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Biological therapy and dentistry:

A review paper

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Abstract

In recent years, a new class of drugs has revolutionized the treatment of autoimmune, allergic, infectious and many more diseases. These drugs are classified into three groups, cytokines, monoclonal antibodies and fusion proteins. Biological drugs have less side effects compared to conventional drugs, and may target special damaged cells, but not all the cells. There may be side effects such as infection, hypersensitivity, hematological disorders, cancer, hepatotoxicity and neurological disorders, but there is not enough evidence or long term studies of the mechanism of action and side effects of these drugs. Patients on biological therapy may need some special consideration in dentistry. This paper is a review regarding the classification, mechanism of action and side effects of these drugs, and dental consideration for patients on biological therapy.

Introduction

A new class of therapeutic agents known as biologicals was recently introduced to the medical world that is helpful in treatment of some medical conditions such as autoimmune diseases and cancers. This class of medications, which uses living organisms or a synthetic version of them, is manufactured by using recombinant DNA technology.[1] The US agency FDA (Food and Drug Administration) defines biologic products as “any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of disease or injuries of man”.[2] The application of a biological artificial valve or genetic therapy is also an example of biological therapy.[3] Thus, biological drugs include, vaccines, blood and blood-derived preparations, antitoxins, growth hormones, human insulin, gene therapy, recombined therapeutic proteins and allergens, along with the new biologics, which

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can be cytokines, monoclonal antibodies or fusion proteins.[3] In treatment of autoimmune diseases, biologicals can enhance or replace conventional immunosuppressive therapies, and sometimes can be used in combination. In treatment of cancers, immunotherapy can increase anticancer immune response or prevent the cancer cell signals against the immune system. Biologicals utilize the natural ability of immune system to detect and destroy abnormal cells. Advances in immunology and understanding the pathogenesis of the autoimmune diseases have directed researchers to new treatment targets. Compared to conventional treatments (see Table 1 for comparison of biological with traditional drugs), biological therapies are possibly more beneficial due to the fact that they target the molecules involved in pathogenesis of the disease. For this specific characteristic, their general side effects are less than conventional treatments, such as anti-inflammatory, immunosuppressive, or cytotoxic drugs (Table 1).Biological therapy is shown to be effective in neoplastic, autoimmune, inflammatory, cardiovascular, dermatologic, infectious, and allergic reactions.[4]

In cancer therapy, monoclonal antibodies showed significant results. These agents can be directed toward several targets such as cell surface proteins of solid tumors or circulating cancer cells, targets in the tumor stroma (comprised blood vessels, fibroblasts or inflammatory cells), or targets in the tumor vasculature. Hematologic neoplasms such as lymphoma were shown to be easier to target with monoclonal antibodies, since antibodies can easily penetrate the tumor cells.[5]

Biologicals are divided into 3 subclasses (see Table 2): 1) key signaling proteins (cytokines or natural antagonists), 2) monoclonal antibodies, and 3) fusion proteins (soluble).[1]

1. Signaling proteins, cytokines

The signaling proteins can process information from their immediate environment (outside the cells) or from integration of the several simultaneous signals from close or distant cells to produce an action. The signals can be made by chemicals such as hormones or neurotransmitters that act locally or travel to the far sites of action, or mechanical stimuli such as sensory cells in the skin. Signaling molecules bind to receptor proteins expressed on the cells to initiate physiological changes. Receptors can be cytoplasmic or nuclear. In these cases, receptors bind to carrier molecules that facilitate passage through the cell membrane (such as estrogen).[6]

Cytokines are a large group of soluble proteins, peptides, or glycoproteins that help cell signaling. Cytokines are immunomodulators that regulate the host responses to inflammation and infections. Interferon α and β, and interleukin 2 (IL-2) are the example of the cytokines.[5] (Dinarello, 2000 cytokines) Soluble cytokine receptors have the suffix -cept at the end of their name, e.g. etanercept, and abatacept.[1]

2. Monoclonal antibodies

Antibodies are very specific naturally evolved molecules that bind to antigen or pathological cells to eliminate a disease. Monoclonal antibodies (mAbs or moAbs) are a singular molecular species that are active against a single target antigen. They are synthetic molecules, clones of a unique parent immune cell that will be identical with the same

affinity and bind to the same target or epitope. Monoclonal antibodies are engineered to bind specific cells or a part of a specific cell to enhance immune recognition.[7]

