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RESEARCH ARTICLE

MONOCLONAL ANTIBODY AN UPDATED REVIEW IN DENTISTRY

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ABSTRACT

The increasing demand for monoclonal antibodies (mAbs) used for diagnostic and therapeutic applications has led to the development of large scale manufacturing processes, with improvements in production achieved through continuous optimization of the inherent systems. The number of monoclonal antibodies (mAbs) that have already been approved for therapeutic applications and for use in clinical trials have significantly increased in the past few years. In view of the side effects and limitations of mAbs, several improvements and modifications to monoclonal antibodies have been developed. These modifications have facilitated the use of mAbs in various forms of therapeutic applications such as treatment of infectious diseases caused by bacterial, viral, fungal and parasitic organisms. Monoclonal antibodies have also been applied in the treatment of non-infectious diseases such as cancer, immune diseases, arthritis and other disorders resulting from organ transplantation. This review highlights mAbs applications in biomedicine, and discusses state-of-the-art technologies related to their potential uses.

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INTRODUCTION

The immune system acts as defence system against various infectious agents that cause different forms of diseases. Two major components are the humoral (antibody-mediated) and cellular (cell-mediated) immune responses. The humoral immune system which comprises B-lymphocytes recognizes the type of foreign invading antigens and produces specific antibodies against them (Treviño, 2006). The two important characteristics of an antibody are its specificity and its assurance to provide continual resistance to that particular type of antigen (Smith, 2012). Considering their unique features, scientists use them for the protection of humans against diseases. Techniques for in vitro production of antibodies was also developed, resulting in the production of mAbs for diagnostic and therapeutic applications (Ribatti, 2014). Although antibody production has several procedures, the principles generally remain similar to those illustrated in Figure 1. Due to development of new phase of therapy in the field of medicine, application of mAbs in the treatment of several disease conditions have been at the forefront (Wang, 2011). In 2002, the first human mAb for use in clinical practice was approved by the Food and Drug Administration of the United States. Since then, the mAbs production industry has exponentially expanded (Nelson, 2010).

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The use for which mAbs are anticipated determines the exact amount required for carrying out the different activities. Only a small quantity of mAb (0.1 g) is required for carrying out most research and analytic work (Ghosh, 2013). About 30 mAbs were recently accepted for clinical use as therapeutics, with several others been at various trial stages (Li, 2010). Although there are current studies that are aimed at improving the efficacy of existing mAbs through optimisation processes, there still exist some limitations one of which include lack of efficient mAb generation models (Reff, 2002). However, despite these shortcomings, there remains to exist an interest by pharmaceutical companies to develop mAbs for clinical use. This is expected to control the management of many diseases in future based on both clinical and economical perspectives [9]. Types of therapeutic MAbs Progress in antibody engineering has yielded various types of mAbs for application in life science and biomedicine. These types of antiboies may have similar principles but different targets and applications. In addition, the choice of one method over another may be guided by several factors, including purpose of application, availability and effectiveness (Figure 2).

Applications of monoclonal antibodies

MAbs have proved to be extremely valuable for basic immunological and molecular research because of their high specificity feature. They are used in human therapy, commercial protein purification, suppressing immune response,

diagnosis of diseases, cancer therapy, diagnosis of allergy, hormone test, purification of complex mixtures, structure of cell membrane, identification of specialized cells, preparation of vaccines, and its increasing the effectiveness of medical substances (Fig. 3) (Zola, 2010 and Tyagi, 2011 and Edwards, 1981).

