Mesenchymal Stem/Stromal Cell Therapy for Radiation-Induced Xerostomia in Previous Head and Neck Cancer Patients: A Phase II Randomized, Placebo-Controlled Trial

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ABSTRACT

Purpose: No effective treatment exists for radiation-induced xerostomia. The objective of this study was to compare the effect of adipose-derived mesenchymal stem/stromal cell (ASC) injection, relative to placebo, on salivary gland function in patients with radiation-induced xerostomia.

Patient and Methods: In this single-centre, double-blind, placebo-controlled trial, patients with hyposalivation were randomised to receive ultrasound-guided injections of allogeneic ASCs or placebo into the submandibular glands. Patients were followed for 4 months. We evaluated unstimulated whole salivary flow rate (UWS), stimulated salivary flow rate, and patient-reported outcomes. Adverse events were recorded and immune response determined in blood samples.

Results: We enrolled 120 patients. ASC treatment resulted in a statistically significant UWS increase of 0.04 [95% confidence interval (CI), 0.02–0.06] mL/min (38%) compared with pretreatment baseline whereas placebo treatment did not cause a significant increase [0.01 (95% CI, −0.01 to 0.04) mL/min (21%)]. Both the ASC and placebo treatment yielded notable symptom reductions, with dry mouth decreasing by 13.6 and 7.7 units, sticky saliva decreased by 14.8 and 9.3 units, swallowing difficulties decreased by 7.9 and 8.0 units, and the summary score of the Xerostomia Questionnaire decreased 5.9 and 5.1 units for the ASC and placebo arms, respectively. We found no statistically significant group difference between the ASC and placebo arms for any of the outcomes.

Conclusions: We could not confirm superiority of the ASC relative to placebo. ASC therapy significantly improved UWS in previous patients with head and neck cancer, whereas placebo resulted in an insignificant increase.

Introduction

Head and neck cancer (HNC) affects more than 900,000 new patients worldwide annually and in the majority of the patients radiotherapy is offered (1). Even though advances in radiotherapy aim to minimize the damage of healthy tissue including the salivary glands (SG), the SGs are highly sensitive to radiotherapy. This results in chronic inflammation, loss of SG cells, and progressive fibrosis (2). Xerostomia, dry mouth syndrome, and hyposalivation are the most common side effects among HNC patients treated with radiotherapy, and affects the health and quality of life (QoL) of up to 80% of the patients (3). Xerostomia is a debilitating disorder impairing crucial oral functions including talking and eating (4). Currently, only symptomatic treatment for xerostomia exists and there is an unmet need for new treatment strategies (5–7).

Mesenchymal stem/stromal cells have been proposed as a therapeutic option for the restoration of damaged SGs (8). Although the precise mechanism of action is not fully elucidated, the cells are thought to function through regenerative and immunomodulatory mechanisms, likely employing a "hit and run" approach (9). These cells release cytokines that promote immunosuppression, anti-fibrotic, anti-scarring, and angiogenic effects (10–12). In addition, they can induce nearby cells to divide, repair, or regenerate (10–12).

We have previously completed two pilot studies to assess adipose-derived mesenchymal stem/stromal cell (ASC) therapy to restore SG function in patients suffering from radiation-induced xerostomia (13, 14). The studies demonstrated that ASC therapy was safe (13, 14). In addition, patients receiving ASCs produced more saliva and QoL significantly improved (13, 14). Larger randomized, clinical trials are needed to assess the effectiveness of ASC treatment to restore SG function.

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Translational Relevance

Salivary gland hypofunction and xerostomia impairs essential oral functions such as eating, swallowing, and speaking, substantially affecting patients' quality of life (QoL). Xerostomia is a common side effect of radiotherapy treatment for head and neck cancer, and currently, only symptomatic treatments are available. Mesenchymal stem/stromal cells (MSC) have emerged as a promising candidate treatment for xerostomia, due to their remarkable regenerative capabilities. We conducted an investigator-initiated, randomized, double-blind, placebo-controlled trial to investigate the use of MSCs for the treatment of xerostomia. The study affirmed the safety of MSC treatment. Further, the study demonstrated that MSC treatment resulted in an improvement in patients' salivary gland function and QoL, however we could not confirm superiority of ASC treatment relative to placebo. The study investigated the potential of MSC treatment and denotes a notable progress in the field of rehabilitation for individuals who have undergone radiotherapy for head and neck cancer.