In vitro production of murine mAbs from hybridomas (hybrid cell lines) was introduced by Kohler and Milstein in 1975.[8] With the development of human antibody and hybridoma technology, immunotherapy developed in cancer and immunological therapy. A major advantage of these drugs is their specificity. By identifying the right antigen to target, which is not always easy in cancer therapy, the side effect of these drugs could be limited.[9] Monoclonal antibodies are identified by the suffix of "*mab"* such as adalimumab or omalizumab, rituximab and tocilizumab.[5]

Monoclonal antibodies are in four categories: murine, chimeric, humanized, and human. In the late 1980s, murine mAbs were developed, but due to short half-life in humans, association with allergic reaction, induction of anti-drug antibodies, and some other drawbacks, these constructs were not quite desirable.[10,11] With more development of the technology, other mAbs including chimeric, humanized and fully human were developed. Chimeric mAbs are characterized by "– ximab" in their name and consist of 50–90% human protein such as abciximab. Humanized mAbs are named using "– zumab". They are consist of 95% human antibody such as omalizumab, are in 95% humanized. Fully human antibodies such as adalimumab have the suffix of "– mumab".[1] A mouse monoclonal antibody such as ibritumomab has the suffix of "–momab".[12] The middle part of the drug name reflects the disease that the drug was initially intended to treat such as: -lim- for inflammatory, -cir- for cardiovascular, and -tu- for tumors or neoplastic diseases.[13]

Monocolonal antibodies are mostly created using the spleen of a mouse that has been exposed to the target antigen of interest. Resulting mAbs act by binding with their specific molecular targets to send signal arrest, which lead to apoptosis in targeted tumor cells, modulation of the receptor, or interfering with ligand binding.[14] In cancer therapy, mAbs bind to cancer specific antigens, then either alter the signaling system of the cancer cells or mask bound surface antigens. Monoclonal antibodies (naked antibody) can also be used to deliver agents such as radioisotopes, toxins, and cytokines to directly kill tumor cells. The agents carried by mABs are called "payloads".[5] Monoclonal antibodies can be conjugated with chemotherapy (chemolabeled, e.g. brentuximab vedotin for treatment of Hodgkin's lymphoma), or conjugated with radioactive particles (radiolabeled antibody, e.g. britumomab tiuxetan for treatment of non-Hodgkin's lymphoma). Conjugated antibodies could be stronger mABs alone (naked antibody), and possibly have more side effects.[7]

In organ transplant recipients, some mABs such as asiliximab, daclizumab, and muromonab-CD3 are used as adjunctive immunosuppressive agents. Muromonab-CD3 blocks the function of T cells. Meanwhile, basiliximab (Simulect®) and daclizumab (Zenapax) are interleukin-2 receptor antagonists and inhibit T-cell activation and proliferation.[15]

3. Fusion proteins

Fusion proteins (soluble cytokine receptors or ligands) are composed of transmembrane proteins, connected to another molecule. Usually the linker is the Fc portion of human immunoglobulin. The connected Fc portion of the fusion receptor can be manipulated to

have a function or not. Fusion receptors competitively inhibit the binding of a ligand to its specific receptor to prevent unwanted effects. Biological properties of a therapeutic cytokine can be improved or modified by using fusion techniques. For example, investigation has shown half-life can be expanded (fusion to Fc, albumin), cytotoxicity can be enhanced (fusion to bacterial toxins), or activity can be increased (fusion to cytokine agonists).[16]

Table 2 shows most common therapeutics biologics, their indications and side effects (See table 2).

Side effects of biologicals—Different biological agents can produce various side effects. A common side effect is related to the site of injection/infusion which including rash, itching, pain, redness, and swelling. Less common but potential serious side effects are flu-like symptoms, hypersensitivity reaction, hematological disorders, infection, cancer, hepatotoxicity and neurological disorders.[3]

Perhaps the most important adverse reaction to biologicals is susceptibility to infection. Increased incidence of opportunistic infections such as tubercular, hepatic, and fungal have been documented.[17]

