Adverse Events of Biological Drugs

Subjects: Pathology

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The aim of this study is to know the biological therapy drugs that are related to adverse events, what dental treatments are associated with the appearance of these events, their severity, and how they are resolved.

Keywords: target therapy ; antiangiogenic agent ; denosumab ; osteonecrosis of the jaw ; monoclonal antibody ; stomatitis ; dental infection ; MRONJ

1. Introduction

Biological therapies are a new method of treating some autoimmune diseases and cancer. They were defined by the FDA (Food and Drugs Administration) as any virus, therapeutic serum, toxin, antitoxin, or similar product applicable to the prevention and treatment of human diseases. These biologics include vaccines, blood and blood-derived preparations, antitoxins, growth hormones, human insulin, gene therapies, recombinant therapies, proteins, and allergens, along with the newer biologics: cytokines, monoclonal antibodies, and fusion proteins [1][2].

Cytokines are immunomodulators that regulate the host's response to inflammation and infections. In this way they work by signaling molecules that will bind to protein receptors on cells, generating a physiological change in them.

Monoclonal antibodies are synthetic molecules that activate against certain antigens to improve immune recognition. They are divided into four subgroups: murine, chimeric, humanized, and human.

Fusion proteins are composed of transmembrane proteins connected to another molecule through the Fc portion of human immunoglobulin.

The mechanisms of action of biological therapies involve a series of physiological changes that can trigger side effects in the patient. One of these mechanisms is the inhibition of molecules such as TNFα, which are essential in the inflammatory response. This produces a change in the immune system that can lead to these patients having a greater predisposition to infections [1].

Other mechanisms of action to take into account, due to their physiological repercussions, are antiresorptive and antiangiogenic, influencing osteoclasts and vascular endothelial growth factor (VEGF), respectively [2][3].

Despite the efficacy and safety of these drugs in the vast majority of patients, there is a significant risk of producing adverse effects such as mucositis, hyperkeratotic lesions, mucosal dyschromia, geographic tongue, dysgeusia, lichenoid lesions, telangiectasias, xerostomia, dysesthesia, and, the most prominent, osteonecrosis of the jaw, due to its antiangiogenic and/or antiresorptive power [4]. This osteonecrosis will be considered related to these medications when the following characteristics described by the AAOMS (American Association of Oral and Maxillofacial Surgeons) are present in a patient:

- Previous or current treatment with antiresorptive or antiangiogenic agents.
- Exposed bone or bone that can be probed through an intra- or extra-oral fistula in the maxillofacial region, which has persisted for more than 8 weeks.
- Absence of radiotherapy or previous metastasis in the jaw [2].

In 2014, the AAOMS changed the term "Bisphosphonate-Related Osteonecrosis of the Jaws" (BRONJ) to "Medication-related Osteonecrosis of the Jaws" (MRONJ) to include all other drugs related to osteonecrosis. However, since 2017 there are only three monoclonal antibodies officially recognized by the FDA as causing MRONJ: denosumab,

bevacizumab, and sunitinib. The rest of the reported drugs have not yet been recognized as such due to the lack of scientific evidence [5].

2. Management of Patients Undergoing Treatment with Biological Therapies

The management of patients undergoing treatment with these biological therapies requires monitoring and special measures by the dentist to avoid the adverse effects previously described.

Before starting therapy, it is essential to carry out a complete dental treatment. Dental treatment includes a comprehensive dental examination with orthopantomography and intraoral radiographs, extraction of teeth with impossible prognosis, conservative dental treatments and periodontal interventions, prosthesis adjustment, factor control risks such as tobacco and diabetes, as well as patient education on the importance of oral care.

Infection is one of the most important adverse effects, but not enough scientific evidence has been found to support the use of antibiotic prophylaxis in these patients when performing surgery. The considerations prior to a surgical treatment that we will have to take into account are [1]:

Complete blood count if the procedure involves bleeding.

Prothrombin time (PT) and INR, if the patient has liver damage. This is one of the possible adverse effects in long-term treatment with biological therapies [6].

