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Perspective

Monoclonal antibodies as potent therapeutics in dentistry.

Anticuerpos monoclonales como terapéutica potente en odontología.

Chandni Proothi.[1]
Pratichi Tripathi.[1]
Vathsala Patil.[1]
R. Vineetha.[1]

Affiliations: [1]Department of Oral Medicine and Radiology, Manipal College of Dental Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India.

Conventional treatment modalities may have numerous adverse effects. To overcome this, a new class of drugs called biologics (biological drugs) have been developed. Biological drugs are produced by recombinant DNA technology using living organisms or their synthetic versions. They have revolutionized the treatment of autoimmune conditions, different types of cancer and other diseases and therefore deserve special consideration in medicine and dentistry.[1] There are three types of biological drugs: cytokines, monoclonal antibodies (mAbs) and fusion proteins that target only damaged cells by using the natural ability of immune system sparing normal cells.[2] Monoclonal antibodies are highly specific molecular antibodies produced by clones of single hybrid cells and are active against single target antigen.[2] They can replace, enhance or work in concurrence with conventional treatments. They are referred to a Biologic Response Modifiers or Immunotherapeutics as they affect the immune system and do not interfere with cell growth directly. It is a type of passive immune therapy where antibodies are produced outside the body and do not require a person's own immune system to take an active response in fighting diseases, such as cancer.[2]

Orofacial and dental applications of monoclonal antibodies

Pemphigus: Pemphigus affects the skin and oral mucosa and is a life threatening autoimmune blistering disorder. Desmoglein 1 and desmoglein 3 are adhesion molecules of the epidermis that are responsible for the cohesion between keratinocytes in the skin and mucosa. In pemphigus, autoantibodies target the adhesion molecules thus leading to easy breakdown of the skin and blister formation. High doses of systemic corticosteroids are considered the standard treatment for pemphigus. They are also combined with immunosuppressive drugs mostly azathioprine and mycophenolate mofetil and used as first line of treatment of pemphigus.

However, it has been seen that in many patients, pemphigus becomes refractory. Rituximab, a monoclonal antibody directed against the CD20 antigen of B lymphocytes has been shown to be effective in severe types of pemphigus. As seen in a study conducted by Joly *et al.*,[3] rituximab showed promising results for the treatment of pemphigus. Also, its use as a first line treatment might permit rapid tapering of corticosteroid doses.

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Pemphigoid: Bullous and mucous membrane pemphigoid are a group of autoimmune disorders that are characterized by autoantibodies against structural proteins of the dermal-epidermal junction. These present with tense blisters, erosions and urticaria on the skin and oral mucosa.

Yu *et al.,*[4] evaluated the therapeutic effects of omali-zumab in patients suffering from bullous pemphigoid. Bullous pemphigoid is associated with increased levels of IgG and IgE. Omalizumab is a humanized monoclonal antibody which blocks the binding of IgE to its receptors. Compared to systemic corticosteroids, omalizumab exhibits a more selective action. The pharmacokinetics of omalizumab is such that free IgE decreases within hours of the dose also resulting in down regulation of IgE receptor and circulating eosinophil. Hence the authors postulated that omalizumab can be a therapeutic option for pemphigoid.

Head and neck cancer: Cancer is a serious threat to public health, next to coronary diseases. Oral cancer is one of the major cancers in developing countries.[5] Surgical resection, chemotherapy and radiotherapy are the routinely followed treatment modality.

Platinum based chemotherapy using cisplatin or carboplatin has been used in cancer patients for a long time. It has been seen that platinum based chemotherapy along with fluorouracil and rituximab improves overall survival rate when given as first line treatment in patients with recurrent or metastatic squamous cell carcinomas of the head and neck cancer.[6] Cancers associated with epidermal growth factor receptor (EGFR) mutation have been noticed to have a poor outcome. Cetuximab is an IgG1 monoclonal antibody that inhibits ligand binding to the EGFR and stimulates antibody dependent cell mediated cytotoxicity. Hence cetuximab can be a better drug option which can yield better prognosis.[7] A randomized controlled trial by Bonner *et al.,*[8] reported that a combination of cetuximab and radiation therapy resulted in improved clinical responses and survival compared to plain radiation alone for locally advanced head and neck squamous cell carcinoma patients. h-R3 is a humanized monoclonal antibody, which has demonstrated a remarkable anti-proliferative, pro-apoptotic and anti-angiogenic effect.[9] h-R3 is a well-tolerated drug that can enhance tumor radio-curability in head and neck squamous cell carcinoma.[5]

Face transplantation: A face transplant is a medical procedure to replace all or a part of a person's face using tissue harvested from a cadaver. The first partial face transplant was done in France in 2005 and the first full face transplant was completed in Spain in 2010. Unlike solid organ transplantation such as kidney, liver, or heart, which is potentially lifesaving, facial transplantation is life-changing in various ways. It includes various aspects of surgical, immunological and psychological importance. Normal facial structure is needed not just for physiological functions like chewing, humidifying of inhaled air, among others, but also for maintaining a healthy psyche and social integration. Since the procedure is followed by life-long immunosuppression in otherwise healthy individuals, the risks must be weighed against the benefits.[11]

There have been very few recipients of composite facial allografts to conduct a randomized control trial till date. A few reports using a combination of immunosuppressant drugs along with the monoclonal antibody rituximab have shown better results, however no strong information exists yet in the literature.

