

RECENT ADVANCES IN THERAPEUTIC ORAL MEDICINE

Abstract

Oral mucosal lesions which are treated in Oral Medicine department includes, Recurrent Aphthous Stomatitis, Allergic stomatitis, Lichen Planus, Pemphigus, Pemphigoid, OSMF, Leucoplakia, Erythema Multiforme, Herpes Simplex Viral Infections, Herpes Zoster viral infection. There are various treatment modalities available in this literature. This chapter aims to review only the recent advancement in therapeutic Oral Medicine in the management of oral mucosal lesions which are enlisted below.

- Crocin delivery system through Thiolated chitosan hydrogel-embedded niosomes
- Amlexanox-loaded nanoliposomes in oral mucosal lesions.
- Management of oral mucosal lesions with montelukast.
- Anti-TNF α F(ab) delivered through electrospun patch for the management of inflammatory oral mucosal diseases.
- Topical calcineurin inhibitors (TCI).
- Kinase inhibitors.
- Topical 5-fluorouracil be used as a viable treatment option for oral premalignant lesions and tumors.
- Diethylcarbamazine, an anti-filarial medication, is used to treat oral submucous fibrosis.
- Molecular targeted therapies.
- ICI-based therapies
- Immunotherapy for malignancies of the keratinocytes. Section II: Determination and treatment of cutaneous immunotherapy adverse effects
- Botulinum toxin in the management of head and neck disorders

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- Trends in orally viral vector gene delivery and therapy
- A novel approach to the oral delivery of bionanostructures for systemic disease
- Oral administration of therapeutic proteins that are plant cell-encapsulated

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I. THIOLATED CHITOSAN HYDROGEL-EMBEDDED NIOSOMES: CROCIN DELIVERY SYSTEM

1. **Crocin:** One medication with anti-inflammatory qualities is crocin. As a natural carotenoid, it is. Thiolated chitosan (TCS)-based hydrogels containing niosomes are the mucoadhesive hydrogels that have been recently exploited for the administration of the medication crocin. For aphthous stomatitis, these act as a mucoadhesive crocin delivery mechanism. Niosomes are vesicular carriers based on non-ionic surfactants that create a closed bilayer structure in aqueous fluids. This allows them to carry both lipophilic and hydrophilic actives. Niosomes are preferred over alternative bilayer carriers due to their many benefits, which include low toxicity, chemical stability, biocompatibility, biodegradability, and lower cost. Controlled release of local drug delivery and improved skin penetration are achieved through the use of niosomes, which serve as a local depot and can shield pharmaceuticals from biological environments. Due to the chemical composition, morphology, mucoadhesive qualities, and viscosity, the hybrid system demonstrated good efficacy when loaded with hydrogel niosomal formulation. Niosome-containing hydrogel improved ulcer healing, decreased tumor necrosis factor-alpha (TNF- α) and p53 expression, and raised VEGF and alpha-smooth muscle actin (α -SMA) expression, according to Taghizadeh F et al. These factors make TCS hydrogel-embedded crocin-loaded niosomes an excellent choice for the treatment of aphthous stomatitis.

- **Therapeutic Effects of Crocin:** Crocin, a carotenoid found in the stigmas of saffron flowers (*Crocus sativus*), has several medicinal uses, such as anti-inflammatory, anti-nociceptive, and antioxidant capabilities. Through reducing the production of pro-inflammatory cytokines and reactive oxygen species, crocin successfully demonstrates its strong anti-inflammatory and antioxidant properties.
- **Therapeutic Effects of Crocin in the Management of Aphthous Ulcer:** Crocin demonstrates therapeutic efficacy in treating aphthous ulcers. Nonetheless, its limitations encompass low retention time, physicochemical instability, and limited bioavailability. These drawbacks, especially the low physicochemical stability, brief retention time, and suboptimal bioavailability, may hinder its successful topical application. The development of a drug delivery system holds promise for surmounting these challenges and regulating the controlled release of crocin. Among these strategies, vesicular systems have garnered substantial attention within the realm of topical drug delivery.

2. **Niosomes:** Niosomes are bilayered non-ionic surfactant-based in aqueous media which has the ability to carry both hydrophilic and lipophilic active.

