From the Department of Skin and Venereal Diseases, Patna Medical College, Bihar, India[a]*; Department of Dermatology and Dermoscopy, Skinnocence: the Skin Clinic and Research Centre, Gurugram, India*[b]*; and Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.*[c]

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Correspondence to: Keshavamurthy Vinay, MD, DNB, MNAMS, Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India

E-mail: vinay.keshavmurthy@gmail.com

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Management of oral reactions from immune checkpoint inhibitor therapy: A systematic review

To the Editor: In previous reports characterizing dermatologic immunorelated adverse events from immune checkpoint inhibitors, oral reactions are not well described. A systematic review of the literature was conducted (search terms and outline in Supplemental Figs 1 and 2, available via Mendeley at https://doi.org/10.17632/c265tmrbhm.1) to detail oral reactions from immune checkpoint inhibitors and treatments used. Rashes with oral involvement were excluded because of potential for results nonspecific to the oral manifestation (eg, latency

Table I. Included studies detailing oral reactions from immune checkpoint inhibitor therapy in this analysis

Oral reaction	Study type	ICI used	Cases	Biopsy	Latency period,* weeks	Treatment used†	Treatment outcome
Oral mucositis/stomatitis							
Cao et al, *Dermatopathology (Basel)* 2017;4(1-4):13-17	CR	Niv	1	ND	12	Oral prednisone taper, oral oxycodone, oral dexamethasone (swish and spit), "magic mouthwash"	Complete resolution
Acero Brand et al, *J Immunother Cancer* 2018;6(1):22	CR	Pem	1	ND	42	IV methylprednisolone (2 mg/kg/d, 2 wk), oral prednisone (tapered, 5 mo)	Complete resolution
Lederhandler et al, *J Drugs Dermatol* 2018;17(7):807-809	CR	Pem	1	Yes (1 pt) DIF = neg Dx: ulcerative oral mucositis	52	Inpatient: Oral prednisone taper, dexamethasone (swish and spit), topical mupirocin mixed with triamcinolone 0.1% ointment	Complete resolution ICI held

Continued

Table I. Cont'd

Oral reaction	Study type	ICI used	Cases	Biopsy	Latency period,* weeks	Treatment used†	Treatment outcome
						Outpatient: Oral prednisone taper, topical fluocinonide 0.05% gel	
Fukui et al, *Clin Lung Cancer* 2019;20(3):208-214.e2	PCS	Niv	6	NR	NR	NR	NR
Katsura et al, *J Cancer* 2019;10(10):2139-2144	RCS	Niv	6	NR	NR	NR	NR
Zumelzu et al, F*ront Med (Laussane)* 2018;5:268	CR	Pem	1	Yes (1 pt) DIF = pos Dx: MMP	64	Oral doxycycline (100 mg/d, 3 mo), oral betamethasone (2 mg TID, 6 wk)	Complete resolution
Enomoto‡ et al, *Int J Oral Maxillofac Surg* 2019;48(4):488-491	CR	Niv	1	Yes (1 pt) DIF = neg Dx: OLR	22	Oral prednisolone (1 mg/kg, tapered, 3 mo)	Complete resolution ICI held
O'Neil et al, *PLoS One* 2017;12(12):e0189848	OCT	Pem	2	NR	NR	NR	NR
Niki et al, *Oncotarget* 2018;9(64):32298-32304	RCS	Multiple (Niv, Pem)	1	NR	NR	NR	NR
Motzer et al, *N Engl J Med* 2015;373(19):1803-13	RCT	Niv	8	NR	NR	NR	NR
Kiyota et al, *Oral Oncol* 2017;73:138-146	RCT	Niv	5	NR	NR	NR	NR
Sibaud et al, *Eur J Cancer* 2019;121:172-176	CR	Niv	1	Yes (1 pt) DIF = pos Dx: MMP	8	Topical clobetasol cream 0.05% BID	No change
Okada et al, *Clin Cancer Res* 2019;25(18):5485-5492	OCT	Niv	5	NR	NR	NR	NR
Coleman et al, *J Am Acad Dermatol* 2019;80(4):990-997	RCS	Multiple (Nivo, Pem, Atez, Durv, Ipil)	1	UTD	UTD	NR	NR
Haug et al, *Br J Dermatol* 2018;179(4):993-994	CR	Pem	1	Yes (1 pt) DIF = pos Dx: MMP	13	Oral doxycycline (100 mg BID), topical mometasone furoate 0.1%	Complete resolution
Bezinelli et al, *J Immunother* 2019;42(9):359-362	CR	Pem	1	Yes (1 pt)	6	Topical betamethasone, oral prednisone	Partial resolution ICI held