This study aimed to evaluate the impact and safety of allogeneic ASCs as a treatment for radiation-induced hyposalivation and xerostomia in previous patients with HNC.

Patients and Methods

Trial design

The study was an investigator-initiated, single-centre, randomized, double-blind, placebo-controlled trial. The study was approved by the Danish Data Protection Agency (protocol #: P-2020–1164), the National Ethics Committee (protocol #: 1802872), and the Danish Medical Agency (EudraCT: 2018–000348–24). The protocol was registered at the ClinicalTrials.gov database (NCT04776538), and published (15). The trial was monitored by the Good Clinical Practice (GCP) unit at the University of Copenhagen. All included patients provided verbal and written consent in compliance with the Declaration of Helsinki.

Patients

Patients (18–75 years) previously treated with radiotherapy ± chemotherapy for a HNC in Denmark, and with clinically reduced salivation [unstimulated whole salivary flow rate (UWS): 0.05–0.25 mL/min], were eligible for inclusion. Patients had to have a minimum of 2 years recurrence-free follow-up. Exclusion criteria comprised other cancers in the past 4 years, xerogenic medications (Supplementary S1), penicillin or streptomycin allergy, known SG disease, prior submandibular gland surgery or stem cells in the SGs, pregnancy, breastfeeding, or recent history of smoking or alcohol abuse (Supplementary S2).

The study was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Copenhagen University Hospital - Rigshospitalet (Supplementary S3). Initially, patients underwent an assessment of their medical history and recieved an ear, nose, and throat (ENT) examination. Subsequently, the UWS and stimulated whole saliva flow rate (SWS) were evaluated by sialometry (Supplementary S4). Patient-reported outcomes were evaluated by two QoL questionnaires: the European Organization for Research and Treatment of Cancer QoL Questionnaire, Head and Neck Module (EORTC QLQ-H&N35) and the Xerostomia Questionnaire (XQ; Supplementary S5). Blood samples were collected to evaluate the presence of preformed human leukocyte antigen (HLA) antibodies. In addition, a pretreatment ultrasound examination of the neck was performed. Four months following treatment, patients were reassessed with sialometry, questionnaires, and ultrasound examination. Blood samples were collected to evaluate the presence of *de novo* HLA donor-specific antibodies (DSA). Furthermore, patients underwent an ENT examination. All adverse events (AE) were continuously monitored throughout the study, starting from the treatment initiation and continuing until the final day of the follow-up period. Patients were provided with the principal investigator's contact number and instructed to report any new medical events. In addition, the patients' medical histories were reviewed during follow-up appointments. This involved both direct inquiries with the patients and examination of their medical records. Moreover, in the event of hospitalization, an automatic notification system alerted the principal investigator.

Interventions

Eligible patients were randomized in a 1:1 ratio to receive ASCs or placebo. Placebo consisted of CryoStor10 (BiolifeSolutions), the freeze media for ASCs, containing 10% dimethyl sulfoxide (DMSO). The ASCs were provided by the Cardiology Stem Cell Centre (CSCC) - Rigshospitalet. ASCs were isolated from abdominal adipose tissue from three healthy female donors, according to good manufacturing practice (GMP) in clean room facilities as described previously (16, 17). Only one donor's cells were used in each cell vial. A total of 0.5 mL of ASCs or placebo was injected without anaesthesia into each submandibular gland, and for the patients receiving ASCs, this corresponded to a dose of approximately 25×10^6 cells per gland. The injections were performed ultrasound-guided by a trained investigator, as described previously (15).

Outcomes

The primary outcome was to assess the impact on UWS, measured as the change from baseline to the 4 months follow-up visit in patients receiving ASC relative to placebo.