Advantages of Niosomes:

- The many benefits of niosomes, including their low cost, chemical stability, biocompatibility, biodegradability, and low toxicity, have made them the preferred bilayer carrier above others.
- Moreover, niosomes have the capacity to serve as a local store, shield pharmaceuticals from biological environments, release them gradually, and enhance skin penetration.

Disadvantages of Niosomes:

- The topical application of niosomal dispersions may be impeded by inadequate retention time resulting from their low viscosity. It makes sense to add niosomes to other carriers—like movies—in order to enhance their topicality.
3. **Hydrogels:** Polymeric networks known as hydrogels possess unique characteristics such their three-dimensional structure, biocompatibility, viscoelastic qualities, physical resemblance to soft tissues, and capacity to shield their contents from abrasive conditions. In the realm of biomedicine, hydrogels made of synthetic polymers and modified biopolymers hold a prominent position.
 4. **Chitosan (CS):** Chitosan (CS) is a biopolymer known for its diverse biological effects, including antioxidant, anti-inflammatory, and antimicrobial properties. Given these advantageous attributes, researchers have recently shown keen interest in utilizing this polymer for the development of drug delivery systems.

TCS hydrogels incorporating crocin-loaded niosomes may prove to be an effective topical drug delivery system for managing aphthous stomatitis, according to a hypothesis that draws inspiration from the anti-inflammatory properties of crocin and the controlled release and mucoadhesive characteristics of niosome-loaded TCS hydrogels.¹

II. AMLEXANOX-LOADED NANOLIPOSOMES WITH ITS ANTI-INFLAMMATORY ACTIVITY IN CULTURED MACROPHAGES: A POTENTIAL FORMULATION FOR TREATMENT OF ORAL APHTHOUS STOMATITIS

Using a thin-film hydration technique, soya phosphatidylcholine (SPC) and cholesterol (Chol) were combined at three different molar ratios to form nanoliposomes. Following that, the size, zeta potential, and entrapment efficiency of these liposomes were evaluated. After sonication, the formulation with the highest drug entrapment efficiency, SPC:Chol 3:1, was found to be 94% effective. This demonstrates how AMX nanoliposomes, a cutting-edge and promising formulation, may be used to improve the effectiveness of AMX treatment for treating inflammatory diseases of the oral mucosa.

Amlexanox (AMX) is a low molecular weight compound with a molecular weight of 298.29 g/mol. It is characterized by its limited solubility in water (146 µg/mL) and lipophilic nature. AMX is a widely recognized anti-inflammatory immunomodulator employed for the treatment of conditions such as recurrent aphthous stomatitis (RAS), asthma, allergic rhinitis, and minor aphthous ulcers.

AMX acts through different mechanisms of action as it is an immunomodulatory drug.

- It stops the release of histamine and leukotrienes by inhibiting the enzyme arachidonate 5-lipoxygenase.
- AMX blocks the heat shock protein Hsp90, which prevents the release of S100A13 protein. Numerous essential biological processes, including angiogenesis, cell differentiation, neurogenesis, and tumor progression, are linked to S100A13. Acidic

fibroblast growth factor 1 (FGF1) is present in S100A13. FGF1 essentially initiates a cell signal transduction cascade by binding to FGFRs, which are cell surface tyrosine kinase receptors.

- AMX also prevents the actin cytoskeleton from being stimulated by FGF1. Consequently, AMX can counteract FGF1's angiogenic and mutagenic effects.
- The most recently revealed mode of action for AMX is its ability to inhibit the non-canonical IKK- ϵ and Tank Binding Kinase (IKB & TBK1). This process is believed to be connected to improvements in insulin sensitivity, reversible weight loss, and inflammation reduction.
- Because topical treatment of AMX has been shown to reduce ulcer number, size, erythema, and discomfort, it is clinically very effective in managing RAS.

The FDA approved AMX in 2004 as an anti-inflammatory treatment for oral aphthous stomatitis ulcers. Aphthasol is the brand name of the mucoadhesive paste that is made accessible under this medication. Clinical trials showed that compared to patients who received a placebo, those who used AMX 5% paste topically had significantly smaller ulcers, faster healing times, and shorter pain durations. Notably, AMX dramatically reduced the likelihood that patients would proceed to complete ulcers when taken during the prodromal stage.

Adverse Effects of Amlenox: Transient pain, stinging, and burning, contact mucositis, nausea, and diarrhoea.

