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Review Article

Current Concepts in Autoimmune Diseases Affecting Orofacial Region

Shubha Vinyasa[1], Shraddha Bahirwani[2], Jigna V. Raja[3]

[1]Postgraduate Student, [2]Professor and HOD, [3]Senior Lecturer,
Dr. Syamala Reddy Dental College Hospital & Research Centre, Affiliated To Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka, India

Corresponding Author: Shubha Vinyasa

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ABSTRACT

The immune system is comprised of biological structures and processes within an organism that protects against diseases. This system has been discussed extensively since the introduction of medicine and yet has remained the most enigmatic. Continuous research in the field has yielded better but not complete understanding of concepts of autoimmunity and related disorders. Various autoimmune disorders affecting oral cavity have been described and uninterruptedly studied with newer concepts emerging with each research. Therefore to be successful as oral physicians, it is imperative to stay abreast with contemporary concepts particularly related to etiopathogenesis, clinical presentation, newer investigative techniques and management of autoimmune diseases affecting orofacial region. This review aims at providing brief overview of autoimmune disorders with particular emphasis on latest ideology.

Key Words: Autoimmune diseases, lichen planus, recurrent aphthous stomatitis, pemphigus, SLE, Rhuematoid arthritis, Sjogrens syndrome.

INTRODUCTION

Autoimmune diseases are the result of specific immune responses directed against structures of the self. [1] As it's said that the 'mouth is the mirror that can reflect the overall health of your body' various autoimmune diseases manifests themselves in the oral cavity in their earliest stages and early diagnosis by a dental examination can be the key for improved outcomes. The past decade of research on immune system has yielded a wealth of new information and extraordinary growth in conceptual understanding of immune system Thus thorough and updated knowledge of these diseases helps in early recognition and treatment, improving therapeutic outcome and disease prognosis. This review attempts to describe the latest trends and current concepts related to autoimmune diseases that affect orofacial region.

Pathophysiology

No single theory or mechanism can adequately explain all features or pathogenesis of autoimmune diseases. A

complex interplay of many factors like inheritance of susceptible genes; environmental triggers such as infections and tissue damage; activation of self-reactive lymphocytes of immune system and hormonal disturbances lead to the development of autoimmunity. [2] (Table-1)

Even at molecular level, several hypotheses have been formulated to explain the breakdown of tolerance. Tolerance may be broken both at the T and the B-cell levels and different mechanisms involved in the process are described in (Table2). [3,4]

Table1-These multifactorial considerations help to explain not only the diversity of various clinical diseases encountered but also the differences in clinical manifestations from patient to patient within the same disease group. [2]

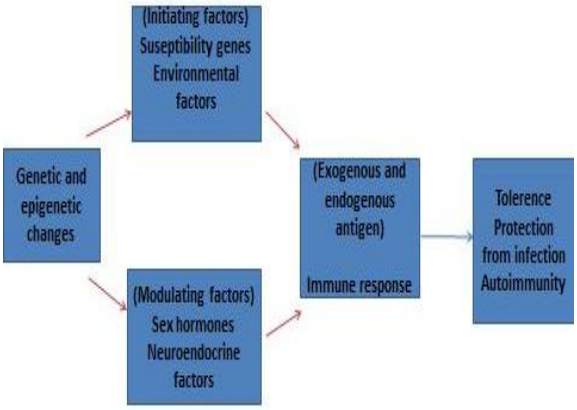

Table2 Mechanisms involved in the process of breakdown of tolerance [3,4]

