Review

Management of Patients under Treatment with Monoclonal Antibodies and New Biological Therapies

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Abstract: Objective: 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. Study design: Analysis of cases described in the literature on patients undergoing treatment with biological therapies who have developed adverse effects associated with these drugs. Results: Of the 62 articles reviewed, 49 describe 68 cases of MRONJ, most of which appeared in the jaw and received surgical and/or conservative treatment. Conclusions: Biological therapies can potentially develop adverse effects in the oral cavity, so strict monitoring by the dentist is necessary.

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

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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 TNF α , 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].

The objective of this study is to know the drugs related to adverse events in oral surgery, what effects they produce, and to record how they have been resolved according to the available literature.

2. Material and Methods

An electronic search was carried out in the National Library of American Medicine (MEDLINE) through Pubmed, with the combination of the following terms: “MRONJ”; “Adverse effect” AND “dental disease” AND “targeted therapy”, applying the results filters by year between 2005 and 2020, in humans, and with the full text available.

The following inclusion criteria were established: articles published since 2005, but due to the lack of described literature on the subject, the search was extended to those published since 2005; in English or Spanish; performed in humans; patients being treated with biological therapies; and in relation to the objective of this review. Following the exclusion criteria, those articles published prior to 2005 were eliminated from the search; in a language other than Spanish or English; performed on animals; those duplicates; and those that, after reading the abstract, were not related to the main objective of this review.

3. Results

A total of 374 articles were obtained, to which the criteria described above were applied, going to read full text 83 articles, and finally selecting a total of 54 for this review (Figure 1).

Within our selection, a total of 49 articles have been compiled in relation to osteonecrosis of the jaws [5–22], two articles in relation to lesions in the oral mucosa [4,23], two with oral infections [24,25], and, finally, one article reporting a case of exudative erythema multiforme [26] (EEM) associated with the use of biological therapies.

Of the total of 49 articles related to osteonecrosis of the jaws, 14 cases were collected that refer to bevacizumab [10,27–39], eight cases to sunitinib [17–22,29,39], six cases to denosumab [10–14] and everolimus [29,39–43], five cases to rituximab [5,11–14], four cases to temsirolimus [14,26,29,34], three cases referred to sorafenib [19,29,33] and aflibercept [44–46], two cases related to trastuzumab and pertuzumab [15,39], imatinib [39,47], and pazopanib [39,42]. Finally, only one article was found referring to tacrolimus [5], lenvatinib [16], erlotinib [33], ipilimumab [48], cabozantinib [49], afatinib [39], nilotinib [39], dasatinib [39], or tocilizumab [50].

Regarding the treatment carried out for osteonecrosis, in a total of 38 cases a surgical treatment was carried out, in 23 cases a conservative treatment was carried out, and in seven of them the treatment followed was not specified.

The surgical act is the triggering factor reported in most cases, with a total of 27; this is followed by a poor fit of the prostheses, mentioned in five cases; finally, in 31 the triggering

factor for osteonecrosis is not described and in the remaining five cases a factor other than those previously mentioned is related.

Figure 1. Flowchart of eligibility studies.

Oral complications related to biological therapies have been found, such as lesions at the mucosal level as described in the reviews of the literature by Vigarios et al. [4] (2017) and Watter et al. [23] (2011). Cases of infections at the oral level have been reported in patients treated with adalimumab and infliximab, as described by Cillo et al. [24] (2019) and Filler et al. [25] (2005), as well as a case of exudative erythema multiforme (EEM) in a patient treated with infliximab as described by Edwards et al. [26] (2013). Within the literature, the complication of which more cases have been found is osteonecrosis of the jaws, in patients receiving one or more biological therapies (Figure 2).

Within our search, 49 articles containing a total of 68 cases establish a possible relationship of biological therapies with osteonecrosis of the jaws (Table 1). In 62.69% of the cases, osteonecrosis was related to denosumab (16.42%), an antiresorptive agent; bevacizumab (28.36%) or sunitib (17.91%), both antiangiogenic agents, coinciding with the three drugs described in 2014 by the AAOMS as producers of MRONJ.

Table 1. MRONJ cases to biological therapies. Results of systematic review are shown: Author, patient's age and sex, diseases, medication, biological therapies, causal factor of the complication, MRONJ stage, and treatment.