III. LIPOSOMAL DRUG DELIVERY

Liposomal drug delivery has emerged as a top choice for the development of sophisticated drug delivery methods and has a strong chance of being clinically translated.

The drug cellular uptake and its enhancement is through different postulated mechanisms including fusion with phospholipid cell, endocytosis, and adsorption.

Advantages of Liposomal Drug Delivery:

- Liposomes can act as a reservoir for regulated medication release and can protect encapsulated drug molecules from metabolic enzymes. In addition to their biocompatibility and biodegradability, these lipid-based nanocarriers also demonstrate the ability to target specific targets selectively.
- Furthermore, it has been shown that liposomal carriers naturally target the mononuclear phagocytic system, namely macrophages, where they are phagocytosed, and that they display site-specific drug localisation in ulcerated locations. The anti-inflammatory drug's therapeutic efficacy is increased by these characteristics.
- By adding AMX to liposomes made with naturally existing cell membrane components like cholesterol and phospholipids, it may be possible to use these liposomes as a localized delivery system that will improve selective cellular uptake at the oral mucosa's ulcerated sites. With this strategy, the anti-inflammatory effects of AMX can be increased while their negative effects are reduced. Abouzids A et al. carried out a study to look into this, in which they created liposomal formulations loaded with AMX utilizing different molar ratios of soya phosphatidylcholine (SPC) to cholesterol (Chol). Particle size,

distribution, zeta potential, and AMX entrapment efficiency were all measured for these formulations.

- The study used pro-inflammatory M1 phenotype macrophages to evaluate the anti-inflammatory effects. The Human Leukemia Monocytic cell line THP-1 was used to differentiate into a resting state macrophage (M0), which was then polarized into the M1 phenotype using lipopolysaccharide (LPS) and interferon gamma (IFN γ). This process produced these M1 macrophages. The assessment concentrated on the M1 phenotype's expression levels of the pro-inflammatory cytokine TNF- α . Aspirin-positive controls, unloaded liposomes, loaded liposomes with AMX, and cases treated with AMX were compared.
- The possibility of using AMX-loaded nanoliposomes for specific macrophage targeting and the control of their inflammatory responses was shown in a study by Abouzids A et al. It was observed that increasing the concentration of AMX-liposomes led to a reduction in TNF α expression by macrophages. The combination of AMX and nanoliposomes, employing specific lipids, exhibited a more pronounced anti-inflammatory effect compared to AMX alone or empty liposomes. This enhanced effect is likely attributed to the SPC component within the liposomal formulations, which has been reported to suppress LPS-induced NF- κ B activation, resulting in a significant reduction in TNF α expression mediated by AMX.
- Furthermore, the study revealed increased cellular uptake within 2 hours of treatment with FITC-loaded nanoliposomes, indicating improved drug delivery to target cells. In order to obtain a more profound comprehension of the anti-inflammatory response of this system, additional mechanistic studies are necessary to investigate how E-Lipo and AMX-loaded nanoliposomes interact with LPS-induced macrophages and the ensuing intracellular signaling cascade.
- In conclusion, the findings suggest that AMX-loaded nanoliposome formulations with mucoadhesive properties hold promise for the management of oral mucosal lesions and warrant consideration in future research and development efforts.²

IV. TREATMENT OF APHTHOUS ULCERS WITH MONTELUKAST

The most prevalent lesions of the oral mucosa are phathous ulcers. There are various treatment aspects available for treating aphthous ulcer, one of them includes treatment with montelukast. It is also hypothesised that the efficacy of montelukast is better in comparison to corticosteroids prednisone which was shown in a randomized placebo-controlled trial and also less adverse effects compared to prednisone.

The montelukast dosage prescribed was 9 mg daily, with a range of 4-10 mg. Pediatric patients received a dosage of 4-5 mg, while individuals aged 15 and older were administered 10 mg. Notably, in the previously mentioned randomized controlled trial (RCT), approximately 10% of the participants reported experiencing diarrhea as a side effect of montelukast.