Interruption of treatment with biological agents before the procedure. The so-called drug holiday is a subject of controversy between different authors. With bisphosphonates, drug holiday protocols exist before performing invasive surgical treatment, although continuing with the controversy, a recent study in Japan [7] suggests that the withdrawal of BPs would not reduce the risk of developing adverse effects after surgery such as osteonecrosis [8]. This may be due to the fact that BPs have a long-lasting skeletal retention, while biological drugs such as denosumab have a reversible effect. For this reason, the use of drug holiday in patients receiving denosumab could be endorsed. However, the temporary suspension of medications must be compatible with the underlying pathology and be authorized by the prescriber. To date, there is insufficient scientific evidence to confirm the effectiveness of the drug holiday [9][10].

Regarding the surgical technique used in this type of patients, it should be as atraumatic as possible and can be accompanied by the use of plasma rich in growth factors (PRGF) to promote bone and soft tissue regeneration after surgery, reducing thus the risk of infection, and the time of exposure of the wound to bacteria. After surgery, experts recommend the use of antimicrobial rinses and systemic antibiotics.

3. Management of Complications Associated with Biological Therapies

Oral toxicities are one of the adverse effects in treatment with biological therapies. The management of these oral toxicities consists of:

Mucositis, stomatitis, and aphthous lesions: Basic oral care, corticosteroids (topical, intralesional, or oral), morphine rinses, systemic analgesics, LLLT (Low Level Laser Therapy), and change in medication and interruption of previously agreed radiotherapy sessions with the oncologist.

Hyperkeratotic lesions and dyschromia of the mucosa: Monthly reviews and biopsy in case of suspicion.

Geographic tongue: Avoidance of irritants, rinsing with corticosteroids in painful lesions.

Dysgeusia: Nutritional recommendations such as abundant consumption of liquids and cold meals; Changes in the medication previously agreed with the dentist can be proposed.

Lichenoid lesions: Topical corticosteroids for painful lesions and periodic reviews, as well as change in medication.

Telangiectasias and mucosal bleeding: Basic oral care and change in medication.

Xerostomía: Basic oral care, hydration, use of sialogogues such as pilocarpine or artificial salivary substitutes (palliative).

Dysestesia: Basic oral care, avoidance of irritants and symptomatic treatment with analgesics. In case of neuropathy, use drugs such as clonazepam or gabapentin.

MRONJ: This complication is divided by the AAOMS into four grades with a specific treatment for each of them [2]. (Table 1)

Table 1. Complication grades divided by the AAOMS and specific treatment. Complication grades according to AAOMS and recommended treatment are shown.

Grade	Treatment
Risk: No apparent necrotic bone	**Treatment not indicated, patient education**
Grade 0: No clinical evidence of bone necrosis, but nonspecific clinical findings, radiographic changes, and symptoms.	**Systemic management, including the use of analgesics and antibiotic.**
Grade 1: Exposure and bone necrosis, or fistulas that can be probed to bone in asymptomatic patients without evidence of infection.	**Antibacterial rinses, clinical follow-up, patient education.**
Grade 2: Exposure and bone necrosis, or fistulas that can be probed to the bone, associated with infection with pain or erythema in the region of exposed bone with or without purulent drainage.	**Symptomatic treatment with oral antibiotics, antibacterial rinses, pain control, debridement to relieve soft tissue irritation and control infection.**
Grade 3: Presence of one of the following signs: bone exposure and necrosis that extends beyond the alveolar region, pathological fractures, extraoral fistulas, oro-nasal or oro-antral communication, osteolysis that extends to the lower border of the mandible or floor of the breast.	**Antibacterial rinses, antibiotic therapy and pain control, surgical debridement or resection to alleviate infection and long-lasting pain.**

It has been observed that the use of hyperbaric oxygen therapy as an adjunct to surgical and non-surgical treatment produces improvements in wound healing, pain, and quality of life. However, there are no statistically significant differences with respect to the control group [2][11].

Other studies mention the use of low-frequency lasers, parathyroid hormone and BMPs (Bone Morphogenetic Protein) as strategies in non-surgical treatment, but more studies are needed to verify their efficacy [2].

4. Study Limitations

The present study meets a series of limitations: There is a lack of scientific evidence about the possible adverse effects that these drugs may present at the oral level, in addition, it is difficult to relate them to a single drug in polymedicated patients. Likewise, in most cases, the adverse event is not easily related to dental treatment due to the time elapsed until it appears.

Despite this, this review presents all the oral adverse events reported to date in relation to these drugs.

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