				DIF = pos Dx: MMP		(0.75 mg/kg tapered), IV infliximab (5 mg/kg), oral mycophenolate (1 g/d, 12 h/12 h), IV methylprednisone (1g pulse therapy, 3 d), oral prednisone (0.5 mg/kg), IV rituximab (375 mg/m^2, 4 wk), IVIG (21 g/mo), oral prednisone (1 mg/kg), lowlevel laser therapy (660 ± 10 nm, 100 mW, 10 s, 0.04-cm^2 spot area, 1 J/point)	
Xerostomia							
Teyssonneau et al, *Ann Oncol* 2017;28(12):3108	CR	Pem	1	ND	36	Oral prednisone (10 mg), artificial saliva, oral pilocarpine (4 mg QID), oral prednisolone (40 mg tapered)	Complete resolution
Takahashi et al, *Respirol Case Re* 2018;6(5):e00322	CR	Niv	1	Yes (1 pt) Dx: sialadenitis	12	IV prednisolone (1 mg/kg/d), oral pilocarpine (12 d), oral prednisone (tapered, 7 wk)	Complete resolution
Cappelli et al, *Ann Rheum Dis* 2017;76(1):43-50	RCS	Multiple (Ipil, Niv)	4	ND	12 8 32 32	Oral pilocarpine, oral prednisone (1 mg/kg/d tapered, 2 pts), prednisone (40 mg qd, 1 pt), oral cevimeline	Improvement (3 pts) No change (1 pt)
Warner et al, *Oncologist* 2019;24(9):1259-1269	PCS	Multiple (Avel, Niv, Pem, Ipil)	20	Yes (20 pts) Dx: sialadenitis (20 pts)	10	Corticosteroids (10 pts)	Minimal improvement: corticosteroids + ICI held (2 pts) Moderate improvement: corticosteroids + ICI held (5 pts) Significant improvement: corticosteroids + ICI held (3 pts) ICI held only (2 pts)

Continued

Table I. Cont'd

Oral reaction	Study type	ICI used	Cases	Biopsy	Latency period,* weeks	Treatment used†	Treatment outcome
							Unable to determine: ICI held (4 pts)
Ramos-Casals et al, *Clin Exp Rheumatol* 2019;118(3):114-122	RCS	Multiple (Niv, Pem, Durv)	25	Yes (15 pts) Dx: sialadenitis (15 pts)	26	Oral pilocarpine (2 pts), corticosteroids (2 pts)	No change (2 pts) ICI held (6 pts)
Motzer et al, *J Clin Oncol* 2015;33(13):1430-7	RCT	Niv	11	NR	NR	NR	NR
Rizvi et al, *Lancet Oncol* 2015;16(3):257-62	OCT	Niv	7	NR	NR	NR	NR
Oral lichenoid reaction							
Obara et al, *J Dermatol* 2018;45(5):587-591	CR	Niv	2	Yes (2 pts) DIF = neg Dx: OLR (2 pts)	6 25	Topical triamcinolone acetonide (2 pts), prednisone (60 mg qd tapered, 1 pt)	Complete resolution (2 pts) ICI held (2 pts)
Shazib et al, *Oral Dis* 2020;26(2):325-333	CS	Multiple (Niv, Pem)	10	Yes (4 pts) DIF = neg (2 pts) Dx: OLR (4 pts)	13.57	Topical corticosteroids (10 pts): (dexamethasone solution 0.1 mg/mL, clobetasol 0.05% gel, fluocinonide 0.05% gel, clobetasol 0.05% solution), oral prednisone (1.0 mg/kg/d, 14 d)	Complete resolution (10 pts)
Enomoto‡ et al, *Int J Oral Maxillofac Surg* 2019;48(4):488-491	CR	Niv	1	Yes (1 pt) DIF = neg Dx: OLR	22	Oral prednisolone (1 mg/kg/d tapered, 3 mo)	Complete resolution ICI held
Miyagawa et al, *Acta Derm Venereol* 2019;99(7):687-688	CR	Niv	1	Yes (1 pt) DIF = neg Dx: MLP	26	Oral prednisolone (30 mg/d tapered)	Complete resolution ICI held

Atez, Atezolizumab; *Avel*, avelumab; *BID*, twice a day; *CR*, case report; *CS*, case series; *d*, day; *DIF*, direct immunofluorescence; *Durv*, durvalumab; *Dx*, diagnosis; *ICI*, immune checkpoint inhibitor; *Ipil*, ipilimumab; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *MLP*, mucosal lichen planus; *MMP*, mucous membrane pemphigoid; *mo*, month; *ND*, not done; *neg*, negative; *Niv*, nivolumab; *NR*, not reported; *OCT*, open-label clinical trial; *OLR*, oral lichenoid reaction; *PCS*, prospective cohort study, *Pem*, pembrolizumab; *pos*, positive; *pt*, patient; *pts*, patients; *qd*, daily; *QID*, four times a day; *RCS*, retrospective cohort study; *RCT*, randomized clinical trial; *TID*, three times a day; *UTD*, unable to determine.