The idea that montelukast is a safe and efficient treatment option for recalcitrant aphthous ulcers is further supported by a study by Aquminoa TM et al., which shows a decrease in the quantity and frequency of these ulcers. It's worth noting that montelukast has less side effects than other systemic drugs used for management, even when treatment is

continued for an extended period of time. It is important to remember that more investigation is needed to determine the recurrence rate after stopping montelukast therapy.³

V. THERAPEUTIC ASPECTS OF ELECTROSPUN PATCH DELIVERY OF ANTI-TNF α F(AB) FOR THE MANAGEMENT OF INFLAMMATORY ORAL MUCOSAL DISEASE

A micron-scale, non-woven mesh of polymeric fibers (PDF) is created using the process of electrospinning, which involves applying a high voltage electric field to an extruded polymer solution. This mesh can be utilized to treat inflammatory oral mucosal diseases.

Electrospinning System and Fabrication of Mucoadhesive Dual-Layer Patches: Edmans J et al. state that an Alpha IV Brandenburg power source and a PHD2000 syringe pump were used in the system to create electrospun membranes. At ambient temperature, the electrospinning procedure was conducted using a potential difference of 19 kV. Membranes with mucoadhesive proteins were made from solutions comprising dissolved PVP (10% w/w) and Eudragit RS100 (12.5% w/w) in 97% v/v ethanol. A magnetic stirrer was used to dissolve PVP and RS100 in ethanol at room temperature, and F(ab) solutions were subsequently added. Electrospinning commenced within 1 minute of this addition. To create the hydrophobic backing layers, Polycaprolactone (PCL) at a concentration of 10% w/v was mixed with a blend of DCM and DMF (90:10 v/v) and stirred at room temperature.

Following the mucoadhesive layer, additional hydrophobic layers of PCL were introduced through successive electrospinning. After that, the components were heated to 70 °C in a dry oven for 15 minutes in order to melt the PCL layer and create a continuous film.

Common ulcerative oral lesions on the oral mucosa, such as oral lichen planus and recurrent aphthous stomatitis, often result in significant pain. Unfortunately, the current management approaches for these painful lesions remain less than optimal. In recent years, monoclonal antibodies have emerged as a treatment option by targeting and inhibiting the activity of cytokines. Rheumatoid arthritis and psoriasis are two immune-mediated inflammatory disorders that these antibodies have shown promise in treating. Treatment options for inflammatory illnesses affecting the oral mucosa may be drastically altered by the possibility of locally administering comparable therapeutic substances to the oral epithelium. Pro-inflammatory cytokines, including tumor necrosis factor- α (TNF α), are noteworthy for being key players in the development of various diseases.

In order to incorporate the medical grade polymer to electron spun mucoadhesive patch, this double layer medical grade polymer was fused with F(ab) biologics. Using ethanol as a solvent, can be added to mucoadhesive membranes by electrospinning.

The confocal microscopy is utilised to visualise which revealed the F(ab) within the fibres and biotinylated F(ab) was rapidly eluted from the patch without loss of antigen-binding activity. After the application of patch to oral epithelium there was rapid binding of F(ab), which was seen as fluorescent F(ab) was demonstrated on confocal microscopy within the tissue. There was good cumulative transepithelial permeation. SDS-PAGE verified that neutralizing anti-TNF α F(ab) fragments were produced from entire IgG by papain cleavage and subsequently added to patches. TNF α neutralizing efficacy of F(ab)-containing patches

was demonstrated by the inhibition of TNF α -mediated production of CXCL8 from oral keratinocytes grown in monolayer culture. On lipopolysaccharide-stimulated, immune-competent oral mucosal ulcer analogues containing primary macrophages, patches were administered. The application of an anti-TNF α patch resulted in a decrease in both active TNF α and disease-implicated T-cell chemokine (CCL3, CCL5, and CXCL10) levels to baseline levels. As the first report of an efficient method for delivering biologics based on antibodies to the oral mucosa, this will pave the way for the future development of novel therapeutic approaches to alleviate painful diseases..⁴

Advancement in therapeutic strategies for immune-mediated oral diseases

- **Topical calcineurin inhibitors (TCI):** Calcium ions Tacrolimus and cyclosporine are examples of inhibitors that are used to suppress the immune system in a variety of situations, including organ transplant recovery. By blocking calcineurin, calcineurin inhibitors decrease the production of pro-inflammatory cytokines and prevent the development of activated T cells. For severe disorders such as Steven-Johnson syndrome, refractory psoriasis, severe atopic dermatitis, and Crohn's disease, systemic usage of these medications is recommended.
- **Kinase Inhibitors:** Phosphotransferases, also known as protein kinases, are essential for catalyzing phosphorylation processes. Tyrosine kinases aid in the phosphorylation of immune recognition receptors, such as TCR, BCR, and Fc receptors, and this process is known as phosphorylation within the immune system. Although kinase inhibitors have been used for a long time in cancer treatment, their use in immune-mediated and anti-inflammatory illnesses is a more recent development. One prominent instance is the non-receptor tyrosine kinase family, which includes Janus kinase (JAK).

