Role of biologics in oral diseases- A therapeutic intervention

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Abstract
Biologic therapies are innovative treatments involving immune modulating agents. There are classified into three broad categories: tumour necrosis factor-alpha inhibitors, lymphocyte modulators and interleukin inhibitors. These are increasingly being used in the treatment of inflammatory immune mediated conditions and neoplastic conditions. However, their role in oral diseases is limited as they are mainly used in refractory cases. Important side effects of Biologic agents are severe life threatening infections and their high economic cost. Therefore, patients receiving biologic therapies should be carefully guided and monitored to avoid potential complications. Hence, a proper understanding of these agents is required. The purpose of this review is to give a brief outlook on the biologic agents and their use in oral diseases.

Keyword: Oral diseases, Biologic agents, Refractory patients.

Introduction
Biologic Agents (BAs) are a group of drugs that are generated by recombinant biotechnology. They are also known as Targeted Immune Modulators and Biological Response Modifiers. They consist of humanised or chimaeric monoclonal antibodies or variant fusion proteins that block specific pathways involved in the pathophysiology of immune mediated and neoplastic diseases. They are used in the treatment of a variety of inflammatory immune-mediated conditions i.e they have an anti-inflammatory or immunosuppressive action. The basis of treatment with BAs is pathogenesis-based and not just organ- based palliative therapy.[1-4]

The three broad classes[1,2,4] of BAs are:
1. Proinflammatory cytokine: Tumour Necrosis Factor-Alpha (TNF-a) inhibitors e.g. infliximab, etanercept, and adalimumab.
2. An Antibody: Interleukin (IL) inhibitors which inhibits IL-12/IL-23 e.g. ustekinuma,
3. Fusion Proteins: Lymphocyte Modulators
   a. T-cell modulators, e.g. alefacept and efalizumab.
   b. B-cell modulators, e.g. rituximab.

A variety of BAs are used for oral diseases that include Adalimumab, Etanercept, Infliximab, Alefacept, Efalizumab, Rituximab, Epratuzumab and Basiliximab. Mode of administration and schedules vary but overall they are all available in injectable preparations.
1. Infliximab and Rituximab: Periodic intravenous infusions (IV).
2. Etanercept and Adalimumab: Regular subcutaneous (SC) injections (biweekly, weekly, every 2 weeks or monthly)
3. Alefacept: Weekly intramuscular (IM) injections.[2]

Use of Biologic Agents in Oral Diseases
Oral Lichen Planus (OLP)
It is a chronic inflammatory disease that involves skin and mucosa. Although exact etiology is unknown, but the role of immunologic system, in the pathogenesis is well documented. Different drugs have been used for treatment of OLP broadly in two forms, topical or/and systemic which include corticosteroids, immunosuppressives, retinoids, and immunomodulators etc. Biologic agents have been recently introduced as a treatment modality in a limited number of cases of severe recalcitrant OLP unresponsive to other treatments.[5-8] According to various studies conducted the following drugs (Table 1) have been used. In a case study titled "Lichen planus secondary complications associated with the use of biologic therapy for rheumatoid arthritis" by Chiriac A et al[19] in 2013, a known patient of rheumatoid arthritis and lichen planus was studied for the possibility that lichen planus lesions could potentially become complicated by secondary infections in patients treated with Etanercept. However, it was concluded that the case was not a lichen planus induced by Etanercept, but it was aggravated and secondarily infected with Methicillin-sensitive Staphylococcus during the therapy. The use of BAs as a treatment modality for OLP, is still limited. Hence, less expensive drugs more familiar to everyday use are preferred.

Oral Pemphigus Vulgaris
Oral Pemphigus vulgaris (OPV) is an acquired autoimmune disease in which circulating IgG antibodies target desmosomal proteins desmoglein 1 and 3 to produce acantholysis, intraepithelial, & mucocutaneous blistering. Oral mucosa is the first and most common site affected. First line of treatment is systemic steroids.[20-22] In cases of severe OPV, after a number of one arm clinical trials, a promising new agent with promising results is Rituximab, but all authors underline the risk of serious infections.[23-29]

The mode of action of Rituximab is however unclear but it is proposed that is works by eliminating the B-cell precursors which results in reduction of plasma cells secreting auto-antibodies against the main targets desmoglein 1 and 3; and it decrease desmoglein-specific T-cells.[30-33] On reviewing literature, the use of infliximab and etanercept in oral and cutaneous pemphigus has also demonstrated beneficial result.[34-36]

