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RESEARCH ARTICLE

NEED FOR PROPHYLACTIC ANTIBIOTIC COVER FOR INVASIVE DENTAL PROCEDURES IN PATIENTS ON BIOLOGIC THERAPY

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ABSTRACT

Biologics are a novel category of drugs which are a solution to modern medicine's problems. They are derived from human genes and are genetically engineered proteins. Biological therapy is shown to be effective in neoplastic, autoimmune, inflammatory, cardiovascular, dermatologic, infectious, and allergic reactions. This article elaborates on the role of biologic therapy in patients undergoing invasive dental treatments and the need for antibiotic cover in such patients.

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INTRODUCTION

In the recent years, a new class of drugs has revolutionized the treatment of many diseases which may be of autoimmune, allergic, infectious or of any other origin. These drugs may be classified into three groups: cytokines, monoclonal antibodies and fusion proteins. Biologics are genetically-engineered proteins that are derived from human genes. (Radfar *et al*., 2015) Biological drugs have less side effects compared to conventional drugs, and may target especially damaged cells, but not all the cells. They are designed to inhibit specific components of the immune system that play pivotal roles in fuelling inflammation. There may be adverse effects such as infection, hypersensitivity, haematological 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. There are currently three broad classes of biologic therapies, tumour necrosis factor-alpha inhibitors, lymphocyte modulators and interleukin inhibitors. (Mazurek and Jahnz-Różyk, 2012) These are increasingly used currentlyin the treatment of immune-mediated conditions of inflammatory origin, and several have potential applications in oral medicine. Guidelines for their application in licensed indications, such as, rheumatoid arthritis, psoriasis, inflammatory bowel disease, include recommendations for patient selection, and subsequent monitoring with discussion of potential adverse effects. An understanding of these is important when managing patients receiving biologic therapy for systemic disease, and compliance is essential in any use in oral medicine.

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Role of biotechnology

Biologics have revolutionized the treatment of chronic diseases like rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn's disease, and multiple sclerosis, and are widely used in treating a variety of cancers. (Rosman *et al*., 2013; Abhishek *et al*., 2016) Some of these products include Enbrel, Humira, Remicade (infliximab), Avonex(inteferon beta-1a), Betaseron (interferon beta-1b), Tysabri, Cimzia (certolizumabpegol), Herceptin (trastuzumab), Rituxan (rituximab), Neupogen (filgrastim), Neulasta (pegfilgrastim) and Leukine (sargramostim). (Weinberg, Jeffrey 2003) Biologics, as the name implies, are derived from living organisms.The first-generation biologics include products that are obtained from humans or animals, such as human blood, insulin (bovine or porcine), or influenza vaccine, the viruses for which are grown in chicken eggs. The second-generation biologics have come to the market only in the past 10 to 15 years. Second-generation biologics rely on biotechnology for their manufacture. (O'Neill and C. Scully) The second-generation biologics are complex

proteins and cannot be manufactured chemically. But since all living cells know how to manufacture proteins, second-generation biologics are made by exploiting this fact. Using biotechnology, we "trick" certain cells to manufacture these proteins by using recombinant DNA technology. A variety of cells have been used to make biologics, but the key is that they have to be alive and fully functioning. Yeast and bacteria (E coli), and even cells that come from mammals have been used. One of the most commonly used mammalian cells is called CHO because it originally came from the Chinese hamster. (Nagle *et al*., 2003) The "O" signifies that the specific cell used is an ovarian cell. There are two fundamental requirements for manufacturing a biologic. One is that the cells in which the product will be made have to be grown in extremely large quantities. Huge vats of yeast, bacteria or CHO cells are required, and they require high maintenance under conditions that allow them to live and function normally. Since the cellular instructions for making all proteins are carried by the DNA in the genes, isolating the right gene would give the blueprint to the cell as to how to manufacture the protein.

Once the right gene is isolated, utilisation of special techniques is done to insert that gene into the host cell's DNA. From one normal cell (yeast, bacteria or CHO cell line) new genes are plugged in where it becomes incorporated and permanent. Also some special bits are plugged in, that basically informs the cell of that gene's utmost importance and that while the cell should function how it must to stay alive, it should focus all its other energies on following this gene's instructions for manufacturing the desired protein. The cell has been "tricked" into becoming a specific protein-making factory. A large number of these dedicated protein machines produce the biologic product, ready to be tested and eventually used by people who need them. (O'Neill, 2008) The entire process, from isolating the gene, to inserting it into the cell, to growing vast quantities of the modified cells, and finally, to siphoning off just the desired protein devoid of other cellular contaminants is complex, requiring state-of-the art knowledge in molecular biology, recombinant biotechnology and cell culture techniques. (O'Neill, 2008) This justifies why biologics are expensive. The standard drug manufacturing facilities, however new or sophisticated, are wholly inadequate for biologic production. Entire new facilities must be built from the ground up. A wide variety of highly trained scientists is needed to figure out the biotechnology required, and these personnel cannot simply come from the ranks of chemists already employed by pharmaceutical companies. Moreover, the number of people able to be treated with these new products is often relatively small, compared to drugs designed to treat common disorders. The fewer the people to be treated, the harder it is to recoup the start-up costs. (O'Neill, 2010)

