thus not as an alternative, with fluoride application chlorhexidine rinses can be used. However, the indication is limited to the number of *Streptococcus mutans* in saliva: >1×10^6 counts/ml saliva. If the number cultivable counts of *S mutans* exceeds the limit 1×10^6 a twice daily rinse can be used during one minute for two weeks. Because of the bioavailability of fluoride in rinses, chlorhexidine should not be used simultaneously with fluoride in one solution.

discouraged. *Candida* species can lodge in the denture acrylate. Therefore, dentures should be cleaned with chlorhexidine solution 0.2% overnight or a chlorhexidine gel 1% two times a day in case of clinical manifestations of oral candidiasis. Oral candidiasis can be treated with topical use of miconazole gel 2%, topically applied, four times per day for at least two weeks. In cases of refractory candidiasis, amphotericin B lozenges (10 mg) can be used four times a day for at least two weeks.[92] Continuous application of an anti-fungal mouthrinse to prevent oral candidiasis is still a matter of debate. Particularly formulations containing chlorhexidine or cetylpyridinium chloride might be significant, but need further study.[93]

In SS dental decay is a common complication that needs preventive oral care.[94] It was found that in patients with SS 62% of the subjects were completely or partially edentulous (>12 teeth loss) compared with 21% in the control patient group.[18] Two thirds of the Sjögren patients had lost the teeth before the age of 45 compared with 10% in the control group. This indicates that the onset of dental loss in SS may occur at an early stage, possibly related to the increased caries risk in these patients.

The mainstay of prevention against dental decay in patients with SS is through removal of dental plaque by excellent oral hygiene. The literature is, however, heterogeneous in recommendations of (preventive) treatments of dental decay in hyposalivation. The use and application time of common fluoride containing dentifrices is important, preferably with mild flavouring because of the tender oral mucous membranes. Cleansing the teeth, at least two times a day, for 5 to 10 minutes is recommended. If the patient is not able to handle a normal toothbrush, for example, for reasons of arthritis, the use of an electrical toothbrush may be helpful. Because of the tenderness of the mucous membranes, the taste of oral

hygiene products can highly influence the acceptance and compliance of extensive oral care.[95]

Upon progression of the hyposalivation, extensive oral hygiene including interdental cleaning and application of topical fluoride neutral gels and/or chlorhexidine gels are needed. The most suitable formulas of topical fluoride gels contain 0.4 to 1.25 per cent fluoride, have a neutral pH and should be used at least once a week. In cases of extreme hyposalivation the frequency of application has to be increased up to two times per day.[96] [97] The use of acidulated phosphate fluoride gels in patients with a (severe) dry mouth is not recommended because of the dental erosive effects of these gels and patient compliance (tenderness of the mucous membranes).

Combinations of a fluoride and chlorhexidine containing agent have proved to be highly effective in irradiated patients, and may also be suitable for patients with SS.[98] This can be combined with the use of fluoride containing saliva substitutes. In vitro experiments show potential benefits of low dose fluoride intake to inhibit demineralisation (acid attacks).[99] [100] Table 4 summarises comprehensive recommendations of oral care in patients with SS.

Candidiasis and dental caries, are relatively simply defined because of the involvement of very few microbial species (*Candida spp* and *Streptococcus mutans*, respectively). Infection of the periodontium is more complicated by a higher number of different bacteria and also immunological as well as non-immunological factors of the host.[102] Treatment of RA and SS with DMARDs or anti-inflammatory drugs may worsen the course of periodontal disease in such patients.[103] Whether this is the result of the suppression of the immunological response by anti-inflammatory drugs, a reduced salivary output, or an increase of inflammatory activity in SS is still a matter of debate.[104] Indeed, an odds ratio of 2.2 observed by Najera and coworkers[83] suggests a higher risk of periodontal disease in SS. However, these studies in

van der Reijden, Vissink, Veerman, et al

which the periodontal disease has been correlated with RA or SS lack an adequate well documentation of the microbial ecology of the individual patients. Therefore, it is too preliminary to speculate about the onset of periodontitis in SS notwithstanding it is worthwhile to take into account.

Future prospects

With respect to several trials with systemic drugs in primary SS the administration of current drugs is not successful yet (table 2). Primarily, more insight in the pathogenesis is needed to develop new drugs that can modulate the hyperactivity of lymphocyte B cells in those organs that are affected in SS.

At present different strategies for treatment of xerostomia in SS are being explored. In the field of pharmacological stimulation of salivary glands, slow release delivery systems for pilocarpine have been introduced.[60] A significant increase in both whole and parotid salivary secretion lasting over 10 hours seems to be promising. No side effects were observed, probably because of the absence of a peak concentration directly after administration. The benefit of the pilocarpine controlled release tablet in patients with xerostomia warrants future research in a double blinded, placebo controlled study.