Periodontitis: Periodontitis is the inflammation of the supporting tissues of the teeth, which involves the periodontal tissues and the alveolar bone. Numerous microorganisms have been recognized in association with this disease, including *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Prevotella spp., Fusobacterium spp.,* and *Spirochetes*. Primary etiology of periodontitis is a biofilm that forms on the tooth surface and can progress below the gingival margin.

In a study by Booth *et al.,*[12] it was observed that topical application of specific monoclonal antibodies (most important being MAb 61 BG 1.3) subgingivally in individuals with severe periodontitis, was effective in avoiding recolonization by *P. gingivalis* when administered at intervals of 6-8 months. Moreover, the results were significantly improved when the pathogen load was reduced prior to administration.

Periodontal "pockets" that form around affected teeth

provide a larger space for the accumulation of pathogenic microorganisms thus worsening the disease. To prevent this, growth of gingival epithelium that covers the external surface of gingiva as well as epithelial lining of gingival sulcus and the junctional epithelium must be prevented. Merely providing a mechanical barrier in the form of guided tissue regeneration is usually insufficient. Therefore, a study was conducted by Gräber *et al.,*[13] reported that monoclonal antibodies against integrins (proteins that attach the cell cytoskeleton to the extracellular matrix) subunits were used and their effectiveness with respect to proliferation of epithelial keratinocytes was evaluated.

It was found that their application lead to a significant decrease in cell proliferation on a molecular level. Moreover, the monoclonal antibodies used did not have any inhibitory effects on the proliferation of remaining gingival tissues.

In this way, only the growth of gingival junctional epithelium is suppressed in a controlled manner thus preventing worsening of the disease.

Dental caries: *Streptococcus mutans* has been considered as one of the most significant pathogens in the etiology of dental caries. Glucosyltransferase-B (GTFB) of S. mutans is considered as an important virulence factor because of its role in the production of insoluble glycans that aid in the attachment of bacteria onto dental surfaces. Local passive immunization with monoclonal antibodies against GTFB is useful against dental caries as they inhibit the production of insoluble glycans.[14]

Sjogren's syndrome: Sjogren's Syndrome is a chronic autoimmune condition which causes destruction of salivary and lacrimal glands. It affects women more frequently, over the age of 40 years and has an estimated prevalence of 1-3% in the general population. Two types are seen: primary Sjogren's syndrome with only exocrine gland involvement and secondary Sjogren's syndrome which is associated with concurrent rheumatological disorders.[5] CD6 is a receptor ligand on T and B cells and humanized anti CD6 monoclonal antibody was found effective in the management of Sjogren's syndrome.[6] Another study showed epratuzumab (humanised anti-CD22 antibody) as a promising therapy is primary Sjogren's syndrome.[7]

Systemic Lupus Erythematosus: Systemic lupus erythematosus (SLE) is an autoimmune disease that affects skin, joints, kidney, brain and other organs. Currently, the mainstay treatment of SLE is corticosteroids and immunosuppressant drugs, but long term use of these drugs can lead to iatrogenic morbidity impairing the quality of life of patients. Hence there is an ongoing search for alternative therapies for SLE. The most frequently used monoclonal antibody is rituximab, which is directed against CD20, a membrane protein expressed on B Lymphocytes. According to Ponticelli *et al.,*[18] review paper a few uncontrolled trials have exhibited an improvement in SLE activity in non-renal patients and in patients with severe lupus nephritis who were unresponsive to conventional treatments. Nonetheless, two randomized trials failed to show a benefit of rituximab over conventional treatments. Even though preliminary studies have reported promising results with rituximab, epratuzumab and belimumab no robust conclusion regarding the risk-benefit profile of these monoclonal antibodies can be drawn for the management of SLE.

Side effects of monoclonal antibody therapy: Owing to their effect against pro-inflammatory molecules, monoclonal antibodies have been associated with various side effects ranging from skin lesions at the site of administration to more serious and potentially life-threatening ones like hepatotoxicity and neurological disorders.[1] In cancer patients receiving monoclonal antibody, opportunistic and non-opportunistic infections can be noted. Opportunistic infections include viral reactivations (*e.g., cytomegalovirus* and *Epstein-Barr* virus) and fungal infections.[9] The occurrence of side effects from monoclonal antibodies is also influenced by age, and other patient characteristics that also influence the outcome of therapy.

Lower respiratory tract infections including tuberculosis constitute a major side effect of this therapy, especially in immunocompromised individuals. Reactivation of latent tuberculosis is seen in patients shortly after commencement of biologic therapy.[20] Suppression of stem cell differentiation and bone marrow hypoplasia by monoclonal antibodies or other tumor necrosis factor α (TNF-α) antagonists is a

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possible side effect. Spontaneous abortion in women on anti-TNF-α has been reported and its discontinuation before conception is required. Although no concrete evidence has been yet gathered, carcinogenesis and progression of tumor in individuals receiving monoclonal antibody therapy has been discussed. Drugs like infliximab and adalimumab have been associated with varying degrees of liver disease. Progressive multifocal leukoencephalopathy (PML) is a rare but serious complication of natalizumab, rituximab and efalizumab .[21]

Conclusion: Monoclonal antibodies are a newer emerging treatment option for the treatment of cancer and autoimmune conditions, and for patients who do not respond to conventional treatment modalities. In recent years, monoclonal antibodies are being used in various head and neck disorders. Hence it is essential for dental specialists to enhance their knowledge regarding mechanisms of action, side effects and applications of monoclonal antibodies in different related fields. However further randomized clinical trials on the use of monoclonal antibodies are required for confirmatory knowledge regarding their specific applications in dentistry.

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