Failure to delete autoreactive lymphocytes	
Central tolerance failure Peripheral tolerance failure	In certain individuals there might be a genetically determined inability to delete all auto-reactive T- and B-cell clones during ontogenesis (Burnet, 1957).
Molecular mimicry	An immune response may be mounted against a microbial antigen that is similar or identical to a self antigen. The result will be an immune attack against the microorganism and the self tissue.
Abnormal presentation of self antigens	
• Aberrant expression of major histocompatibility complex class II molecules	In conditions of inflammation, the in situ release of cytokines (e.g. interferon gamma (IFNg)) may induce the expression of MHC class-II molecules on cells that do not usually express such molecules.
• Coupling of self and nonself antigens	An autoantigen may become coupled to an exogenous antigen which acts as a carrier.
• Overproduction of self antigens	Clones with low affinity for self epitopes may escape clonal deletion and reach the periphery, where they do not become activated because the auto-antigens. This immunological ignorance may be broken by the release of an excess of auto-antigens .
• Disclosure of cryptic T-cell epitopes	Auto-reactive T-cell clones specific for cryptic epitopes and released from the thymus will be able to circulate freely and harmlessly unless a triggering event subverts the hierarchy of epitopes, and allows presentation of cryptic epitopes
• Release of sequestered self antigens	It is known that immunologically privileged sites exist within the body (i.e. the brain, eye, testis and uterus) which are usually not patrolled by the sentinels of the immune system. Once the barrier that hides these tissues is broken, they immediately become targets for autoimmune reactions.
Epitope spreading	Irrespective of the nature of the mechanism that allows the presentation of a self epitope, once the self-specific immune response has been initiated it may spread to other self epitopes, previously ignored, for which the deletion of autoreactive T-cell clones is less likely to have occurred in the thymus.
Polyclonal lymphocyte activation	T and Bcells may be massively activated in the absence of a nominal antigen.

Description of Each Lesion

As many as *22 types* of autoimmune diseases affecting oral cavity have been described in literature among which reccurentaphthous stomatitis, lichen planus, pemphigus and pemphigoid, sjogrens syndrome, rheumatoid arthritis and SLE are most commonly encountered by oral physicians and dermatologists [5,6] (Table3). A female predisposition is noted in most of these autoimmune diseases. A detailed description of these lesions is provided in the following sections.

Table-3- Prevalence rate of some important autoimmune disease affecting orofacial region [5,6]

DISEASE	PREVALENCE
Recurrent aphthous stomatitis	20% Of population
Lichen planus	O.5-2.2% of population
Pemphigus	0.1-0.5/100000 Population
Sjogrens syndrome	1–3% of population
Rhuematoid arthritis	0.8% of population
Systemic lupus erythematosus	12-64/100000 population

Lichen Planus

Lichen planus(l.P), an inflammatory autoimmune type of mucocutaneous disease affects stratified squamous epithelium of skin, oral mucosa and genitalia. The exact pathogenesis is unknown, but cell-mediated immunity and humoral immunity have been implicated. [5] It is well known that activation of the cell-mediated immune response destined toward keratinocyte apoptosis is the prime event in the pathogenesis of LP. Various potential triggers e.g. viral or bacterial antigens, metal ions, drugs or physical factors, could initiate the autoimmune process. [7] Recent literature suggest the role of *hepatitis c virus*(HCV) [8] *reactive oxygen species* (ROS) and *heat-shock protein* (HSP) 27 [9] in the pathogenesis of lichen planus.Data also suggest that *Th17, Th0, and Th2* cells [10] respectively, may have a role in the pathogenesis of erosive and reticular oral lichen planus.

LPis commonly seen on the buccal mucosa,tongue and lips.Oral lesions are characterized by classic radiating white or grey velvety thread like papules in a linear, annular or reticular arrangement with tiny elevated dot at intersection of white lines called striae of wickham. [5] Clinically 6 types are well recognized including-reticular, papular, plaque like, erosive, atrophic and bullous [7] (FIG1).Recently, OLP is considered as a *dynamic disease*and has been evaluated by a quantitative method by *Kaplan et al, in 2011*. According to the study, three successive stages can be distinguished, without sharp limits between them. The initial stage (6–12 months or more) is clinically characterized by white dots on the mucosa, followed in a second phase by the white Wickham striae and histologically by a normal epithelial thickness and a mostly lymphocytic infiltrate located mainly around the tip of the rete ridges. In the intermediate stage (<10 to more than 20–30 years), the course of the disease may include alternate periods of variable activity and quiescence, and the most prevalent OLP types of this stage are erythematous and erosive OLP. Histologically, there is para-keratosis or ortho-keratosis, the inter-papillary rete pegs that initially acquire a saw-tooth appearance may become atrophic with a flat epithelium/corium interface. Finally, the late stage (many years or even decades after the onset of the disease) presents with an atrophic or hyperkeratotic oral mucosa and still shows white plaques or Wickham striae. It often ends in a clinically little-known, inactive cicatricial postlichen stage, in which the epithelium thickness is often reduced, with destroyed rete pegs, the basal membrane appears thickened and the epithelium/corium interface is rectilinear. [11]