Indications of biologics

Biological therapy is shown to be effective in neoplastic, autoimmune, inflammatory, cardiovascular, dermatologic, infectious, and allergic reactions.In treatment of autoimmune diseases, biologics can enhance or even replace the conventional immunosuppressive therapies, and sometimes they can be used in combination. (Nakagawa, 2010) In treatment of cancers, immunotherapy can increase anticancer immune response or prevent the cancer cell signals against the immune system. Biologicalsutilise the natural ability of immune system to detect and destroy abnormal cells. In cancer therapy, monoclonal antibodies showed significant results. (Adams and Weiner, 2005) These agents can be directed toward several targets such as cell surface proteins of solid tumours or circulating cancer cells, targets in the tumourstroma (comprised blood vessels, fibroblasts or inflammatory cells), or targets in the tumour vasculature. Haematological neoplasms such as lymphoma were shown to be easier to target with monoclonal antibodies, since antibodies can easily penetrate the tumour cells.All patients with drug-induced immunosuppression, prosthetic joint replacement, immunocompromised or immunosuppressed patients, patients with inflammatory arthropathies (e.g.: rheumatoid arthritis, systemic lupus erythematosus) are indicated for biologic drug therapies. (Nakagawa, 2010)

Classification of antibiotics

Antibiotics may be informally defined as the subgroup of anti-infectives that are derived from bacterial sources and are used to treat bacterial infections. Although there are several classification schemes for antibiotics, based on bacterial spectrum (broad versus narrow) or route of administration (injectable versus oral versus topical), or type of activity (bactericidal vs. bacteriostatic), the most useful is based on chemical structure. Antibiotics within a structural class will generally show similar patterns of effectiveness, toxicity, and allergic potential.

Antibiotics are classified into: (Fair, Richard and Yitzhak Tor, 2014)

- Beta-Lactams (Penicillin & Cephalosporin)
- Macrolides
- Fluroquinolones
- Tetracycline
- Aminoglycoside

Invasive and non invasive dental procedures

It is important to understand the difference between invasive and non-invasive procedures as invasive dental procedures call for extra care in preventing spread of infection. (Santhosh Kumar and Sneha, 2016)

Invasive Dental Procedures

Invasive dental procedures include those that involve manipulation of the oral tissue or perforation of the oral mucosa such as:

1. Periodontal therapy
   - Prophylaxis
   - Scaling and root planing
   - Surgical therapy
2. Surgical tooth extraction
3. Simple tooth extraction
4. Dental implant
5. Biopsy
6. Endodontic therapy

Non-Invasive Dental Procedures

A non-invasive procedure is a conservative treatment that does not require incision into the tissues or the removal of tissue, to remove the least amount of tooth structure, bone or soft tissue

as necessary to eliminate what is unhealthy or diseased. Non-invasive dentistry seeks to make the procedure as conservative and comfortable as possible. Non-invasive dental procedures include dental restorations, crowns, bridges, removable prosthodontic devices such as dentures, flouride treatment, orthodontic treatment, veneers, teeth whitening and bleaching, and laser dentistry.

Need for antibiotics in patients on biologics

An increasing number of patients receiving biologics are now being seen by clinicians in dental practice. Although sufficient data not available, there may be a potentially increased risk of adverse effects associated with invasive dental procedures. Evaluation of any association between dental treatment and infection in patients on biologicsis critical. Potential for adverse effects with these agents have direct implications for management in this setting. This is recognised by consulting physicians for a thorough evaluation of the patient's health undergoing biologic therapy, in an attempt to exclude any focus of chronic infection during the dental treatment. (Lee and Kavanaugh, 2005) When considering dental treatment, an appreciation of an increased risk of infection and its sequelae should regulate treatment-related decisions. For most routine dental treatment, such as dental restorations, there are no special concerns. With respect to periodontal therapy, the significance of TNF-a blockade is meagre. Studies evaluating the periodontal health of patients receiving biologic therapy for Rheumatoid Arthritis provide no clear evidence of a direct benefit to the periodontal status, although some suggest a potential benefit of periodontal therapy upon the arthritis. (Pers *et al*., 2008) However, in one study that documented active periodontal treatment, no concerns regarding post- treatment adverse effects were reported. (Ortiz *et al*., 2009) As such, for routine periodontal therapy, no special precautions would seem necessary. However, for invasive procedures, including endodontic treatment, periodontal surgery, dental implant placement, dental extractions or dentoalveolar surgery, the potential for post-treatment infection and other adverse sequelae must not be overlooked. While concerns of endocarditis risk have been raised, available data does not support the routine use of antibiotics in the context of endocarditis prophylaxis. (Armstrong *et al*., 2006) Nevertheless, the reported association of postextraction osteomyelitis and also postendodontic sepsis suggest that it would seem prudent to consider perioperative antibiotic prophylaxis in patients undergoing dental extractions, dentoalveolar surgery, dental implant placement, periodontal surgery and possibly in acute endodontic therapy. (Ciantar and Adlam, 2007; Favero *et al*., 2009a) Where doubt exists, guidance should be sought from relevant specialists.

Conclusion

Thus to conclude, special care is needed for patients with organ transplants, poorly controlled diabetes and pregnancy so as to avoid any infection. Antibiotics should be used only as an adjunct to dental treatment and never alone as the first line of care. It is evident that biologics are providing therapeutic solutions and may resolve several dead ends such as antibiotic resistance and the absence of a wide range of antiviral drugs.

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