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is an autoimmune subepithelial vesiculobullous condition in which auto-antibodies target base-membrane auto-antigens (against proteins of the hemidesmosomes). It is characterized clinically by the development of blisters and erosions. The first line of treatment is with steroids and immunosuppressants. On reviewing literature, various case series-studies conducted in 2010, 2011 demonstrated the role of an anti-B cell agent, Rituximab in remission of MMP. Its mode of action is by reducing the population of autoantibody by producing B-cells. The use of anti-TNF agents infliximab and etanercept has also been reported.[37-41] Use of anti-TNF agents can be based on the rationale that in MMP there is formation of subepithelial blistering which is caused by multiple cytokines including TNF. Hence, BAs can be considered a "third-line" treatment modality in severe cases of MMP.[42] To use BAs as a conclusive treatment modality further research is required.

Recurrent aphthous Stomatitis

Recurrent aphthous stomatitis, or RAS, is a common and indolent inflammatory ulcerative condition in which recurring ovoid or round painful oral mucosal ulcers cause pain on eating, swallowing and speaking.[43] There are numerous factors contributing to etiology of RAS based on which various treatment protocols are followed. Amongst these are anti-inflammatory drugs, steroids, antivirals, antibacterials or vitamin supplements. In persistent recurrent aphthous stomatitis, several studies have concluded the positive effect of the use of BAs namely, infliximab and etanercept but are very expensive therapeutic option.[44-49] These are drugs are effective because TNF is the major cytokine involved in the pathogenesis of aphthae.[50-51]

Behçet's Disease

Behcet's disease is a rare autoinflammatory vasculitis with a triad of clinical characteristics of oral aphthous-like ulcers, genital ulcers, ocular uveitis. As a systemic disease, it can also involve gastrointestinal tract, major blood vessels, musculoskeletal system and central nervous system. Hence, various subtypes are referred to as: Ocular uveitis, Neuro-Behçet, Entero-Behçet, Major Vessel Disease, & Joint Involvement. The drug of choice includes steroids and traditional immunosuppresive drugs. However, these drugs are not effective in refractory cases like some patients with ocular, intestinal, vascular and neurologic involvement. Therefore, BAs can be regarded as a reasonable alternative solution (Table 2). Anti-TNF-α inhibitors have proven to be beneficial in ophthalmic, neurologic and joint involvement cases.[52-55] The most frequently prescribed Anti-TNF agent is interferon alpha 2a and occasionally used include infliximab, rutiximab, tocilizumab, canakinumab, rutiximab and anakinra

Table 1: Various Biologic Agents used for the treatment of Oral Lichen Planus

Category	Name of Drug	Dose	Mode of Action	Drawbacks
Anti T-Cell Agents[9-13]	Alefacept	15 mg/week IM for 12 weeks	Interacts with LFA-3 and T-cell activation.	
	Efalizumab	0.7 mg /kg-1 mg/kg/week for 3-10 weeks	Interacts with the leukocyte-function antigen-1 (LFA-1) and T-cell activation.	Withdrawn since 2009 due to the progressive multifocal leukoencephalopathy (PML) risk, hence no other data exist.
Anti-TNF Agents[14-17]	Etanercept	25 mg/twice weekly	TNF has been proposed to be one of the major cytokines involved in the pathogenesis of OLP	Lichenoid reactions occurrence because of the deregulation in the balance between TNF and interferon-alpha (INF-α).
	Adalimumab	40mg every other week		
Anti IL-2 Receptor Agent[18]	Basiliximab	Bolus intravenous infusion of 20 mg, 2 doses, 4 days apart	Interferes with Tcell regulation	The cost and infection risk of basiliximab probably would form a barrier to planning appropriate clinical studies.