The secondary outcomes were to assess change in SWS from baseline to 4 months follow-up in patients receiving ASC compared with placebo. Further, change in patient-reported xerostomia was evaluated by the EORTC QLQ-H&N35 and the XQ questionnaires. The EORTC QLQ-H&N35 was used to measure the impact on dry mouth, sticky saliva, and swallowing. A high score for both the EORTC QLQ-H&N35 and the XQ corresponds to an increased symptom burden.

Safety was evaluated by registration of treatment-related AE, serious adverse events (SAE), or death. Evaluation of the immune response to ASC was measured by the development of de novo HLA antibodies (Supplementary S6).

Sample size and power considerations

On the basis of the results from our previous study (13), we estimated that after 4 months, the UWS would increase by approximately 33%. Including 100 patients would yield a power of 80% and an α of 0.05. We included 120 patients to account for a possible 20% dropout.

Randomization and masking

At the beginning of the trial, a predetermined randomization code was established for all 120 patients based on their treatment order. To prevent treatment clustering, randomization was conducted in blocks of 6, with 3 patients receiving ASCs and 3 receiving placebo. The

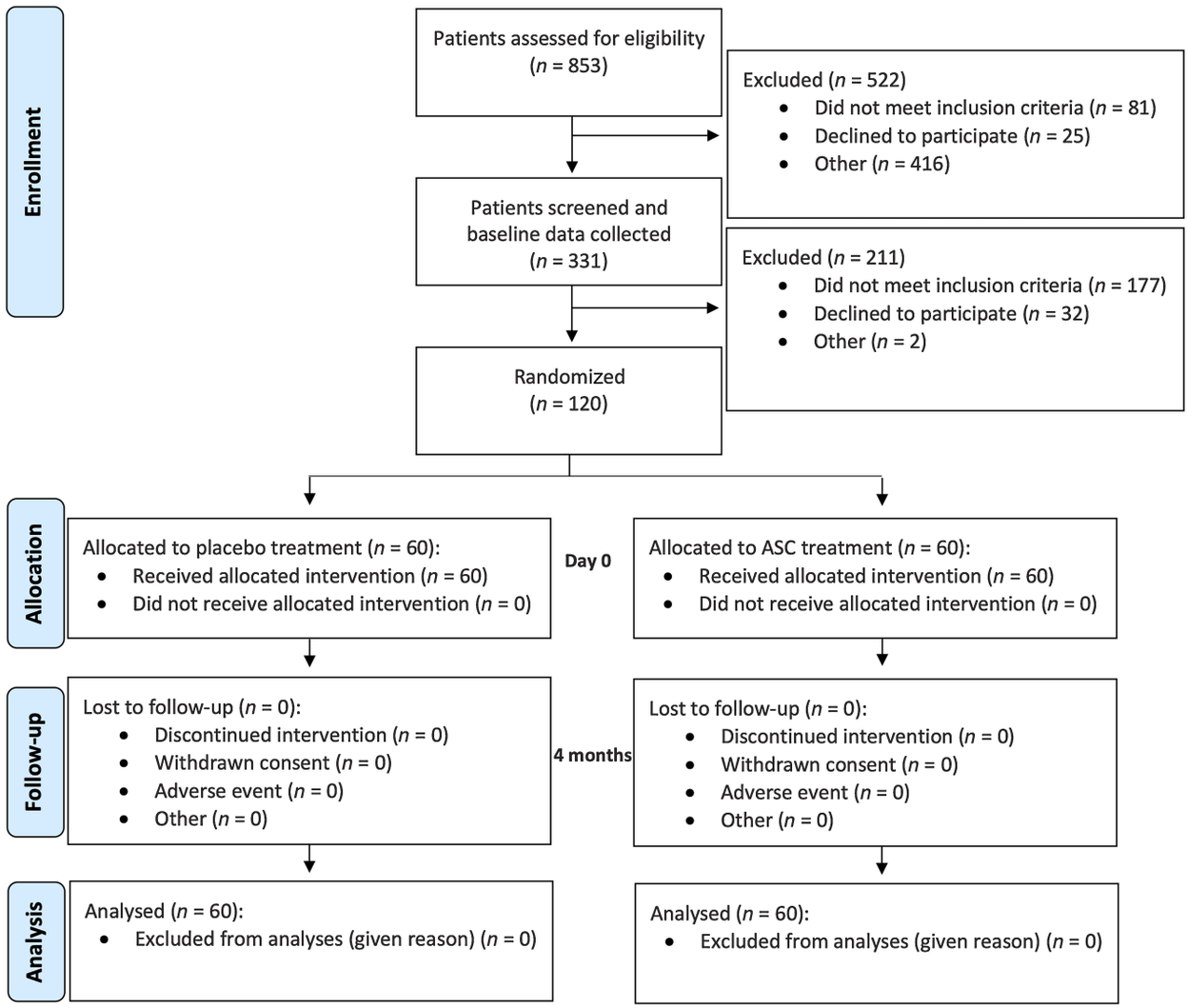

Figure 1.
CONSORT diagram illustrating the trial flow.

allocation sequence was generated by one person at the CSCC - Rigshospitalet using the website www.randomization.com. The table containing the randomization numbers was only accessible to that person. This person was not involved in analyzing the results of the study.

The sponsor, investigators, research staff (except for staff involved in treatment preparation and bioanalytical analyses), and patients were blinded to treatment assignment. The outcome was assessed before the investigators and outcome assessors were unblinded to the assigned treatment.

Statistical analysis