Biologicals inhibit molecules such as TNF, which are essential in normal inflammatory responses. Composition and function of the immune system would change, therefore, patients become more predisposed to infection.[13] TNFα is a pro inflammatory cytokine, and inhibition of it may be a potential risk for immunosuppression. Literature have shown an intact cell-mediated, humoral, and innate immune responses during treatment with TNF inhibitors. (Lee et al, 2003) Animal studies suggested that TNF-alpha inhibition may interfere with wound healing. If the interfering is facilitating (Mooney et al, 1990) or delaying (Rapala et al 1996, salomon et al, 1991) is not cleared. But clinical experiences are controversial. Some studies showed serious infection, and others rarely showed any problems. There are several factors that could influence outcome of anti-TNF therapy. These factors include underlying diseases being treated, dose of biologics, duration of therapy, and using biologics concomitantly with other medications (Lee et al, 2003). Historically, patients with severe disease are treated with biologics. There is also presence of confounding factors such as increased risk of infection and lymphoproliferative response (non-Hodgkin's lymphoma) in patients with rheumatoid arthritis since TNFα plays a role in etiopathology of rheumatoid arthritis (Symmons et al, 2004).

Postoperative infection and wound healing was evaluated after foot and ankle surgery in patients with etanercept or infliximab and controls (patients without these drugs). Healing and infection complications were almost the same in both groups, and patients on TNF-alpha blocker even performed better.(Bibbo et al, …)

Injection /infusion site reaction have been documented with etanercept, adalimumab, and infliximab.[19,21] In a postoperative study of patients with Crohn's disease who used infliximab preoperatively, Marchal et al found no significant differences in complications between patient and control groups after adjustment for age, gender and surgical procedures (Marchal et al, 2004). Furthermore, in a retrospective study of the 270 Crohn's disease

patients receiving infliximab and/or immunomodulating medications prior to abdominal surgery, early postoperative complications were almost the same (Colombel et al, 2004) . Despite the encouraging results, all of the researchers recommended caution and close observation for possibility of infections.13

However, biological therapy is only rarely associated with serious infections. On the basis of their underlying predisposing medical conditions, patients are at higher or lower risk of developing infections. Ten cases of *Pneumocystis carinii* (now known as *Pneumocystis jiroveci*) pneumonia (PCP) infection were reported during treatment with infliximab by postmarketing surveillance through June of 2001. PCP is an uncommon infection during standard medical treatment of inflammatory bowel disease.[18] While uncommon, serious infections are mostly seen during the first month of therapy. Opportunistic infections have been seen mostly in immunocompromised patients.[3,19]

Lower respiratory infections including tuberculosis are a significant side effect of biologics. Among biologicals, TNF inhibitors impart the highest risk. Tuberculosis, which is a reactivation of a latent infection, usually occurs shortly after the beginning of the biologic therapy.[19] Patients with chronic obstructive pulmonary disease (COPD) treated with abatercept had more serious lower respiratory infection than placebo group.[3]

An increase of viral infections, including hepatitis C and B, was reported in patients on biologic therapy. Susceptible patients are also at risk for reactivation of hepatitis B. Other possible opportunistic viral infections are herpes zoster and CMV. Herpes zoster is reported more in patients who are using monoclonal therapy.[19,20] Fungal infections have also been reported. Histoplasmosis was found in 9 patients using infliximab and 1 patient using etanercept within 1 week to 6 months after the first dose. All reported cases were from areas endemic for histoplasmosis, which includes most of central North America. All patients were receiving concomitant immunosuppressive medications in addition to infliximab or etanercept.[13] Although fungal infections (candidiasis, histoplasmosis, aspergillosis) are not a common opportunistic infections in patients receiving biologic therapy, clinicians should monitor the patients carefully for possibility of these infections, especially in endemic areas. Patients with HIV are not appropriate candidates for biological therapy. These patients are immunocompromised and are at increased risk of infection such as tuberculosis.[9]

Since biological drugs are essentially large peptides and various hypersensitivities can be seen as immediate or delayed (mediated by IgE or T cells). These drugs are considered immunogenic and the degree of humanization of the applied protein could be a factor determining the level of their immunogenicity. Monoclonal antibodies can induce an immunological reaction at the antigen binding sites. Manifestations of the immunogenicity of biologics include rash, fever, anemia, edema, and injection-site reaction.[13]