There are differing views about the malignant potential of oral lichen planus. Most of the reported transformation rates are strikingly uniform, the ranges being limited between 0.4 &5%.The presence of dysplasia

in an OLP-like lesion increases the risk of malignant transformation, mandating management and close follow-up. [12]

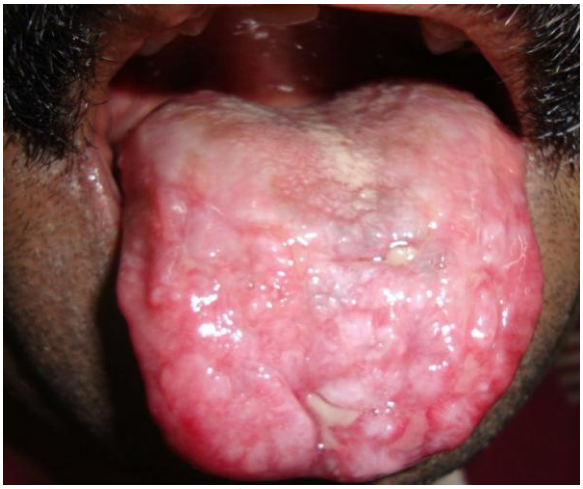

FIG1-Clinicalappearance of erosive OLP

Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS) also known as aphthae or canker sores is characterized by multiple recurrent small round/ovoid ulcers with circumscribed margins erythematous haloes and yellow or grey floors. Haematinic deficiency, malabsorption in GI disorders, stress, trauma, endocrine factors, allergies to food/SLS a content of toothpaste, immune deficiencies are all associated with RAS. [5,7] *Helicobacterpylori* are also suggested as the etiological agent of recurrent aphthous stomatitis. [13] Role of *TNF alpha, IL-6* and other *cytokines* is being explored as etiologic agent. [13] Recently the role of specific *cow's milk proteins* in the etiology of RAS was studied and strong association between high levels of serum anti-SCMP IgA, IgG, and IgE antibodies, especially to caseins: α, β, and κ-casein from cow's milk and clinical manifestations of RAU was found. [14]

There are three main clinical types, Minor aphthous ulcers (mikulicz ulcer) occurs mainly in 10-40 yrs age group with small round or ovoid ulcers 2-4mm in diameter surrounded by erythematous halo, found onnon-keratinized mobile mucosa and heal in 7-10 days and leave little or no scarring (fig2a). Major aphthous ulcers also known as Sutton's ulcers or periadenitis necrotica recurrens are round or ovoid ulcers which reach a large size about 1 cm, found on any area of oral mucosa and heal slowly over 10-40 days with scarring.(fig2b) The third type, herpetiform ulcers begin with vesiculation, pass into multiple pin headed discrete ulcers which coalesce to large, ragged ulcers and heal in 10 days or longer. [5,7]

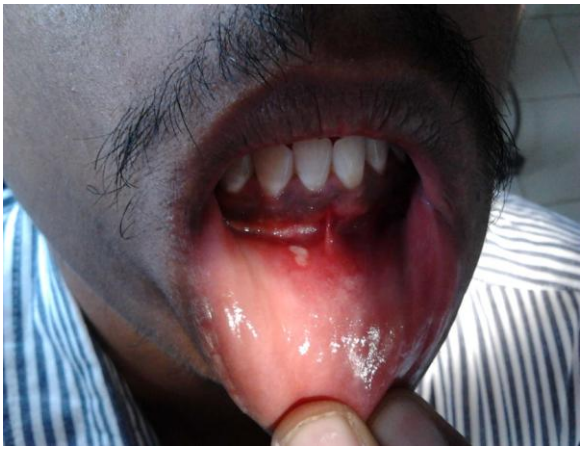

FIG2a-Minor aphthous ulcer on labial mucosa

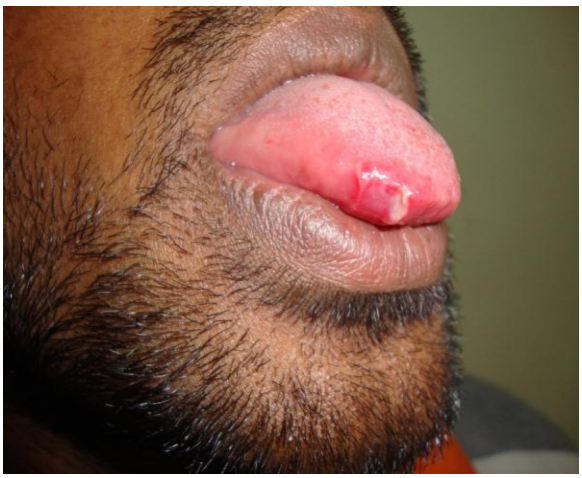

FIG2b-Major aphthous ulcer on the tongue

Behcet syndrome, also known as adamantiades syndrome is the association of triple symptom complex of RAS with genital ulceration and eye disease though a

number of other systemic manifestations may be seen. [5,7]