A statistical analysis plan was completed before the end of the trial (Supplementary S7). The analyses were prespecified to correspond to the intention-to-treat population. Descriptive statistics for categorical data were reported as number and percentages whereas continuous data were reported as means and SDs. Continuous outcome measures were analyzed using ANCOVA models with treatment group as a class variable and the baseline value as a continuous covariate (18). Results are reported for each randomised group as least square means with SEs, and the differences between these are reported with 95% confidence intervals. Safety was descriptively reported. In case of missing data, a sensitivity analysis was conducted. All 95% confidence intervals and *P* values were two-sided. All statistical analyses were performed in SAS- and R-studio.

Data availability

The data produced in this study are not publicly accessible due to privacy considerations, however, data are available upon reasonable request from the corresponding author.

Results

From January 19, 2021 to February 16, 2023, 853 patients were refered or invited to participate in the project. Of these, 331 patients were screened at the Department of Otorhinolaryngology, Head and

Neck Surgery & Audiology, Copenhagen University Hospital, Denmark (**Fig. 1**). A total of 120 patients were included to receive ultrasound-guided ASCs or placebo injections to each submandibular gland. All patients were followed for 4 months.

One patient (receiving ASCs) only received treatment to one submandibular gland and 2 patients receiving ASCs received a smaller dose; a total amount of 0.93 and 0.84 mL, respectively. Besides this, no major deviations to the protocol were made (Supplementary S8). Patients receiving ASCs and placebo had similar baseline clinical characteristics (**Table 1**).

The mean age of the included patients was 61 years (range: 43–75 years), with 26.7% female. Majorty of patients were previously treated for an oropharyngeal cancer (90.0%), and of these 95.4% were p16-positive. Most patients were diagnosed at UICC8 stage I/II (74.1%), and most patients had N-site disease at the time of diagnosis (90.0%). Majority of patients received concurrent chemotherapy (85%) as a result of locally-advanced disease, extra-nodal extension, or incomplete resection.

Table 1. Baseline characteristics in the intention-to-treat population.