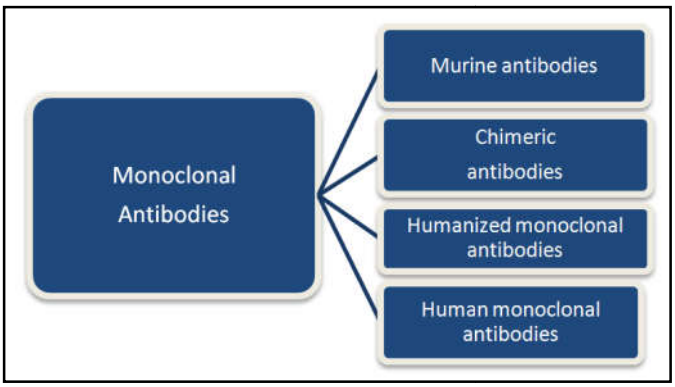

Figure 1. Types Therapeutic of Monoclonal antibodies

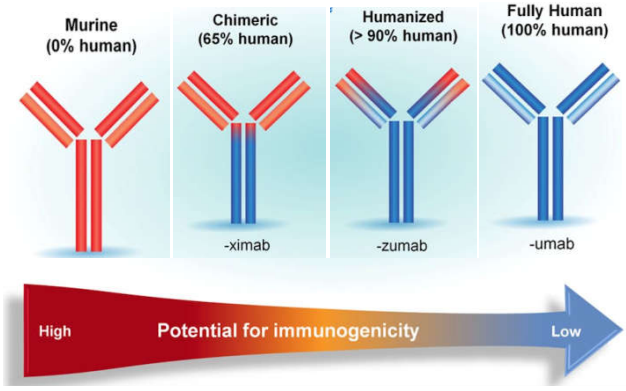

Figure 2. Efficency of Monoclonal Antibodies

Head and Neck cancers

Cancer cells are mutated versions of normal cells arising within the body; as a result, the immune system doesn't recognize them as threats, so an immune response is not activated. Conversely, in cases of autoimmune disease, the body mistakenly identifies healthy cells as antigens and launches an inflammatory attack against them. Consequently, the immunomodulatory properties of antibodies have been exploited for use as therapeutic agents for the treatment of such diseases National Cancer Institute, 2017 and Caspi, 2008). Monoclonal Abs (mAbs) are synthesized in the laboratory and used to therapeutically target specific self-antigens (constituents of the body's own tissues), such as those found on cancer cells (and, in the case of autoimmune disease, healthy cells). Monoclonal antibodies recognize and bind exclusively to the self-antigen on the cell surface. Destruction of the targeted cells results from a variety natural functions rendered by antibodies (Suzuki, 2015 and Cohen, 2013). The U.S. Food and Drug Administration (FDA) has approved more than 30 mAbs to treat cancers and autoimmune diseases. [Table 1] offers a condensed list of the more commonly administered mAbs, their therapeutic indications, and when they first became available in the United States (Scott, 2012 and Ecker, 2015). When used in the treatment of autoimmune diseases, immunotherapies suppress inappropriate and/or exaggerated immune responses that stimulate inflammation, whereas cancer immunotherapies help the immune system overcome the mechanisms utilized by tumors to evade destruction. In addition, some types of cancers can interfere with the immune system's ability to function properly (Caspi, 2008). Tumor necrosis factor (TNF) is a family of cell-signaling proteins that trigger a wide range of proinflammatory actions, including cell death. Studies have shown that targeting/blocking receptors of this protein in tumor cells not only impede their survival, but also inhibit tumor-promoting properties, such as angiogenesis (Sasi, 2012 and Schaer, 2014). Furthermore, TNF blockage can decrease the inflammatory activity in patients with autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and severe chronic plaque psoriasis (Silva, 2010 and Baumi, 2016). The immune system plays a key role in the development and progression of head and neck squamous cell carcinoma (HNSCC). Research has shown that a breakdown or substandard functioning of the immune system may contribute to the establishment and progression of this type of cancer. Head and neck cancers may be distinctively conducive to successful treatment from immunotherapy due to the extent of genetic and immune system defects involved[11].Additionally, most patients present with locally advanced disease and receive a combination of therapeutic approaches with significant toxicity and morbidity. Up to a third of patients eventually develop recurrent or metastatic disease. The prognosis for such patients is bleak and palliative treatment options are limited (Baxi, 2012). Novel treatment for HNSCC patients is essential due to the minimal improvement in patient survival in recent decades. Immune-directed therapies offer a unique therapeutic strategy beyond cytotoxic chemotherapy and physiologically destructive surgical and radiation interventions (Tyagi, 2011). For example, epidermal growth factor receptors (EGFR) are found to be over-expressed in 80% to 90% of head and neck cancers; EGFR over-expression is associated with reduced survival, making EGFR a logical target for immunotherapy. Inhibition of vascular endothelial growth factor receptor and a group of proteins known as tyrosine kinases has shown potential applications as curative therapy for HNSCC. The mAb cetuximab has been used for more than 10 years as initial treatment of HNSCC, while novilumab was recently approved by the FDA to treat recurrent or metastatic disease. Moreover, several new approaches — including therapeutic vaccines and adoptive T-cell therapy — are under development for treatment of HNSCC in various stages of progression (Lalami, 2016) (Lalami, 2016).