Development of saliva substitutes based on novel thickening agents that may provide longer retention on the mucosal surface is a subject of current interest. Two new saliva replacement products that have been shown to be effective in Sjögren patients[48 81] are currently available in Europe, namely substitutes based on linseed polysaccharide (Salinum, Miwana AB, Gällivare, Sweden) or xanthan gum polysaccharide (Xialine, Lommerse Pharma BV, Oss, the Netherlands). Other mucoadhesives such as carbomer (polyacrylic acid) are also potentially useful, but its application in saliva substitutes is restricted by the calcium binding properties, and thus dental demineralising properties of this polymer.[99] Such substitutes, which are not on the market yet, would be applicable in edentulous patients only. A moistening mouth gel based on polyglycerylmethacrylate (Oral Balance, Laclede Inc, Gardena, CA, USA) shows moistening for more than one hour in severe xerostomic patients.[82] With regard to saliva substitutes, addition of fluoride is the only confirmed caries preventive agent that is successful.[99 100]

A novel development is the application of natural anti-microbial compounds such as lactoperoxidase, lysozyme and lactoferrin in saliva substitutes for maintaining oral health.[105] In this area, much research is aimed at the production of anti-microbial peptides, originally derived from histatins. Histatins are antifungal proteins naturally originating from the serous salivary glands, to prevent oral candidiasis. Such synthetic peptides display about 10-fold more activity against *Candida albicans* than natural histatins. Although these compounds have not been tested clinically, the results from in vitro studies with synthetic peptides are promising.[106]

A more sophisticated but also more complicated treatment is offered by gene therapy. Theoretically, the water secreting capacity of salivary glands can be increased by insertion of water transporting proteins (aquaporins) in the cell membrane of the ductal cells. Because these cells are considered to be impermeable to water, such intervention should be done to create new secretory units. From the kidney it is known that water transport is conducted by aquaporins.[107] Introduction of a recombinant aquaporin in the submandibular glands of the rat by gene transfer showed a twofold increase of the saliva secretion in irradiated rats.[108] If a similar mechanism is applicable in SS, it needs to be studied in a SS model because the ductal system is affected as well by the underlying disease. The susceptibility of epithelial cells to adenoviral infection is related to a distinct integrin. The integrins observed in the rat submandibular gland are also localised to the human submandibular gland. This corresponding integrin type in humans may be able to mediate the gene transfer of aquaporins to salivary glands of human patients.[109] However, the main disadvantages of this technique for clinical application is its rather symptomatic and organ specific character, and, the treatment is not curing.

This last mentioned treatment is in contrast with the ongoing research in T cell receptor vaccination in some autoimmune diseases that may be applicable in SS. Vaccination with autoreactive T cells has been applied experimentally in patients with RA,[110] and multiple sclerosis.[111] In these studies, specific autoreactive T cells have been targeted with antibodies from an induced immune response against the T cell receptor by using whole pathogenic T cells. To induce a specific immune response against patient's own autoreactive T cells, vaccination with these selected T cell clones is necessary. The results are rather promising: in a paired controlled trial the existence of myelin basic protein autoreactive T cells were completely depleted.[111] In three of eight patients the autoreactive T cells reappeared with concomitant worsening of lesions or relapses.

Vaccination with T cell receptor peptides is another way to induce an anti-idiotypic T cell response by immunisation with T cell receptor peptides derived from the Vβ5.2 gene product, the myelin basic protein T cell receptor sequence.[112] The success rate in multiple sclerosis patients varied among patient's vaccine response. In a double blind trial only six of 15 patients with multiple sclerosis were determined as responders to Vβ5.2–28–58 peptide or the 49-tyrosine-threonine substituted peptide. Clinical improvement or stability was observed in all responders. The T cell frequency to myelin basic protein was decreased or stable in four and two patients respectively indicating a good correlation between vaccine response and clinical outcome.[113] In an uncontrolled study, decrease of activated T cells was observed in RA patients who were vaccinated with different doses T cell receptor Vβ17 peptides.[114] Concomitantly, a decrease of lymphocyte proliferation was observed in about 40

per cent of the patients. Finally, the mean painful joint score has been improved significantly. The association between vaccination response, reduction of lymphocyte proliferation and clinical benefit in T cell (peptide) vaccination suggests a very promising step forward to treatment of autoimmune diseases such as multiple sclerosis and RA, notwithstanding the number of responding patients, which is below 50 per cent. Intensifying of the research in this field is definitely worthwhile because of its curing character.

Conclusions

The oral component is a main symptom in SS.[115] However, the pathogenesis is not understood yet, and more research is needed to develop effective systemic treatments, both curative and symptomatic. The treatment to relieve dryness related symptoms is mainly based on stimulation of the residual secretory capacity of the affected salivary glands and, if this is no longer successful, replacement of natural saliva with a saliva substitute. Worthwhile saliva substitutes contain a thickening agent to provide longer retention on the oral mucosa and biologically active compounds for the prevention of dental decay and (fungal) opportunistic infections. Such additions may support the optimal oral care that is a sine qua non. New prospects are incorporation of antimicrobial compounds in saliva substitutes and mouth gels, and the ongoing research in gene therapy by integration of water channels into the ductal cells of the salivary glands to increase the secretory potency of these glands. Immunomodulation using vaccination with attenuated T cells or T cell receptor epitopes has not been proved successful in a 100% of the patients with multiple sclerosis or RA tested but it will be the new challenge for treating autoimmune diseases.

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