Pemphigus and Pemphigoid

Pemphigus is a group of potentially life threatening chronic autoimmune diseases characterized by epithelial blistering affecting muco-cutaneous surfaces. Pemphigus vulgaris is the most common variant and usually responsible for oral lesions. It begins with blister formation which readily ruptures and forms erosions which are irregular. The lesions are seen mainly on soft palate, buccal mucosa, lips, gingiva. The oral lesions are invariably followed by involvement of skin or other epithelia. [5,7]

Pemphigoid is the term given to a group of subepithelial immunologically mediated vesiculo-bullous disorders which can affect stratified squamous epithelium. It is characterized by damage to one of protein constituents of BMZ anchoring filament components. The main types of pemphigoid that involve mouth termed 'oral' or 'mucous membrane pemphigoid' and includes; mucous membrane pemphigoid, oral mucosal pemphigoid, bullous pemphigoid ocular pemphigoid. Desquamative gingivitis is the most common oral finding with erythematous, ulcerated tender gingival. [7]

Sjogrens' Syndrome

Sjogren syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration and subsequent destruction of the exocrine glands principally involving the salivary and lacrimal glands, resulting in xerostomia (dry mouth) and xerophthalmia (dry eyes). [5,7] The etiology of the disease is unknown. *Infections* could play a pivotal role: compared to normal subjects, patients with SS displayed higher titers of anti-Epstein-Barr virus (EBV) early antigens, but lower titers of other infectious agent antibodies such as rubella and cytomegalovirus (CMV) suggest that some infections may have a protective role against the development of autoimmune disease. Recent findings seem to show that *low vitamin D levels* in patients with SS could be associated with severe complications such as lymphoma and peripheral neuropathy. [15] This could open new insights into the disease etiology.

Clinical manifestations of SS can be divided into glandular and extra glandular manifestations. Glandular manifestations may be dry mouth, dry eyes, dry nose, dry skin, chronic cough and dry vagina. Extra glandular manifestations may be manifested as malaise, fibromyalgia, low grade fever, arthralgia, synovitis, Raynaud's phenomenon, vasculitis, peripheral neuropathy etc. The dry mouth represents the most common symptom of Sjogren's syndrome. The tongue is red, smooth and dry and in severe cases there is difficulty in swallowing dry food. Dental caries is often severe and progressive. Chronic oral candidiasis is frequent. [5,7]

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic multisystem disease with characteristic feature of persistent inflammatory synovitis usually involving peripheral joints in a symmetric distribution. The onset is frequent during the fourth and fifth decades of life. RA is a chronic polyarthritis, begins insidiously with fatigue, anorexia, generalized weakness until synovitis becomes apparent. Specific symptoms usually appear gradually as several joints, especially those of hands, wrists, knees and feet become affected in symmetric fashion. Pain swelling and tenderness of the joints are the initial symptoms followed by generalized stiffness of joints with limited movement. Temporo-mandibular joints (TMJ) are involved in 40-80% of RA patients. The TMJ'S are usually bilaterally

involved. Pain is present in acute phase along with Morning stiffness, joint sounds, tenderness and swelling over joints. [16]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic generalized inflammatory connective tissue disease with characteristic autoantibodies primarily affecting the skin, musculoskeletal system serous membranes kidneys CNS and cells of blood. SLE has been classified into various subsets- systemic lupus erythematosus, discoid lupus erythematosus, chronic cutaneous LE and subacute cutaneous LE, neonatal lupus erythematosus, drug induced lupus erythematosus. Oral manifestations of SLE are erythematous lesions and ulcerations of hard palate. DLE oral lesions clinically appear with a central atrophic red area with small white dots and a slightly elevated border with zone of radiating white striae and telangiectasia. [17]

Investigations

The various investigative procedures for the autoimmune diseases are described below in Table4.

Table 4- Commonly used disease specific investigative procedures.