Side-Effects and Limitations of MAbs

MAbs given intravenously have usually mild side effects as compared with chemotherapy. A mild allergic reaction (rash) may be occurs with first administration of the drug. Common side effects include fever, headache, weakness, chills, nausea with vomiting and diarrhea, and low blood pressure. Other side effects of MAbs are related to the targeted antigens. Bevacizumab (used against tumor blood vessel growth) can have side effects such as kidney damage, high blood pressure, bleeding with poor wound healing, and blood clots. Inhalational anthrax (potent biological terrorism) is caused by breathing the bacterial spores of Bacillus anthracis. The FDA-approved drug raxibacumab (MAb) injection is used to treat infectious inhalational anthrax when alternative therapies have failed. Common side effects include rash with itching, extreme pain, and drowsiness (Chames, 2009; Scolnik, 2009; Rohrer, 2012 and Borrebaeck, 2001).

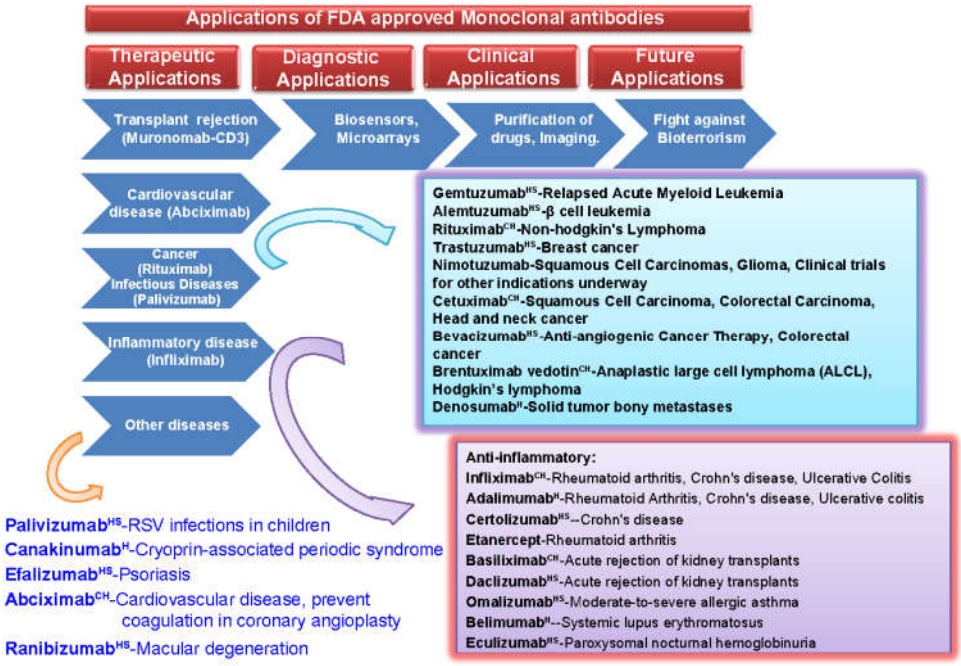

Figure 3. FDA approved Therapeutic Monoclonal antibodies

Table 1. Summary of Therapeutic mAbs, Indication and Adverse Events

Trade Name	Generic Name	FDA Approval	Therapeutic Indications	irAEs* (most common/severe)
Rituxan	rituximab	1997	• Non-Hodgkin's lymphoma • Chronic lymphocytic leukemia • Rheumatoid arthritis	• Abnormally low blood pressure • Bronchospasm • Increased risk of infection • Increased potential of abnormal bleeding • Rash • Itching
Remicade	infliximab	1998	• Crohn's disease • Ulcerative colitis • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis	• Abnormal liver function • Abnormally low blood pressure • Anemia • Hives • Hypersensitivity reaction
Herceptin	trastuzumab	1998	• Breast cancer • Metastatic gastric or gastroesophageal junction adenocarcinoma	• Anemia • Decreased neutrophil count • Dizziness • Rash • Trouble breathing
Humira	adalimumab	2001	• Rheumatoid arthritis • Juvenile idiopathic arthritis • Psoriatic arthritis • Ankylosing spondylitis • Crohn's disease • Plaque psoriasis	• Acute infection of nose, throat or sinus • Cellulitis • Extreme loss of body water • Rash
Avastin	bevacizumab	2004	• Metastatic colorectal cancer • Non-small-cell lung cancer • Metastatic breast cancer • Glioblastoma multiforme • Metastatic renal cell carcinoma	• Decreased white blood cells • High blood pressure • Painful, red and/or swollen mouth • Skin rash with sloughing • Trouble breathing
Erbitux	cetuximab	2004	• Head and neck cancer (initial treatment of local/regional advanced) • Colorectal cancer	• Anemia • Dizziness • High blood pressure • Infection • Rash • Trouble breathing
Simponi	golimumab	2009	• Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis	• Acute infection of nose, throat and/or sinus • Cellulitis • Infection • Throat irritation
Prolia	cenosumab	2010	Osteoporosis	• Trouble breathing • Low energy • Weakness
Yervoy	ipilimumab	2011	Melanoma	• Inflammation of large intestine • Abnormal liver function • Thyroiditis • Skin inflammation