A considerable portion of the world's population is afflicted with immune-mediated illnesses, such as lichen planus, pemphigus, and pemphigoid, which are linked to high rates of patient morbidity. As a result of their prolonged usage, corticosteroids and cytotoxic drugs such thalidomide, azathioprine, and cyclosporine come with serious adverse effects. Because of this, it is essential to establish alternate solutions.⁵

Recent advances in management of premalignant lesions

1. Topical 5-Fluorouracil is used as a Viable Treatment Option for Oral Premalignant Lesions and Tumors?

5-Fluorouracil (5-FU) is a medication employed in the management of cancer, known for its cytotoxic effects. Its mechanism of action involves the inhibition of thymidine synthase, leading to a reduction in the availability of nucleotides essential for DNA synthesis and repair. Within this pathway, the enzyme dihydropyrimidine dehydrogenase (DPD) plays a crucial role.

2. **Adverse Effects:** 5-Fluorouracil (5-FU) side effects include diarrhea, stomatitis, palmar-plantar erythema, hyperpigmentation, bone marrow suppression, and nausea. When topical treatment is used, common side effects include erythema, ulceration,

photosensitivity, and, very infrequently, hyperpigmentation. It's important to remember that using 5-FU topically might also have serious negative consequences.

Nonetheless, 5-FU has demonstrated its efficacy in reducing the recurrence rate of high-grade vaginal dysplasia. Additionally, a number of dermatological disorders, including actinic keratosis, melanoma, squamous cell carcinoma, and basal cell carcinoma, are widely considered to be treated with it. Recent trials conducted by Weinstock et al. have concluded that fluorouracil cream can reduce the need for surgery in cases of squamous cell carcinoma for up to 1 year. Additionally, for keratoacanthomas, the short-contact topical application of 5% 5-FU has yielded excellent cosmetic outcomes and has been well-tolerated by patients.

It is well-established that 5-FU boasts a remarkable 90% success rate in the treatment of potentially malignant skin lesions. In the context of oral lesions, historical records indicate that as far back as 1989, there was a suggestion for the use of topical 5-FU and carbon dioxide laser in the management of oral squamous cell carcinoma in situ, which yielded positive outcomes. More recently, in 2014, 5-FU in orabase form emerged as a valuable resource for the treatment of potentially malignant oral lesions.

Regarding oral tumors, Ledderhof et al. reported that the use of 5-FU in the treatment of "keratocystic odontogenic tumors" (KCOT) alongside enucleation and peripheral ostectomy resulted in lower recurrence rates and reduced morbidity compared to the use of Carnoy's solution. It's worth noting that KCOTs were initially classified as odontogenic keratocysts (OKC), but in 2017, they were reclassified under the WHO classification of odontogenic developmental cysts, reverting to their original terminology as "OKC." In 2016, Singh et al. similarly concluded that aggressive treatment should be reserved for select cases, in contrast to other authors who advocate aggressive treatment for all OKCs, making the recent reclassification an essential consideration. Additionally, Pinheiro et al. observed substantial bone neoformation, particularly in the mandible's basilar region, when treating a case of OKC with marsupialization and intralesional 5-FU.

Only two studies on the use of 5-FU in preventing transformation in premalignant lesions over nearly three decades were identified in the journal OOOO, despite significant investigation conducted across many databases. It is critical to address premalignant lesions and their progression to cancer via chemopreventive techniques and by overcoming the obstacles related to preventing malignant transformation in premalignant lesions. In order to lower the rates of malignant transformation and recurrence, we, the authors, fervently support more studies and research initiatives to better understand the role of 5-FU in oral premalignancy and malignancies.