*Listed as an average for each case/study reported.

†Listed in order used or as described in the publication, if applicable.

‡Study describes 1 patient who clinically presented as having severe stomatitis and on biopsy was found to have OLR and is a repeated entry in this table.

Table II. Suggested management of oral reactions from immune checkpoint inhibitor therapy

Clinical presentation	Management*
No oral involvement	Supportive oral care[†]
Xerostomia	Mild[‡]: Supportive oral care,[†] no additional intervention Moderate[§]: + moisturizing sprays, artificial saliva, sugar-free gum or candy, sialogogues (eg, pilocarpine, cevimeline), topical corticosteroids[‖] Severe[¶]: + systemic corticosteroids[#] Management of ICI therapy (continuation, dose reduction, interruption, or discontinuation) to be discussed with treating medical oncologist
Erythema, hyperkeratosis, oral lichenoid reaction, +/− pain	Mild[‡]: Supportive oral care,[†] long-term monitoring with frequent oral examinations and biopsy of any irregularities suspicious for squamous cell carcinoma; no additional intervention Moderate[§]: + cold water and/or ice pops, mucosal coating agents (eg, Gelclair), analgesics (eg, benzydamine mouthwash, topical lidocaine or morphine, ibuprofen, acetaminophen), topical corticosteroids[‖] Severe[¶]: + systemic corticosteroids,[#] systemic analgesics (eg, opioids), +/− adjuvant therapies (eg, cognitive-behavioral therapies, anxiolytics) Management of ICI therapy (continuation, dose reduction, interruption, or discontinuation) to be discussed with treating medical oncologist
Erosions, ulcers, + pain	Mild[‡]: Supportive oral care,[†] long-term monitoring with frequent oral examinations and biopsy of any irregularities suspicious for squamous cell carcinoma; no additional intervention Moderate[§]: + oral antiseptic (eg, chlorhexidine), mucosal coating agents (eg, Gelclair), analgesics (eg, benzydamine mouthwash, topical lidocaine or morphine, ibuprofen, acetaminophen), folic acid, topical corticosteroids,[‖] lowdose doxycycline, lowlevel laser therapy Severe[¶]: + systemic analgesics (eg, opioids), immunosuppressants,[**] systemic corticosteroids,[#] +/− adjuvant therapies (eg, cognitive-behavioral therapies, anxiolytics) Management of ICI therapy (continuation, dose reduction, interruption, or discontinuation) to be discussed with treating medical oncologist

ICI, Immune checkpoint inhibitor.

*Biopsies are recommended when the clinical presentation of moderate to severe oral reactions is not typical or does not respond to treatment. Salivary gland biopsy is recommended for all xerostomia cases.

[†]Oral care, preventative and hygienic measures as tolerated:

- Brushing teeth 2 to 3 times per day with a soft toothbrush and fluoride toothpaste (minimally flavored if discomfort)
  - Avoid toothpaste with sodium lauryl sulfate
  - Use 0.9% saline or water if toothpaste causes irritation
- Mouthwash with nonirritating solutions frequently, every 2 to 4 hours (eg, saltwater, sodium bicarbonate, oral sponge rinses)
  - Avoid alcohol-containing and peroxidase products
- Adequate hydration (≥2 L of water per day)
- Flossing after every meal
- Application of topical moisturizers as needed to lips (eg, petrolatum 3 times per day)
- Regular cleaning of oral appliances (eg, dentures, mouth guards)
- Frequent examinations by dental or periodontal specialist
- Avoidance of tobacco products, alcoholic beverages, and foods that are spicy, acidic, hard, or high temperature

[‡]Mild defined as clinical presentation consistent with Common Terminology Criteria for Adverse Events (CTCAE) grade 1 (mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, and intervention not indicated) (grading definitions adopted from National Cancer Institute (NCI) CTCAE version 5.0 guidelines).

[§]Moderate defined as clinical presentation consistent with CTCAE grade 2 (moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living [refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc]) (grading definitions adopted from NCI CTCAE version 5.0 guidelines).