Table 2: Various Biologic Agents used for the treatment of Behcet's Disease

Types of Behcet's disease		Biologic agents used		
			Added benefits	**Adverse effects**
Ocular disease[55-59]	Posterior uveitis	Interferon alpha (IFN alpha) & Anti-TNF Agents	Revascularization of retinal veins Regression of neovascularization	Cytopenia Depression
	Retinal vasculitis	Interferon alpha (IFN alpha) & Anti-TNF Agents		
	Active uveitis	Interferon alpha (IFN alpha)		
	Refractory uveitis	Anti-TNF Agents: Etanercept, Adalimumab & Infliximab	Reduction in ocular attacks Decrease in mean background retinal/disc vascular leakage	
Neuro-behcet[60-63]	Severe cases	Infliximab & Anti IL-6 Receptor Agent: Tocilizumab		Dural Sinus Thrombosis With Headache And Increase In Intracranial Pressure
Entero-behcet [64-69]	Refractory cases	Infliximab + Thalidomide Or Infliximab+ Methotrexate	Etanercept, Interferon & Adalimumab (still under research)	
Major Vessel Disease[70-72]	Refractory cases	Anti IL-6 Receptor Agent: Tocilizumab		
	Aortic involvement, Arterial thrombosis & Retinal Vasculitis	Infliximab	Maintains remission	
	Bilateral Pulmonary Arterial Aneurysm	Adalimumab		
Joint involvement[73]	Arthritis	Infliximab	Maintains remission	
	Ankylosing pondylitis with Behcet's disease	Anti-TNF agents		

Psoriasis

Psoriasis is an immune mediated chronic inflammatory skin condition clinically characterized by silver white scaly appearance of the skin with erythematous base. TNF-a blockade is an established treatment strategy as the main pathogenesis of psoriasis involves activation of TNF alpha and IFN alpha. Hence, the anti-TNF BAs include infliximab, itanercept, adalimumab and golimumab. However, patients receiving treatment with these agents should be monitored as well as educated about serious infections.[74]

Sjögren's Syndrome

Sjogren syndrome (SS) is a common immune-related inflammatory disease that most commonly involves the tear and saliva glands (primary or secondary when it coexists with other rheumatoid or other autoimmune diseases). Clinically it is characterised by xerostomia (because of hyposalivation) and dryness of eyes. Some patients experience dryness in the nasal passages, throat, vagina and skin. Patients are advised symptomatic treatment which includes: Lubrication of dry eyes with artificial tear drops & stimulation of salivary flow by sugar free lozenges. Lubricant gels are used to treat vaginal dryness and dry skin with moisturizing lotions. Systemic corticosteroids and immunosuppressive drugs such as cyclophosphamide are used for severe extraglandular diseases. BAs effective in SS are rituximab and epratuzumab. Their mode of action is based on the fact that in the pathogenesis of SS, B-cells infiltrate salivary gland and clonal populations of these cells possibly cause salivary gland lymphomas that develop in SS, therefore, anti B-cell agents. Targeting B-lymphocytes appears as a treatment for severe cases of primary SS.[75-77]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune inflammatory condition affecting small joints of hand (knuckles), wrists, feet etc. Treatment of RA has undergone tremendous change in the last few years. No single treatment is there for the patients. Rather a combination of treatments or a change in treatment is required. The conventional treatment begins with disease modifying antirheumatic drugs (DMARDs) followed by Methotrexate (MTX), administered alone or with DMARDs. BAs mainly anti-TNF agents, infliximab, etanercept, adalimumab and golimumab, when administered with MTX, show enhanced efficacy. Lymphocyte modulators like rituximab, which targets CD20+ B cells, may also be effective when combined with MTX. On reviewing literature, it was noted that biologic monotherapy has limited approval as a treatment modality for RA.[78-79]

Biologic Agents in a dental setting

Nowadays a number of patients on biologic agents visit dental setups i.e oral medicine, oral pathology, oral and maxillofacial surgery etc. Biologic therapy is contraindicated in patients who are hypersensitive to the agent, have active infections, have heart associated

problems, pregnancy and lactation or malignancy. Hence, whenever a patient visits a clinic, a detailed case history should be taken to avoid any serious complications due to intervention dental treatment. Before initiating biologic therapy, it is advised to undergo a formal dental evaluation and treatment to exclude any focus of chronic infection. On encountering a patient receiving biologic therapy, patient should be educated and guided about the possible adverse effects, potential opportunistic infections etc. Patients on biologic therapy, undergoing endodontic treatment, periodontal surgery or other invasive procedures should be examined, evaluated and treated with utmost care to avoid any serious complications.[2,3,42,69]

Conclusion

In recent years, immune mediated oral diseases, which have become resistant to conventional therapy or in severe forms are not treated with usual drugs, the line of treatment is shifting towards biologic therapy. The rationale to opt for BAs in various diseases is justified by the pathogenesis of the disease. Biologic agents have considerable side effects, especially infections, hence, studies should be conducted to establish their efficacy and safety. Lastly, the cost of these agents is very high and should be considered prior to their clinical use. To summarize BAs in oral diseases could assist in clinical decision making, revolutionizing the treatment protocols and improving the quality of life of a patient.

Conflict of Interest: None.

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