Characteristics	ASC ($n = 60$)	Placebo ($n = 60$)
Age (years)	61.0 (7.4)	61.8 (6.8)
Female, *n* (%)	19 (32%)	13 (22%)
Performance score (0–1), *n* (%)	60 (100%)	60 (100%)
Previous smoking history, *n* (%)		
0 pack years	29 (48%)	24 (40%)
1–10 pack years	7 (12%)	6 (10%)
>10 pack years	24 (40%)	30 (50%)
Cancer location, *n* (%)		
Oropharynx	53 (88%)	55 (92%)
Cavum Oris	2 (3%)	0 (0)
Hypopharynx	2 (3%)	0 (0)
Larynx	1 (2%)	1 (2%)
Sinonasal	0 (0%)	0 (0)
Cancer of unknown primary	0 (0%)	1 (2%)
Nasopharyx	2 (3%)	3 (5.0)
p16 positive in patients with oropharyngeal cancer, *n* (%)	51 (96%)	52 (95%)
UICC8 stage, *n* (%):		
I	17 (28%)	18 (30%)
II	28 (47%)	26 (43%)
III	10 (17%)	11 (18%)
IV	4 (7%)	3 (5%)
Duration since radiotherapy to intervention (years)	5.8 (3.9)	5.6 (4.5)
Mean radiation dose to the right SMG, Gy	53.6 (14.6)	53.0 (15.5)
Mean radiation dose to the left SMG, Gy	51.8 (16.3)	52.5 (18.2)
Mean radiation dose to the four large salivary glands, Gy	39.9 (7.1)	40.5 (8.9)
Mean radiation dose to the oral cavity, Gy	39.5 (11.4)	39.7 (10.5)
Bilateral radiotherapy, *n* (%)	42 (70)	47 (78)
Received concurrent chemotherapy, *n* (%)[a]	52 (88)	50 (83)
Saliva flow rate (mL/min)		
Unstimulated whole saliva flow rate	0.13 (0.05)	0.13 (0.06)
Stimulated whole saliva flow rate	1.14 (0.59)	0.99 (0.60)
EORTC QLQ-H&N-35 (0–100)		
HNDR	81.9 (23.4)	76.3 (23.2)
HNSS	55.6 (38.2)	57.1 (37.7)
HNSW	33.9 (22.8)	31.8 (19.9)
XQ (0–100)	51.0 (20.5)	47.9 (19.9)

Note: Unless otherwise indicated, estimates are reported as means and SDs.
Abbreviations: Gy, gray; HNDR, domains for dry mouth; HNSS, domains for sticky saliva; HNSW, domains for swallowing; SMG, submandibular gland.
[a]Ninety-five patients received cisplatin, 4 patients received paclitaxel, and 3 patients received carboplatin.

Salivary gland function

Patients receiving ASCs had an increase in UWS of an average of 0.04 (95% CI, 0.02–0.06) mL/min from baseline to 4 months follow-up, whereas the placebo group had an insignficiant increase of 0.01 (95% CI, −0.007 to 0.036) mL/min (**Fig. 2**). This corresponded to an increase of 37.9% (95% CI, 18.06–57.79) for the ASC arm and 20.89% (95% CI, 1.02–40.75) for the placebo arm. We did not detect a significant increase in SWS in patients receiving ASCs (Supplementary S9). After ASC therapy, 13 (21.7%) patients acquired a normal saliva flow rate ≥0.26 mL/min, with two of these patients having an initially high baseline UWS of 0.20 to 0.25 mL/min. Among placebo patients, 8 (13.3%) acquired a normal saliva flow rate ≥0.26 mL/min, with 6 patients having a high baseline UWS of 0.20 to 0.25 mL/min (Supplementary S10). Overall, we did not find a statistically significant difference between the ASC and placebo groups in SG function (**Table 2**).

Health-related QoL

Both the ASC arm and the placebo arm had a statistically significant improvement in all evaluated domains of the EORTC QLQ-H&N35 and the XQ questionaires. However, we did not detect a statistically significant difference between the ASC and the placebo group (**Table 2**). In the domains of dry mouth the patients experienced a decrease in symptom score of 13.6 (95% CI, −19.3 to −7.9) units compared with a decrease of 7.7 (95% CI, −13.4 to −2.1) units for the ASC and placebo groups, respectively. In the domains of sticky saliva the score for the ASC arm decreased with 14.8 (95% CI, −21.4 to −8.2) units compared with 9.3 (95% CI, −15.9 to −2.6) units in the placebo arm. In the domains of swallowing, we found a decrease of 7.9 (95% CI, −11.1 to −4.7) units and 8.0 (95% CI, −11.2 to −4.8) units in ASC arm and the placebo arm, respectively. Finally, the summary score of XQ showed a decrease of 5.9 (95% CI, −9.7 to −2.1) units for the ASC group and 5.1 (95% CI, −8.9 to −1.3) units for the placebo group.