[‖]Topical steroids from reported studies include triamcinolone, clobetasol, fluocinonide, and dexamethasone. Method of delivery includes mouthwash solution (for "swish and spit"), ointment, or gel.

[¶]Severe defined as clinical presentation consistent with CTCAE grade 3 (severe or medically significant but not immediately life threatening, hospitalization or prolongation of hospitalization indicated, disabling, and limiting self-care activities of daily living [refers to bathing, dressing and undressing, feeding self, using the toilet, receiving medications, and not bedridden {grading definitions adopted from NCI CTCAE version 5.0 guidelines}]), grade 4 (life-threatening consequences; urgent intervention indicated), and grade 5 (death related to adverse event) (grading definitions adopted from NCI CTCAE version 5.0 guidelines).

[#]Oral and intravenous steroids from reported studies include prednisone and prednisolone.

**Immunosuppressants from reported studies were used to treat mucous membrane pemphigoid and include infliximab, mycophenolate, and rituximab.

period, treatment used). Oral reactions were defined in this study as oral mucositis/stomatitis, xerostomia, and oral lichenoid reaction. Primary literature (eg, clinical trials, cohort studies, case series and reports) was included. Table I summarizes the following results from included publications: oral reaction, article type, immune checkpoint inhibitor therapy, number of cases, biopsy information, latency period, treatment used, and treatment outcome, if applicable.

Twenty-six articles, which described 125 oral reactions in 124 patients, were included, representing 42 cases (33.6%) of oral mucositis/stomatitis, 69 cases (55.2%) of xerostomia, and 14 cases (11.2%) of oral lichenoid reaction. Latency period, reported in 16 articles, ranged from 6 to 64 weeks. The average latency period was 22.3 weeks, with 27.4 weeks for oral mucositis/stomatitis, 21 weeks for xerostomia, and 18.5 weeks for oral lichenoid reaction. Forty-nine cases (40.0%) were biopsied, with 11 biopsy cases reporting direct immunofluorescence testing; 4 out of 11 direct immunofluorescence cases with positive results were consistent with mucous membrane pemphigoid. Biopsies helped establish diagnosis in 98% of the biopsied cases, and 21 of the patients with biopsy (42.9%) were able to continue immune checkpoint inhibitor therapy.

Treatment strategies included monotherapy or combination therapy of corticosteroids, analgesics, and medicated "magic mouthwash" for oral mucositis/stomatitis, corticosteroids and sialogogues for xerostomia, and corticosteroids for oral lichenoid reaction. Immunosuppressants, low-level laser therapy, and antibiotics were used for mucous membrane pemphigoid cases. Topical, oral, or intravenous forms of corticosteroids were used in all 16 articles that reported treatment. Overall, 29 patients (23.2%) held immune checkpoint inhibitor therapy because of oral reactions.

Corticosteroid use is a unifying factor for all treatment-reporting studies, suggesting an initial therapeutic option for all oral reaction types. However, recent literature on the efficacy of immune checkpoint inhibitor therapy suggests that its concurrent use with early corticosteroids,[1] multiple or prolonged antibiotics,[2] or tumor necrosis factor-α inhibitors[3] may have a negative effect on the efficacy of immune checkpoint inhibitor therapy. Larger studies are needed to corroborate these observations. Caution is recommended when using these therapies to manage oral reactions. Although our results did not describe supportive measures (eg, oral hygienics), previous literature validates its use to prevent and limit oral reactions in conventional cancer treatments.[4] Although not specific to immunotherapy, these measures may prove useful for its oral manifestations. Given the findings of this review, clinical judgment, and previous literature referenced,[4,5] we suggest management strategies as outlined in Table II to assist dermatologists in the effective prevention, assessment, and management of these conditions.

Limitations to this review include a small number of studies, inconsistent characterization of oral reactions, as well as limited and nonuniform description of treatment strategies. There is a need for prospective studies that primarily investigate oral reactions from immune checkpoint inhibitors to define management standards.

Nirav Shah, BA,[a] Leah Cohen, MD,[b] and Lucia Seminario-Vidal, MD, PhD[c,d]

From Morsani College of Medicine[a] and Department of Dermatology,[c] University of South Florida, Tampa; Herbert Wertheim College of Medicine, Florida International University, Miami[b]; and Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, Florida.[d]

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Correspondence to: Lucia Seminario-Vidal, MD, PhD, 13330 USF Laurel Dr, 6th Floor, Tampa, FL 33612

E-mail: luciasem@usf.edu

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