Perjeta	pertuzumab	2012	Breast cancer	• Anemia • Decrease neutrophils • Hypersensitivity drug reaction • Trouble breathing • Acute infection of nose, throat and/or sinus
Opdivo	nivolumab	2014 2015 2016	• Advanced melanoma • Metastatic non-small-cell lung cancer • Metastatic or recurrent head and neck cancer where previous platinum-based chemotherapy was not effective	• Abnormal liver function • Inflammation of large intestine • Acute infection of the nose, throat and/or sinus

*On average, onset of adverse effects typically emerges six to 12 weeks after the start of treatment.

More effective MAb drugs resulting from advancements in MAb engineering along with the development of cell biomarkers for characterizing the patient subpopulations may lead to more cost-effective use of treatment responding drugs. MAb drugs have always been costly, as only a few of nearly 22 FDA regulated drugs are available in the market. A large number of new MAb drugs are under development. The sale of first-generation safe and cost-effective MAbs is quite good in absence of generic competitors. With the high demand of specialty pharmaceuticals, some long-term measures have been taken to prominently transform the way MAbs are developed, commercialized, and marketed. MAb therapies are a financial burden on patients, and with some health plans and step-wise therapies the problem can be resolved (Chames, 2009; Scolnik, 2009; Rohrer, 2012 and Borrebaeck, 2001). Sometimes a new, improved, costly version of an existing MAb competes with the established therapeutic product. Bevacizumab, the parent drug of ranibizumab, after usage by ophthalmologists was found to be more widely available and cheaper than ranibizumab. Additionally, it offers similar efficacy to ranibizumab. In all of these cases, comparative clinical data obtained by clinical trials is required. For a patient, the benefit of the drug does not always justify the cost, but clinical effectiveness of all these drugs should be trialed and demonstrated (Chames, 2009; Scolnik, 2009; Rohrer, 2012 and Borrebaeck, 2001). MAbs is a proven therapeutic agent generating revenues of several billion dollars for the pharmaceutical industry. The typical doses of MAb drugs needed for treatment are significantly higher than those required for other drugs (or products). Thus, large-scale production that is cost-effective in manufacturing processes are required. However, the huge demand to increase production of these drugs and the drive to lower the cost of these expensive medicines is a continuous challenge to the present industry. This will further improve the efficiency of manufacturing processes. These challenges are overcome by streamlining downstream processes to increase product quantities, to implement proper quality with high-concentration product formulations with sufficient stability, dose-effective products, to reduce the cost, to develop methodologies for timeline MAb production, and to develop alternative delivery systems (Rohrer, 2012 and Borrebaeck, 2001).