VI. ANTI-FILARIAL DRUG DIETHYLCARBAMAZINE IN TREATMENT OF ORAL SUBMUCOUS FIBROSIS

Because of its high rate of malignant transformation, oral submucous fibrosis (OSMF) has affected over 5 million people globally and played a major role in both death and morbidity. Owing to the rising incidence of OSMF, there has been a rush to repurpose existing drugs. Diethylcarbamazine (DEC), an anti-filarial drug with anti-inflammatory and immunomodulatory qualities, was covered in this paper as a treatment for OSMF. Due to its anti-fibrotic qualities, DEC is a good alternative for treating OSMF since it lowers the risk of

cancer while simultaneously reducing fibrosis. A thorough discussion of the possible mechanism of action is provided.⁶

- 1. Molecular Targeted Therapies:** Transforming growth factor β (TGF β) is expressed more frequently in OSMF and is known to influence the synthesis and breakdown of extracellular matrix (ECM) components, thus contributing to the pathophysiology of OSMF.
- 2. Imatinib:** Imatinib inhibits TGF β signaling pathways to have an anti-fibrotic effect. When used as an antifibrotic medication to treat scleroderma in preclinical animals, it has shown promising outcomes. As a result, it may be effective in treating OSMF.
- 3. ICI-Based Therapies:** A new strategy for oral potentially malignant disorders Oral squamous cell carcinoma (OSCC) is one of the malignancies that are most likely to develop from oral potentially malignant disorders (OPMDs). Stopping the malignant evolution of OPMDs is crucial because present treatments do not work to prevent them from getting worse and from coming back twice. Adaptive immunological resistance is primarily driven by the immune checkpoint system, which is also crucial in controlling the immune response. It has been shown that, in comparison to healthy oral mucosa, OPMDs and OSCC show increased expression of several immunological checkpoints, however the precise mechanism is yet unknown. This review studies the expression of immunological checkpoints such as programmed death receptor-1 (PD-1) and programmed death receptor-1 ligand (PD-L1) in OPMDs, analyses the immunosuppressive environment within OPMDs, and considers the possible utility of related inhibitors. To provide a more thorough understanding of the role and application of immune checkpoint inhibitors (ICIs) in the context of oral carcinogenesis, transformation, and recurrence, synergistic approaches involving the use of combined immune checkpoint inhibitors, such as cGAS-STING, costimulatory molecules, cancer vaccines, and hydrogels, are also discussed.⁷

VII. FABRICATION OF ASTAXANTHIN-LOADED ELECTROSPUN NANOFIBER-BASED MUCOADHESIVE PATCHES WITH WATER-INSOLUBLE BACKING FOR THE TREATMENT OF ORAL PREMALIGNANT LESIONS

One of the most common oral disorders that affects people's quality of life and may lead to oral cancer is oral premalignant lesions, or OPLs. The majority of the current standard therapies consist of retinoids or steroids in the form of films, ointments, or mouthwashes. These conventional medications and formulations, however, can have serious drawbacks and adverse effects.

In this context, a novel approach has been developed: mucoadhesive patches containing astaxanthin, constructed using electrospun polycaprolactone (PCL) and gelatin (GT) nanofibers, with a water-insoluble PCL nanofiber backing (referred to as PCL/PGA). This innovative design aims to manage OPL effectively. The saliva-insoluble PCL backing plays a crucial role in preventing drug loss after application in the oral cavity.

Once manufactured, the PCL/PGA patches show an optimal rate of astaxanthin release, guaranteeing a high local drug concentration that penetrates the buccal mucosa. Because of their high porosity, these thin patches also show remarkable adherence to moist tissue and great air permeability.

Interestingly, *in vivo* tests have shown that these bioactive mucoadhesive patches, which are similar to the commercial tretinoin cream formulation, dramatically improve OPL recovery by inhibiting the expression of Ki67 and cyclooxygenase-2 (COX-2). Notably, unlike the clinical tretinoin cream formulation, the patches cause no negative effects, including but not limited to hair loss or mouth ulcers. These outcomes highlight this novel electrospun mucoadhesive bilayer patch's enormous potential for treating OPL.⁸

Immunotherapy for Keratinocyte Cancers, Part II: Identification and Management of Cutaneous side effects of Immunotherapy Treatments: Keratinocytic cancers (KCs), which encompass cutaneous squamous cell and basal cell carcinomas, can exhibit responses to various immunotherapies administered topically, intralesionally, or systemically. However, the use of these immunotherapies may lead to the occurrence of cutaneous adverse events (CAEs). Recognizing these risks early and effectively addressing CAEs can potentially allow patients to continue their anticancer immunotherapies without necessitating dose adjustments.