One patient in the placebo group and two in the ASC group omitted one baseline question each. These patients were excluded from the analysis. Further, we evaluated scenarios, considering best and worst-case outcomes (Supplementary S11). No difference in mean scores across domains was observed between these outcomes (Supplementary S12).

Safety

No deaths occurred during the 4-month study period. Three patients experienced a SAE unrelated to the treatment (2 placebo patients and 1 ASC patient; **Table 3**; Supplementary 13). Fifteen patients experienced AE related to the intervention: 9 patients (7.5%) had temporary swelling of the submandibular glands, and all of these patients had received ASCs. The swelling remained for 1 day to 3 weeks, but thereafter, disappeared in all patients. Two patients (1.7%) had a temporary haematoma after the injections; one received ASCs and one received placebo. Finally, 1 patient receiving placebo had a near syncope during the injection. All patients reported that injection in the submandibular gland was accompanied by pain, which quickly subsided (within 1–2 minutes) for most patients. However, 3 patients (2.5%)—2 received ASCs and 1 recieved placebo—had temporary

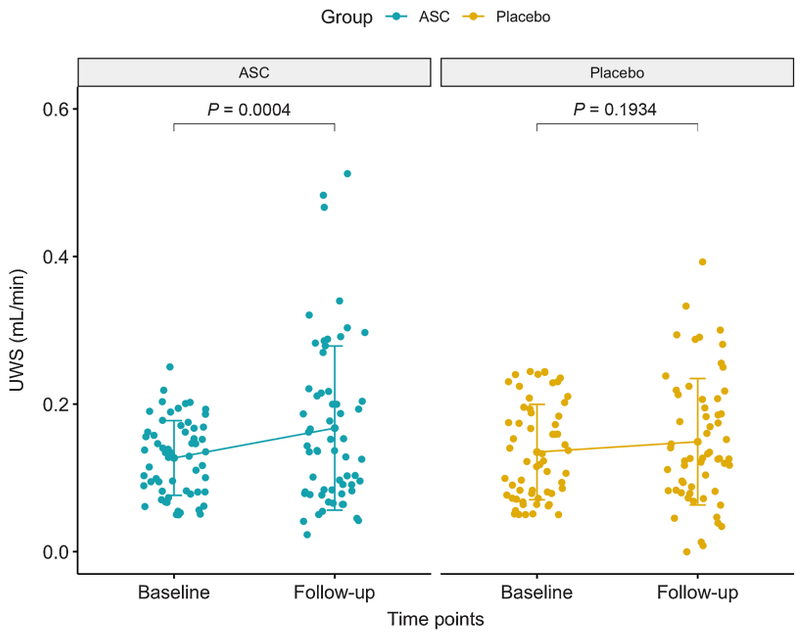

Figure 2.
Unstimulated saliva flow rate.

soreness of the SGs for 1 to 2 days. No patients developed oral discomfort or infection related to the injection site. No patients experienced pareses of the marginal mandibular branch of the facial nerve.

Five patients receiving ASCs had preexistig HLA class I DSA, and 19 (31.7%) developed *de novo* HLA class I DSA (Supplementary 14). No patients developed *de novo* antibodies towards HLA class II. Patients with preformed antibodies against HLA class II were stationary. None of the patients had any clinical symptoms indicating immunization.

Additional analysis

A history of smoking was associated with less improvement in UWS (−0.11; 95% CI, 0.16 to −0.06). A higher mean radiation dose to the four major SGs was accompanied with less increase in UWS [per increase in Gy: −0.007 (−0.011 to −0.003)]. Patients who developed DSA tended to have a lower increase in saliva production, with a mean UWS increase of 15.6 (95% CI, −27.8% to 59.0%) compared with the patients without DSA, who improved in UWS by 50.2 (95% CI, 20.7%–79.7%).