Disease	Investigations
Recurrent aphthous ulcers	A complete blood picture should be obtained. No known laboratory procedure to establish definite diagnosis. Increase in serum IgA, IgG, IgD and IgE have been reported and immunologic aberration involving cell mediated and humoral immunity is reported.
Lichen planus	Histological examination Direct immune flouresence shows shaggy band of fibrinogen in BMZ Indirect immunoflouresence shows circulating antibodies A molecular assessment of OLP may provide the best evidence of malignant risk and will likely become available for clinical use in future.
Pemphigus	Histological examination Indirect and direct immunofluorescence test. Immunohistochemistry for IgG4
Systemic lupus erythematosus	Histological examination Direct and indirect immunofluoresense test Haematological and serological evaluation(Lupus erythematous test)
Sjogrens syndrome	Ocular tests Schirmer test Rose Bengal and lissamine green dye tests Tear break up time Slit lamp examination Oral tests Unstimulated whole saliva collection test Modified schirmer test Check for lipstick and tongue blade signs Sialochemical analysis Salivary electrophoresis Histopathological examination Serological examination-anti RO antibody Radiological examination-sialography demonstrates “fruit laden branchless tree pattern.
Rheumatoid arthritis	Detection of rheumatoid factors along with other autoantibodies Blood investigation-normochromic, normocytic anemia increased ESR rate,increase in acute phase reactants like ceruloplasmin and c reactive protein Synovial fluid analysis Radiographic evaluation

Management

Current therapies for auto immune diseases are not cures but merely palliatives aimed at reducing symptoms to provide the patient with an acceptable quality of life. These treatments provide nonspecific suppression of the immune response and a protective immune response. The goal of treatment should be to limit the progression, reduce exacerbation and relieve symptoms of disease based on the degree of clinical involvement, the predominant clinical type

of lesions, the patient's symptom and age. The most widely accepted and the mainstay of treatment involves the use of corticosteroids. The rationale behind their usage is their ability to modulate inflammation and immune response. Immunosuppressive drugs are another class of drugs used; they slow the proliferation of lymphocytes and cause general reduction in immune responsiveness of the patients. Various pharmacological modalities in the management of autoimmune diseases are described in Table5.

Table 5-Various pharmacological modalities in the management of autoimmune diseases

Drug	DETAILS	USED IN	STUDIES
Corticosteroids	Topical ointments, pastes, lozenges -Options in terms of decreasing potency-0.05% clobetasolproprionate gel, 0.1-0.05% betamethasone valerate gel, 0.05% fluocinonide gel, 0.05% clobetasol butyrate ointment or cream and 0.1% triamcinolone acetonide ointment.	Lichen planus RAS	Carbone et al, 2009 Buajeeb et al, 2000; Thongprasom et al, 2003
	Intralesional triamcinolone acetonide (10-20 mg/ml)	Lichen planus RAS	Mollaoglu N 2000
	Systemic prednisone therapy started at 1.0 mg/kg a day as a single dose and tapered after 1-2 weeks.	Lichen planus RAS	Scully et al, 2000Femiana2003;Femiano 2010
	Betamethasone Oral mini pulse therapy-5 mg betamethasone in a single morning dose after breakfast on 2 consecutive days of a week till the arrest of disease	Lichen planus	M Ramesh et al 2006 Muhammad Munir Rashid 2008
	Pulse therapy using; Dexamethasone-cyclophosphamide pulse Dexamethasone azathioprine pulse Dexamethasone methotrexate pulse	 Pemphigus SLE	 JSPasricha 1995 NVParmar 2013 E Rose - 2005 VK Mahajan - 2003
Immunosuppressive drugs	Cyclosporin Buccal bioadhesive gel formulation containing cyclosporine A solid lipid nanoparticles Cyclosporine A, at a dosage of 3-6mg/kg.	RAS Lichen planus	Scully et al, 1998, 2000; Eisen et al, 2005.Sinem et al 2012
	Azathioprine at 50-150mg/day with intermittent folic acid administration.	RAS Lichen planus	JTI LEAR1996 KK Verma2001
	Cyclophosphamide 50 mg. tablets at an initial loading dose of 2 5 mg./kg. body weight/day. A single daily increment of 50 mg added not less than 8weeks after starting treatment.	SLE	T. HADIDI 1970 YSantiago2013
	cyclophosphamide (average dose: 1.8 mg/kg/day) for 9 months	Rheumatoid arthritis	Alexander S1976 C Gaujoux-Viala2010
Anti-inflammatory agents	Chlorhexidine (CHX) mouth rinsesTopical lidocaine 2% gel/spray, Polidocanol adhesive dental paste,Benzocainelozenges.Diclofenac 3% in hyaluronan 2.5%Triclosan mouth rinse	RAS	RW Matthews1987MA Saxen 1997 AB Skaare 1996
	5% Amlexanox "Dab" applied to ulcers 4x/day until ulcers healed	RAS	Khandwalaetal 1997 Murray et al 2005 J Fu et al 2012
Antibiotic, antifungal, antimalarials	Tetracycline hydrochloride suspension 250mg/15 ml is given four times daily for five to seven days.	RAS	Graykowski et. al,
	Levamisole 150 mg daily for 3 days	Oral lichen planus RAS	De Cree 1978;Drinnan 1978;Weck 2009;
	Griseofulvin 1 g/d for 8 to 10 weeks	Lichen planus RAS	Levy et al 1986 KG Sen2011
	Tacrolimus 0.1% topical 4times/day for 4 weeks	Lichen planus	Giovanni Corrocher et al 2006
	Dapsone (100mg/day) with intermittent ascorbic acid administration.	RAS Lichen planus	DK Falk 1985AC Raj2012