CAEs related to immune checkpoint inhibitors in the context of KCs can manifest in several clinical presentations, with observed types including conditions like psoriasis and bullous pemphigoid. Diagnosing cutaneous toxicities may require biopsies to confirm the specific condition, particularly in cases where patients do not respond to topical or oral steroids. The selection of appropriate biologic drugs depends on an accurate diagnosis.

It's worth noting that different types of CAEs resulting from immune checkpoint inhibitors have been associated with diverse oncologic outcomes in various primary cancer types. However, the impact of CAEs on KC patients specifically is yet to be determined. The field of characterizing and managing CAEs following immune checkpoint inhibitor therapy in KC patients is rapidly evolving and calls for dedicated and prospective studies.⁹

VIII. LOW-LEVEL LASER THERAPY FOR SEVERE ORAL PEMPHIGUS VULGARIS MANAGEMENT

For individuals with PV lesions who are not responding to traditional therapy, LLLT has been presented as a novel therapeutic alternative. Furthermore, LLLT is said to induce cellular mitosis, keratinocyte migration and proliferation, neoangiogenesis, vasodilation, increased adenosine triphosphate (ATP), protein synthesis, and a decrease in prostaglandin levels due to enhanced mitochondrial activity.^{11–13} when irradiation wounds were analyzed biometrically and histologically, the results showed faster lesion contraction, faster reepithelization, and reformed connective tissue with more ordered collagen fibers.¹⁴ Myofibroblast proliferation is increased and inflammatory response is decreased in experimental cutaneous wounds by laser therapy.^{15, 16} LLLT is a painless, non-thermal, nondestructive process that doesn't cause any thermal harm. In addition to increasing systemic microcirculation and tissue oxygenation, cell metabolism, tissue regeneration, and potential tissue repair, LLLT has biostimulatory effects on the surrounding tissues and cells.¹⁰

1. Botulinum Toxin in the Management of Head and Neck Disorders: The polypeptide protoxin known as botulinum toxin, which is generated by *Clostridium botulinum*, causes a limited decrease in muscle activity by preventing the release of acetylcholine at the neuromuscular junction. It was approved by the US Food and Drug Administration in 2004 to treat a variety of illnesses, such as blepharospasm, hyperhidrosis, strabismus, facial wrinkles, and cervical dystonia. Its uses then spread to improve tooth aesthetics and tackle issues such as the "gummy smile." It has been demonstrated that botulinum toxin is a secure and useful substitute for medicinal therapy in the treatment of a variety of neurological head and neck conditions. This review aims to clarify the head and neck disease treatment context of botulinum toxin's mechanism of action and therapeutic benefits.

- **Biochemistry of BTX:** *Clostridium botulinum* is an anaerobic spore-forming bacteria that yields botulinum toxin. It is a 2-chain metalloprotease that is made up of heavy and light chains and has eight different immunological serotypes (A, B, C1, C2, D, F, and G). Everybody except for C2 is a neurotoxic. The most popular kind of Botox, known as Serotype A (BTX type A, or onabotulinum toxin A; Allergan, Parsippany, NJ), is utilized for cosmetic operations as well as a range of movement and spasticity disorders.
- **Neuromuscular Blockade:** The neuromuscular blocking action of BTX is due to its inhibition of acetylcholine exocytosis from presynaptic nerve terminals.⁷ By attaching to either synaptic vesicle-2, synaptotagmin I, or synaptotagmin II, three distinct gangliosides, BTX is absorbed into the cytosol from the neuromuscular junction. The entire molecule is more easily absorbed into the cytosol by heavy chains of BTX, after which light chains cleave the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)
- **Preparation:** The production of botulinum toxin occurs when *C. botulinum* is fermented in a lab, releasing the toxin into the culture. After that, the toxin is extracted, purified, crystallized using ammonium sulfate, and then diluted using human serum albumin. After that, it is sealed, lyophilized, and placed into vials. 100 units of the *C. botulinum* type A neurotoxin complex are contained in each vial of BTX. When kept at ambient temperature (25°C) for nine months, or in a refrigerator (2–8°C) for three years, its efficacy doesn't change.
- **Therapeutic Uses in Head and Neck Disorders:** Botulinum neurotoxins have a long history of application in the treatment of diverse medical and dental conditions. While their initial use was focused on enhancing facial aesthetics, they have since garnered widespread recognition for their effectiveness in pain management and addressing conditions characterized by heightened muscle contractions. Table I provides an overview of the therapeutic applications of botulinum toxin.