Discussion

This study is the largest human clinical trial investigating stem/stromal cell treatment for xerostomia. The study is an investigator-initiated, randomized, placebo-controlled, double-blinded, phase II clinical trial, including a total of 120 patients previously treated with (chemo-) radiotherapy for HNC. In the ASC arm, we found a statistically "significant" increase in UWS after 4 months of 38%, whereas in the placebo arm there was a statistically "insignificant" increase of 21%. We did not detect a statistically significant difference between the two groups [difference in change of 0.03 (95% CI, −0.005 to 0.06 mL/min)].

Table 2. Changes in outcomes at the main trial end point (4 months from baseline).

	ASC ($n = 60$)	Placebo ($n = 60$)	Difference between groups (95% CI)	*P* value
Primary endpoint				
Unstimulated saliva flow rate (mL/min)	0.04 (0.01)	0.01 (0.01)	0.03 (−0.01 to 0.06)	0.11
Unstimulated saliva flow rate (%)	37.92 (10.03)	20.89 (10.03)	17.03 (−11.09 to 45.16)	0.23
Key secondary endpoints				
Stimulated saliva flow rate (mL/min)	0.07 (0.40)	0.12 (0.29)	−0.05 (−0.18 to 0.08)	0.42
Stimulated saliva flow rate (%)	10.75 (41.98)	17.23 (36.40)	−4.19 (−18.23 to 9.85)	0.56
EORCT QLQ-H&N35 (score 0–100)				
HNDR	−13.60 (2.87)	−7.74 (2.85)	5.86 (−2.17 to 13.90)	0.15
HNSS	−14.78 (3.34)	−9.26 (3.37)	5.52 (−3.87 to 14.91)	0.25
HNSW	−7.93 (1.62)	−8.02 (1.61)	−0.09 (−4.61 to 4.43)	0.97
XQ-summary score (0–100)	−5.90 (1.90)	−5.12 (1.91)	0.78 (−4.56 to 6.13)	0.77

Note: Unless otherwise indicated, estimates are reported as least square means and SE. Continuous outcome measures (change from baseline) was analyzed using ANCOVA with randomized treatment group as a class variable and the baseline value as a continuous covariate.

Table 3. Safety and harm profile.

Adverse events	ASC group ($n = 60$)	Placebo group ($n = 60$)
Deaths, *n* (%)	0	0
SAEs, *n* (%)	1 (2%)[a]	2 (3%)[a]
AEs related to the injection, *n* (%)	12 (20%)	3 (5%)
Donor specific antibodies		
De novo, *n* (%)	19 (32%)	NA
Preformed, *n* (%)	5 (9%)	NA

[a]None related to treatment.

For both the ASCs and placebo-treated patients, we found a decrease in symptoms of dry mouth, sticky saliva, difficulty swallowing, and in the XQ score. Previous studies have indicated that a change of 10 units in patient-reported outcomes holds clinical significance (19). In the case of patients with ASC, we observed reductions exceeding 10 units in the domains of dry mouth (−13.6 units) and sticky saliva (−14.8 units). However, none of the domains exhibited reductions beyond 10 units among placebo patients. Despite this, no statistically significant difference was detected between the two groups.

In accordance with previous studies, we did not observe any treatment-related SAE after ASC therapy (13, 14). Approximately 31% of patients developed HLA class I DSA. Our results indicate that patients who acquired DSA may have lesser clinical benefit from ASC therapy than patients who did not develop DSA. ASCs have previously been characterized as hypoimmunogenic as they do not express HLA class II (20). We did not detect any HLA class II DSA.

The principal strength of this study is that it is, to date, the largest clinical trial investigating intraglandular ASC therapy in humans. In addition, no patients were lost to follow-up. Futhermore, our study recruited patients from all across Denmark, enhancing its overall applicability and generalizability, because individuals from both urban and rural settings were included. Despite being the largest trial to date, it is important to note that some subgroups were small, such as those who develop DSA, resulting in imprecise effect estimates. Hence, additional research is needed before these subgroup results can be generalized. Further, a limitation of the study is the single-center design. A multicenter study with a larger patient cohort could strengthen the power of the study and potentially clarify findings. In addition, the 4-month follow-up duration limits conclusive remarks on long-term effects. Consequently, the next-phase necessitates further studies with an extended follow-up period to address these limitations. A follow-up study is planned to accommodate these parameters.

