Review of Emerging Treatments for Benign Salivary Gland Disease

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Abstract

Benign salivary gland diseases encompass a diverse group of conditions, including obstructive, inflammatory, neoplastic, cystic, and autoimmune disorders, which pose significant clinical and therapeutic challenges. Traditional management approaches, while effective for many, often have limitations related to invasiveness, recurrence, and patient quality of life. This literature review explores emerging treatment modalities that aim to address these gaps, emphasizing innovations in non-surgical interventions, minimally invasive techniques, surgical advancements, regenerative medicine, and targeted pharmacological therapies.

Recent advances in sialendoscopy, lithotripsy, and radiofrequency ablation have revolutionized the management of obstructive and neoplastic conditions, offering enhanced precision and reduced morbidity. Similarly, novel pharmacological agents, including biologics and nanomedicine-based delivery systems, show promise in managing inflammatory and autoimmune diseases. Groundbreaking progress in regenerative medicine, such as stem cell therapies and tissue engineering, further highlights the potential for restoring salivary gland function in patients with chronic damage. These innovations are complemented by diagnostic advancements, including biomarkers, advanced imaging, and artificial intelligence, which enhance therapy selection and monitoring.

Despite these promising developments, barriers such as cost, accessibility, regulatory challenges, and the need for long-term efficacy data persist. This review identifies current knowledge gaps and advocates for collaborative research efforts to optimize the implementation of these emerging therapies. By integrating technological innovations and patient-centered approaches, the future of benign salivary gland disease management holds significant potential for improving outcomes and quality of life.

Introduction

Benign salivary gland diseases represent a broad spectrum of non-malignant disorders affecting the parotid, submandibular, sublingual, and numerous minor glands scattered throughout the oral cavity and oropharynx. They range from neoplastic conditions such as pleomorphic adenomas, the most common benign tumor, and Warthin's tumors, which are strongly associated with smoking, to non-neoplastic conditions like sialolithiasis, sialadenitis, and autoimmune disorders such as Sjögren's syndrome.[1] The most frequent causes involve inflammation or infection secondary to salivary duct obstruction by sialoliths, which reduce salivary flow and predispose patients to recurrent infection.[2] Though non-malignant, these diseases cause significant morbidity, leading to pain, swelling, xerostomia, and impaired oral function. Eating, speaking, and maintaining oral hygiene become difficult, making timely diagnosis and effective management essential.

Traditional therapies, including surgical excision, antibiotics, and anti-inflammatory medications, often fall short. Surgery carries risks such as facial nerve injury, cosmetic deformity, or incomplete resection, which may result in recurrence, while conservative therapy has limited benefit in chronic or autoimmune conditions like Sjögren's syndrome. Newer approaches—including minimally invasive procedures, regenerative medicine, and biologic therapies—offer the potential to address these shortcomings and improve both outcomes and patient quality of life.

The aim of this review is to explore these emerging therapies, evaluate their efficacy, and consider how they may reshape future management of benign salivary gland disease.

Non-Surgical Interventions

Botulinum toxin has become a valuable tool in managing sialorrhea and chronic sialadenitis. By blocking cholinergic transmission, it reduces salivary secretion, alleviating swelling and stasis.[3] It is particularly beneficial in neurologic conditions such as Parkinson's disease, muscular dystrophy, and ALS, where sialorrhea is common.[4] A randomized trial in Parkinson's patients showed that type B botulinum toxin safely and effectively reduced salivary flow without impairing swallowing.[5] Case series also suggest benefits in chronic parotid sialadenitis, reducing pain and recurrence. Side effects are minimal, generally limited to dry mouth or transient gastrointestinal and musculoskeletal symptoms, making botulinum toxin a versatile, well-tolerated therapy.

Salivary substitutes and stimulants have evolved to better replicate natural saliva and provide sustained relief of xerostomia. Biomaterial-based solutions such as microgel-reinforced hydrogels provide superior lubrication and longer mucosal adherence than conventional products.[6] Advances in drug delivery, including mucoadhesive pilocarpine tablets, have shown improved efficacy in stimulating salivary flow while minimizing systemic side effects.[7] Together, these innovations represent important progress in managing xerostomia, particularly in patients with chronic autoimmune disease or radiation injury.

Biologic agents are also reshaping therapy for autoimmune salivary gland disease. Rituximab, a CD20-targeted monoclonal antibody, reduces B-cell activity and has demonstrated improvements in systemic symptoms in Sjögren's syndrome, although its ability to restore glandular function remains limited.[8] This underscores the promise of immune-modulating therapies, while also highlighting the need for additional biologics or combination strategies to fully restore function.