Table 5. Continued…			
Antioxidants	Retinoids- 30 mg of acitretin per day for 8 weeks .Etretinate, 50 mg/d for 2 to 3 weeks. Purslane a newer antioxidant.	Oral Lichen planus	Mahrle 1982 Kanzaki 1992 Agha-Hosseini et al 2010
Other noval therapeutics	IV immunoglobulin administration as a 3 day cycle of 0.67g/kg/day every four weeks	Pemphigus	Jean-Claude Bystryn 2002 Masayuki Amagai et al 2009
	Immunoadsorption therapy with tryptophan-linked poly-vinylalcohol adsorbers	Pemphigus	M. LÜftl et al 2003
	Biological agents- Rituximab and Infliximab	Pemphigus RAS Rheumatoid arthritis	Oliver A. Perez2009 ID O'Neill2008Jonathan C.W 2004
	Cemiveline of 30 mg three times a day via the oral route	Sjogrenssyndrome	Petrone D,2002 . Fife RS2002
Herbal medications	Mouth rinse using Chamomile extract solution.	RAS	A Altenburg et al 2007
	2% Aloe vera gel three-times a day for ten days	Lichen planus	NedaBabaee et al 2012 N. Chainani-Wua2012
	Curcuminoids orally 6000 mg/day Green tea (studied in vitro)	Sjogrens syndrome	Hsu SD 2007

Surgical/invasive techniques to manage autoimmune diseases

- PUVA therapy uses photo chemotherapy with 8-methoxypsoralen and long wave ultraviolet light (PUVA) in the treatment of OLP [18,19]
- Photodynamic therapy (PDT) is a technique that uses a photosensitizing compound like methylene blue, activated at a specific wavelength of laser light, to destroy the targeted cell via strong oxidizers in OLP [18,19]
- Cryosurgery and laser A 980-nm Diode laser CO2 laser evaporation biostimulation with a pulsed diode laser using 904-nm pulsed infrared rays and low-dose excimer 308-nm laser with UV-B rays have been tried in the treatment of large ulcers in RAS, lichen planus and pemphigus. [18,19,21]
- Plasmapheresis and Electrocarporeal procedures are the newer theraupetics in treating pemphigus. [20]
- The aims of surgical treatment in rheumatoid arthritis patients are; improvement of the function, relief of pain and improvement in appearance. Synovectomy, total arthroplasty and arthrodesis are the main surgical methods. [21]

CONCLUSION

Although researchers have learned much about the immune system, new technologies for identification of individual immune cells are now allowing scientists to determine which targets are triggering immune response against healthy self. The complexities involved in treating autoimmune diseases are the task of avoiding auto-reactivity while maintaining immune competence. Thus treatment usually concentrates on alleviating symptoms rather than treating underlying cause.The detailed understanding of immunological tolerance, its regulatory network, combination of new technologies and expanded genetic information may increase the awareness to make it possible to control degree of auto-reactivity in the immune system and lay down new hope for treatment of autoimmune diseases in the future.

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