Over time, a range of conservative treatments, medications, as well as minor and major surgical interventions have been employed to address facial pain, secretory issues, and disorders related to head and neck movements. However, some patients have shown limited or variable responses to these therapeutic approaches. As outlined earlier, BTX has evolved from its initial use primarily in cosmetic procedures to

encompass a broader spectrum of clinical applications. It has emerged as a superior treatment choice when compared to pharmacotherapy or surgical interventions for managing head and neck disorders.¹¹

- 2. Trends in Orally Viral Vector Gene Delivery and Therapy:** Based on the available data, oral medication accounts for around 50% of the total amount each year. Due to its noninvasive nature, oral medicine is one of the primary techniques for both illness prevention and treatment. Because of its efficiency, comfort, safety, and ease, it is well-liked in the medical field. Viruses are perfect for using as gene delivery vectors for immunotherapies and gene treatments because they have evolved to efficiently express their genes in host cells. Strong T-cell responses are induced by replication competent (RC) viral vectors encoding foreign or self-proteins, which can be exploited to build efficient cancer treatments. When delivered to a host that is naïve to the cognate virus, replication-defective (RD) viral vectors producing self-proteins do not elicit an immune response. Tolerization therapies for autoimmune illnesses and allergies, as well as gene substitution therapies for hereditary disorders, can be developed using RD viral vectors. Immune reactions and persistent inflammation are linked to degenerative and inflammatory illnesses, causing tissue damage. As such, these illnesses have a striking resemblance to autoimmune disorders. In order to understand the pathophysiology of immune-related disorders and to develop next-generation prophylactics and treatments for today's major diseases, this review examines the use of RC and RD viral vectors.¹²
- 3. A Novel Approach to the Oral Delivery of Bionanostructures for Systemic Disease:** Oral medicine nanostructures have the ability to effectively encapsulate pharmaceuticals at high concentrations, penetrate the cell membrane, and release the pharmaceuticals at the target site under regulated conditions for a predetermined amount of time. In chronic medicines, nanostructures are employed as sustained delivery vehicles to lower frequency doses and dosages, minimize side effects, and improve patient compliance. This chapter focuses on giving a general overview of the function of nanostructures in oral medicine, including their production, characterisation, drug delivery mechanisms, and in vitro and in vivo methods for nanoparticle biodistribution and bioimaging. However, the synthesis of these nanostructures is complicated by their solubility, stability, and absorption in the gastrointestinal tract. This chapter provides information on the oral delivery nanostructures that have been studied in medicine, including synthesis methods and materials that work well for applications including controlled oral medication administration in the treatment of illnesses.¹³
- 4. Oral Delivery of Therapeutic Proteins Bioencapsulated in Plant Cells:** Preclinical and Clinical Advances: The oral administration of protein drugs (PDs) produced within plant cells holds the potential to bring about significant advancements in their production and delivery methods. The expression of PDs in plant cells offers cost savings by eliminating the need for costly fermentation, purification, cold transportation, storage, and sterile injections. Additionally, it extends the shelf life of these drugs for several years. The protective nature of the plant cell wall shields PDs from digestive acids and enzymes, while commensal bacteria aid in the release of PDs within the gut lumen by lysing the plant cell wall. Furthermore, the gut-associated lymphoid tissue plays a role in inducing tolerance, which can be beneficial for preventing or treating allergic reactions, autoimmune diseases, or antidrug antibody responses. The delivery of functional proteins opens up possibilities for treating inherited and metabolic disorders. Recent

advancements, including the development of PDs without antibiotic resistance genes in edible plant cells, long-term storage at room temperature without compromising efficacy, production in Current Good Manufacturing Practice (cGMP) facilities, progress in Investigational New Drug (IND)-enabling studies for clinical advancement, and approval by the Food and Drug Administration for orally administered PDs, bode well for the future of this innovative drug delivery platform technology.¹⁴

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