Dental Considerations

Infection is one of the most important side effects of biological therapy. Tuberculosis, as well as viral and bacterial upper respiratory infections, are the common side effects. TB testing is performed in all patients prior to initiating a biologic. A history of TB exposure while on a biologic agent should prompt repeat TB skin testing (Girolomoni, 2012; De Keyser, 2011; Rosman, 2013 and Azevedo, 2012). Thus, following dental procedures, dentists should monitor patients for possibility of developing opportunistic infection as well as signs and symptoms of mycobacterial infection. Recently, screening has been performed as a routine practice before a biologic is administered. Screening tests consist of evaluation for current or previous tuberculosis infection by patients' history, PPD skin test, and chest radiography. Damage to the liver is one of the side effects of biological drugs (Girolomoni, 2012). Liver enzyme tests, prothrombin time (PT), and international normalization ratio (INR) should be measured (Rosman, 2013). The use of any drug in a patient with severe liver disease should be discussed with the patient's physician. Monitoring platelet count and function, and bleeding time is important in patients on biologics due to the increased risk of hematological disease including thrombocytopenia (Little, 2013). British Association of Dermatologists guidelines for biologic interventions for psoriasis recommended that TNF antagonist therapies should be discontinued at specific times prior to surgery, based on four to five times the half-lives (2weeks for etanercept, 6-8 weeks for adalimumab, 4-6 weeks for infliximab). Biological therapy is restarted post operatively provided that wound healing is satisfactory and there is no evidence of infection (Little, 2013). The American Heart Association scientific statement in 2003 on nonvalvular cardiovascular device-related infections reported that "immunosuppression is not an independent risk factor for nonvalvular device infection". The statement recommended that immunosuppressed patients with nonvalvular device should receive antibiotic prophylaxis as immunocompetent patients (Little, 2013 and Smith, 2009). There is no information regarding antibiotic prophylaxis in patients receiving biologics. Since bacteremia induced by dental procedures is a transient bacteremia, we suggest that antibiotic prophylaxis prior to dental work is not recommended in patients using a biologic.
A study following patients on biologics is required to clear this matter. Administration of live vaccines is not recommended while on biologics, as these agents affect immune system.

Recommendation for dental treatment of patients taking biological agents include:

- CBC and platelet count if bleeding is involved with dental procedure procedure
- PT, INR if the patient has liver disease
- Discontinuation of the biological agents prior to oral surgery (extraction, periodontal surgery) 4-5 time of the drug's 1/2 life.

So, while biologics can affect dental care, it may be that dental health issues affect rheumatic arthritis and its treatment. Periodontal disease is worse in patients with rheumatoid arthritis compared to controls. Furthermore, bacterial causing periodontal disease, specifically Porphyromonas gingivalis, may be an environmental trigger for autoantibodies binding citrullinated self-peptides.This bacteria, a common pathogen in periodontal disease, possesses a unique bacterial enzyme, peptidyl arginine deaminase, which converts arginine residues in citrulline. Antibodies against citrullinated proteins are found in about 80% of rheumatoid arthritis patients. Recent work indicates that severe periodontal impairs the efficacy of anti-TNF agents in treatment of rheumatoid arthritis (Baddour, 2003 and Furst, 2012). The complex relationship of periodontal disease and rheumatoid arthritis is only just being explored, but as understanding increases both physicians and dentists will need to be aware of the implications for treatment of dental disease in these patients (Furst, 2012).

Conclusion

Targeted and biologic therapies offer promising approaches in the treatment of cancer and autoimmune disease. The rising number — and increased survival — of patients treated with biotherapies affirms this as a relevant clinical question when looking to the literature for the best evidence. A high level of awareness of potential irAEs by patients and health care providers is essential for early recognition and timely management. Identifying and managing requires a multidisciplinary approach to help reduce morbidity and prevent interruptions to therapy. Oral health professionals who

are knowledgeable about immune responses are well positioned to work with patients who have undergone, or will undergo, immunotherapy.

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