There are reports of hematological complications, including leukopenia and thrombocytopenia, with use of anti-TNFα agents. (etanercept and infliximab)(Vidal et al, 2003) [19,22] There are case reports of bone marrow hypoplasia (Vidal et al,2003; and #22) in patients receiving TNFα antagonists. Rajakulendran et al (2006) reported 14.3% neutropenia in a total of 133 patients receiving anti-TNF drugs. Only one of the neutropenic patients

developed infection.(Rajakulendran et al) The etiology and causal relationship between TNFα inhibitors and pancytopenia is not clearly understood, but it is thought that since TNFα applies its effects by regulating proinflammatory cytokines that have a role in stem cell differentiation (IL-1, IL6, IL8), blocking the function of TNFα will cause suppression of stem cell differentiation and bone marrow hypoplasia including neutropenia, and thrombocytopenia.(Vidal et al, 2003, and Keystone EC, 2001)

Spontaneous abortion in patients using anti-TNFα at the time of conception was reported. Women who plan to conceive, should discontinue biologics for 3 weeks for etanercept, 6 weeks for infliximab, 6 months for adalimumab, 15 weeks for ustekinumab before conception, as recommended by the manufacturers.[9]

Although new data indicate that biological agents may be useful as an adjunct in advanced cancer treatment, some of these agents may have a role in carcinogenesis and progression of tumors. Some authorities have assumed pre-existing cancer in those patients, since cancers appear in early treatment stage.[23] Development of solid tumors and lymphoma as well as skin cancer following biological therapy involving treatment with TNFα has been discussed in the literature (Girolomoni, et al, 2012). But when comparing national registries of patients with rheumatoid arthritis who receive TNF-specific mAbs with those on methotrexate, there is not a greater risk of developing malignancies (Hansel et al, 2010) (more ref??) Treatment with infliximab has been associated with liver disease ranging from increased liver enzymes to a severe liver damage. Adalimumab has also been associated with hepatotoxicity, and disappearing of hepatotoxicity after switching to etanercept has been reported in patients with psoriatic arthritis. The onset of hepatotoxicity is rare in patients treated with etanercept .(Girolomoni,et al 2012)

Several biological agents have been associated with development of progressive multifocal leukoencephalopathy (PML). This disease was rare, but by using biological agents, mostly natalizumab which significantly decreases migration of T cells into the central nervous system, has been seen more frequently. Natalizumab is an elective medicine for treatment of multiple sclerosis (MS), and it has been associated with development of PML in MS patients who are seropositive for JC virus. Several risk factors put patients at risk for PML, including presence of JC virus, prior immunosuppression exposure, and treatment with natalizomab for longer periods (>2 years). (Langer-Gould et al, 2005; Van Assche et al, 2005; Yamamoto et al, 2007; chalklet et al, 2013)

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.[9,19,24] 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.[19] Liver enzyme tests, prothrombin time (PT), and international normalization ratio (INR) should be measured.[25] 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.[22]

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.[26]

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.[27]. 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.[28]

Recommendation for dental treatment of patients taking biological agents include:

1. CBC and platelet count if bleeding is involved with dental procedure procedure
2. PT, INR if the patient has liver disease
3. 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 (reviewed in Koziel, et al, 2014). 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 (Saliotli et al). 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.

Conclusion

This recommendations are a conclusion from reviewing the literature. A clinical retrospective study is required to determine dental consideration of patients taking biological therapy.

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Table 1

Comparison of biological drugs with traditional drugs[35]

	Biological Drugs	**Traditional Drugs**
Route of Administration	Parenteral (must)	Parenteral or Oral
Metabolism	Not metabolized	Metabolized with reactive intermediates (potential immunogenicity) (haptens)
Structure	Similar to native proteins	Synthetic chemicals
Side effects	-Immune-mediated effects (inherent) -immunoglobulins (IgE, IgG) mediate hypersensitivities (rare)	-Immune-mediated side effects (unexpected & unlike intended action -T-cells mediate side effects -Drug-drug interactions -Organ toxicity

Table 2

Example of commonly used biological medicines:

	Drugs	Indications	Side effects
Cytokines	anakinra (Kineret) [28,29] IL-1 blocking agent	1-Rheumatoid Arthritis 2-Cryopyrin-Associated Periodic Syndromes (CAPS)	Hypersensitivity, injection site reaction, worsening of RA, upper respiratory tract infection, neutropenia, malignancies Pregnancy: category B
	Tofacitinib (Xeljanz) [28,30] Janus kinase inhibitor	Adult patient with moderate to severe active RA with inadequate or intolerance to methotrexate	Serious infections, malignancies, tuberculosis, viral reactivation, non-melanoma skin cancer, gastrointestinal perforation, neutropenia pregnancy category C
Monoclonal	adalimumab (Humira) [28,31] Anti-TNF	1-Rheumatoid arthritis 2-Juvenile idiopathic arthritis 3-Psoriatic arthritis 4-Ankylosing spondylitis 5-Crohn disease 6-Ulcerative colitis 7-Plaque psoriasis	Serious infection, lymphoma and malignancies, hypersensitivity, hepatitis B virus reactivation, demyelinating disease, cytopenia, congestive heart failure, lupus-like syndrome Pregnancy category B
	Actemra(Tocilizumab)	1-Severely active rheumatoid arthritis 2-active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older. 3-active systemic juvenile idiopathic arthritis (SJIA) in patients 2 years of age and older.	Gastrointestinal Perforations, Laboratory Monitoring, Immunosuppression, Hypersensitivity Reactions, Demyelinating Disorders, Active Hepatic Disease and Hepatic Impairment, Pregnancy category C
	Xolair (omalizum) ADCETRIS (brentuximab vedotin)	1-Asthma 2-Chronic Idiopathic Urticaria (CIU)ab) 1-Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) 2-HL in patients who are not ASCT candidates after failure of at least 2 multiagent chemotherapy regimens 3-Systemic anaplastic large cell lymphoma (sALCL) after failure of at least 1 multiagent chemotherapy regimen	Anaphylaxis, malignancy, Pregnancy category B Neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting,stevens-johnson syndrome, Embryo-fetal toxicity Fetal harm can occur. Advise pregnant women of the potential hazard to the fetus.
	Zenapax (dacilizumab)	Prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.py regimen	Constipation, nausea, diarrhea, vomiting, abdominal pain, pyrosis, dyspepsia, abdominal distention, epigastric pain not food-related,edema extremities, edema,tremor, headache, dizziness,oliguria, dysuria, renal tubular necrosis,posttraumatic pain, chest pain, fever, pain, fatigue, hypertension, hypotension, aggravated hypertension,dyspnea, pulmonary edema, coughing,impaired wound healing without infection, acne,insomnia,musculoskeletal pain, back pain,tachycardia,thrombosis; Platelet,bleeding,lymphocele.
	Zevalin (ibritumumab)	1-Relapsed or Refractory, Low-grade or Follicular NHL	Serious Infusion Reactions, Prolonged and Severe• Severe

	Drugs	Indications	Side effects
		2-Previously Untreated Follicular NHL	Cutaneous and Mucocutaneous Reactions, Leukemia and Myelodysplastic Syndrome Pregnancy category B
	Simulect (basiliximab)	Prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids.	Constipation, nausea, abdominal pain, vomiting, diarrhea, dyspepsia, pain, peripheral edema, fever, viral infection, hyperkalemia, hypokalemia, hyperglycemia, hypercholesterolemia, hypophosphatemia, hyperuricemia, urinary tract infection, dyspnea, upper respiratory tract infection, surgical wound complications, acne, hypertension, headache, tremor, anemia.
	ReoPro (Abciximab) Orthoclone OKT3 (muromunab-CD3)	1-In patients undergoing percutaneous coronary intervention 2-In patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours 1-Treatment of acute allograft rejection in renal transplant patients. 2-Treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.	Intracranial Hemorrhage And Stroke, Thrombocytopenia, Allergic Reactions Cytokine Release Syndrome, Infections, Neoplasia, Adverse Reactions by Body System,
Fusion	etanercept (Ebrel) [28,33] TNF blocking agent	1-Rheumatoid arthritis 2-psoriatic arthritis 3-Ankylosing spondylitis 4-Polyarticular juvenile idiopathic arthritis	Serious infection, malignancies (mostly lymphoma), demyelinating diseases, congestive heart failure, hepatitis B reactvation, allergic reaction, Pregnancy category B
	abatacept (Orencia) [28,34] Blocking costimulation of T cell activation	1-Moderate to severe RA 2-Juvenile idiopathic arthritis(older than 6)	Hypersensitivity, serious infection, malignancies, respiratory problems in patients with COPD Pregnancy category C

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