Minimally Invasive Techniques

Sialendoscopy has revolutionized the treatment of obstructive salivary gland disease. By directly visualizing the ductal system, it enables stone retrieval, ductal dilatation, and lavage, achieving symptom relief in up to 97% of cases with minimal morbidity.[9,10] Complications are rare and usually transient, such as lingual nerve paresthesia or mild postoperative sialadenitis.[11,12] Its high efficacy and safety have made sialendoscopy the preferred alternative to gland excision in many patients.

Laser and shock-wave technologies further expand minimally invasive options. Holmium:YAG laser lithotripsy is highly effective for stones up to 15 mm, achieving fragmentation and clearance in up to 90% of cases.[13,14] Extracorporeal shock-wave lithotripsy (ESWL), particularly when combined with intraductal pneumatic lithotripsy, has converted nearly 95% of previously untreatable stones into treatable ones.[13] These methods preserve gland function while reducing the morbidity of open procedures.

Ablation techniques are increasingly applied to benign tumors. Ultrasound-guided radiofrequency ablation of Warthin's tumors can reduce tumor volume by nearly 70% within a year, with low complication rates and improved cosmesis.[15,16,17] Cryoablation, using cycles of extreme cold, has been shown in both animal models and clinical practice to safely eradicate benign lesions such as mucoceles and vascular malformations, with minimal discomfort and no major complications.[18,19]

Robotic-assisted surgery represents another innovation, offering superior visualization, dexterity, and cosmetic outcomes compared to traditional approaches. Techniques such as retroauricular or hairline incisions allow tumor removal while concealing scars and preserving nerve function.[20,21,22] Although operative times may be longer, robotics offers substantial functional and aesthetic advantages for carefully selected patients.

Regenerative Medicine

Stem cell therapy offers one of the most exciting avenues for restoring salivary gland function. Studies have identified c-Kit+ stem cells capable of regenerating glandular tissue after radiation-induced damage, with complete structural and functional restoration observed in animal models within three months of transplantation.[23,24]

Tissue engineering approaches complement this strategy by providing extracellular matrix scaffolds to support salivary cell proliferation and organization. Hydrogel-based systems have shown promise, though replicating the complex branching structure of acinar glands remains a challenge.[25,26]

Gene therapy also offers disease-modifying potential. Delivery of the human aquaporin-1 (hAQP1) gene has been shown in animal models to restore fluid secretion capacity in irradiated glands.[24,27,28] While promising, gene therapy faces hurdles including vector safety, long-term gene expression, and regulatory approval.

Innovative biomaterials such as hyaluronic acid hydrogels, 3D-printed scaffolds, and nanostructured environments provide additional opportunities to support gland regeneration. By mimicking native extracellular matrix and incorporating cytokines or growth factors, these materials encourage stem cell differentiation and functional tissue repair.[29] Collectively, regenerative approaches move therapy beyond symptom relief toward true functional restoration.

Targeted Pharmacologic Therapies

Targeted therapies are increasingly central to autoimmune salivary gland disease management. Rituximab, abatacept, belimumab, and newer agents such as CFZ533 have shown varying degrees of efficacy in improving salivary function and reducing systemic disease activity.[30,31,32] These agents highlight the shift toward mechanism-based treatment, though results vary depending on disease stage and immune profile.

JAK inhibitors such as tofacitinib, filgotinib, and ruxolitinib act by blocking the JAK-STAT pathway, reducing interferon-driven immune activation and lymphocytic infiltration.[33] Preclinical and early-phase trials suggest these drugs can normalize epithelial activation and improve salivary flow without cytotoxicity.[34,35]

The NF-κB signaling pathway, constitutively active in Sjögren's syndrome, represents another promising target. Inhibition has been shown in vitro to reduce pro-inflammatory gene expression and restore epithelial homeostasis, though clinical translation remains limited.[34]

Conclusions

Benign salivary gland diseases significantly impact patients' quality of life despite their non-malignant nature. Conventional therapies, while useful, often fail to provide durable, safe, and function-preserving outcomes. Advances in minimally invasive techniques such as sialendoscopy, lithotripsy, ablation, and robotics, combined with regenerative approaches and targeted pharmacologic therapies, are fundamentally reshaping treatment.

The future of management will likely integrate multiple modalities—combining biologics or JAK inhibitors with minimally invasive surgery and regenerative strategies—to maximize outcomes. Future research should focus on comparative clinical trials, long-term functional outcomes, and quality-of-life assessments. As innovations continue to mature, the management of benign salivary gland disease is poised to transition from symptomatic care to genuine disease modification, offering new hope for patients.

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References