In our previous study, placebo consisted of isotonic NaCl supplemented with 1% human albumin (13). In this study, placebo consisted of CryoStor10 (BiolifeSolutions) supplemented with 10% DMSO. DMSO may act anti-inflammatory and can be a therapeutic agent in several diseases (21, 22). Although the therapeutic impact of DMSO on salivary function has not been explored, our results imply that DMSO might have an influence on xerostomia as we observed a trend towards an increase in salivary flow rate. However, it is important to stress that the percent increase in UWS following placebo injections has a fairly wide CI (95% CI, 1.02%–40.75%).

We demonstrated that mean radiation dose and a previous smoking history affected the improvement in SG function following ASC treatment. To maximize the effects of ASC therapy, repeated treatments could be given to patients who, after initial ASC therapy, have not yet developed normal SG function.

We specifically included patients with a 2-year recurrence-free survival to account for a potential regenerative effect on the SGs over time. This criterion was implemented to mitigate any potential impact on the results of time from radiotherapy on the results, as previous research has demonstrated that SG function stabilizes after a period of 1 to 2 years following radiotherapy (23). However, the most significant decrease in salivation occurs from the initiation of radiotherapy to 3 months after its completion (24). Because of radiotherapy-induced hyposalivation, many radiotherapy-treated patients with HNC later develop dental caries and oral infections. Radiation-induced xerostomia has a prominent impact on QoL and is associated with psychological distress and the development of depression in patients with HNC, especially in the first year after treatment (5, 25, 26). To mitigate the impact of hyposalivation-related issues, future studies could explore early ASC treatment, ideally within 2 months after their initial treatment, to limit later damage to the teeth and oral cavity, and to limit the amount of post-radiotherapy fibrosis.

There is great individual variability in salivary flow rates, and the flow rate is affected by several factors including age, sex, comorbidities, and medication (27). Today, normal saliva flow rate is defined as an UWS between 0.3 to 0.5 mL/min. Following this, we established the study inclusion criteria to only include patients with an UWS below 0.25 mL/min. During the screening phase, we excluded several patients who reported experiencing xerostomia, which significantly affected their QoL, as their UWS levels were slightly outside the predefined reference range for inclusion. It has been recommended that a 50% reduction in flow should be considered indicative of hyposalivation (28). For future studies, we suggest assessing salivary function before and after radiotherapy, and using a 50% reduction as a definition for hyposalivation to improve patient recruitment.

In conclusion, our study provides the first results of a randomized, placebo-controlled, double-blinded, phase II clinical trial on allogenic ASC therapy for radiation-induced xerostomia and hyposalivation in previous patients with HNC. After 4 months, we observed a statistically significant increase in salivary flow rates for the ASC arm and an insignificant increase in the placebo arm. There was no statistically significant difference between the two groups. In addition, we confirmed the safety of ASC treatment. We recommend that the potential effect of intraglandular ASC therapy should be evaluated in a phase III, multicenter study.

Authors' Disclosures

J. Kastrup reports nonfinancial support from Cell2Cure ApS during the conduct of the study, as well as nonfinancial support from Cell2Cure ApS outside the submitted work. J. Kastrup has a patent for WO 2017/068140 A1 issued, and holds a patent application for the investigated stem cell product in "stem cell therapy based on adipose-derived stem cells" (WO2017068140), which is owned by Rigshospitalet and the Capital Region of Denmark. A. Ekblond reports a patent for EP3365432A1 issued and licensed to Cell2Cure. M. Haack-Sørensen reports a patent for "stem cell therapy based on adipose-derived stem cells" (WO 2017-068140) issued. C.D. Lynggaard reports a patent for "stem cell therapy for patients with salivary gland dysfunction" (PCT/EP2020/053878) pending. C. Grønhøj reports a patent for "stem cell therapy for patients with salivary gland dysfunction" pending (PCT/EP2020/053878). No disclosures were reported by the other authors.

Authors' Contributions

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Note

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