Author	Age	Sex	Diseases	Medication	Biological Therapies	Causal Factor	Mronj Stage	Mronj Treatment
Maluf et al. [6] (2016)	69	M	Lung cancer metastasis	Irinotecan (QT)	Denosumab	Implant surgery	Mandibular ONJ 2	Surgical
	44	F	Breast cancer and bone metastasis	Dexamethasone and Fulvestrant	Denosumab y Bevacizumab	Endodontic surgery	Mandibular ONJ 2	Surgical
Sarina et al. [7] (2013)	74	M	Prostate cancer, lung and bone metastasis	QT, Bicalutamida, Goserelina, Dutasterida, Calcium y Vitamin D3 y Zoledronic acid	Denosumab	-	Mandibular ONJ 2	Surgical
Kunimichi et al. [8] (2015)	60	F	Breast cancer	-	Denosumab	Poorly fitting prosthesis	Mandibular ONJ 1	-
Badr et al. [9] (2017)	55	F	Breast cancer	-	Denosumab	Tooth extraction	Mandibular ONJ 3	Hospitable treatment
	76	F	Breast cancer metastasis	Hormone therapy and radiation therapy	Denosumab	Tooth extraction	Mandibular ONJ 1	Surgical
	66	F	Bone, liver and peritoneum metastasis from breast cancer	QT and opioids	Denosumab	Tooth extraction	Mandibular ONJ 3	Surgical
	66	F	Bone metástasis and breast cancer	Hormone therapy and opioids. Prior zoledronic acid therapy.	Denosumab	Poorly fitting prosthesis	Maxillary ONJ 3	Conservative
Nifosi et al. [10] (2017)	47	M	Renal adenocarcinoma	Calcium and Vitamin D	Temsirolimus y Denosumab	-	Mandibular ONJ 2	Conservative
Allegra et al. [11] (2014)	56	M	Waldenström's macroglobulinemia, POEMS syndrome, lymphoplasmacytic lymphoma	QT (Doxorubicin, Cyclophosphamide, Vincristine, Prednisone)	Rituximab	Tooth extraction	Mandibular ONJ 2	Conservative
Keribin et al. [5] (2017)	69	M	Nephropathy IgA	Immunoglobulin, Ranitidine, Trimethoprim + Sulfamethoxazole, Valganciclovir, Ofloxacin, Itraconazol, Manidipine, Nebivolo, Perindopril, Indapamide	Rituximab y Tacrolimus	-	Maxillary and mandibular ONJ 2	Surgical
Baur et al. [12] (2012)	58	M	Lymphoma cells B	Chemotherapy (Doxorubicin, Cyclophosphamide, Vincristine, Prednisone), Diltiazem, Atorvastatin, Meloxicam, Lisinopril, Hydrochlorothiazide, Insulina, Metformin and Aspirin.	Rituximab	-	Mandibular ONJ 2	Surgical

Table 1. Cont.

Author	Age	Sex	Diseases	Medication	Biological Therapies	Causal Factor	Mronj Stage	Mronj Treatment
Javelot et al. [13] (2020)	69	F	Rheumatoid arthritis	Prednisolone, Leflunomid, Valsartan y Vitamin D3. Previous treatment with Risedronate and Infliximab.	Rituximab	Herpetic gingivostomatitis	Mandibular ONJ 2	Surgical
Weigert et al. [14] (2014)	39	M	Non- Hodgkin lymphoma	Ciclofosfamida, Vincristine, Doxorubicin y Prednisone	Rituximab	-	Mandibular ONJ 0	Conservative
Manzie et al. [15] (2019)	76	F	Breast cancer metastasis	Chemotherapy, Carboplatin, Gemcitabine, Epirubicine, Paclitaxel, Amlodipine, Irebsartan	Trastuzumab + Pertuzumab	-	Mandibular ONJ 2	Surgical
Mauceri et al. [16] (2019)	58	M	Hurtle's cell carcinoma, lung metastasis	Radiotherapy, chemotherapy (Doxorubicin, Cisplatin), Ciclofosfamida, Metrotexate	Lenvatinib	Tooth extraction	Maxillary ONJ 1	Conservative
Fleissig et al. [17] (2012)	58	F	Renal carcinoma, Osteoporosis	Levothyroxine sodium	Sunitinib	Tooth extraction	Mandibular ONJ 2	Conservative
Brunello et al. [18] (2009)	59	M	Renal carcinoma with ischial and pulmonary metastasis	Previous zoledronic acid	Sunitinib	-	Mandibular ONJ 2	Conservative
Koch et al. [19] (2011)	59	M	Renal carcinoma, soft tissues metastasis	Interferon, Vinblastine, Ramipril, Hydroclorothiazide, Metropolol, Levothyroxine	Sorafenib y Sunitib	Tooth extraction	Mandibular ONJ 1	Surgical
Melloni et al. [20] (2016)	62	M	Renal carcinoma, cutaneous metastasis	Interferon, IL-2	Sunitinib	Tooth extraction	Mandibular ONJ 3	Surgical
Nicolatou-Galitis et al. [21] (2012)	19	F	Renal carcinoma	Cisplatin	Sunitinib y Everolimus	-	Mandibular ONJ 2	Conservative
	64	F	Renal carcinoma	Prednisolone, L-4	Sunitinib	Prosthesis trauma	Mandibular ONJ 2	Surgical
Agrillo et al. [22] (2012)	65	M	Renal carcinoma	Previous zoledronic acid	Sunitinib	-	ONJ 3 maxilar	Surgical
	67	M	Renal carcinoma	Previous zoledronic acid	Sunitinib y Temsirolimus	-	Mandibular ONJ 3	Surgical
Estilo et al. [27] (2008)	33	F	Glioblastoma multiforme	Radiotherapy, Temozolomide	Bevacizumab	-	Mandibular ONJ 2	-
	51	F	Infiltrating ductal carcinoma	Chemotherapy(Doxorubicin+ciclofosfamida, hormonal therapy, Paclitaxel, radiotherapy, Capecitabine	Bevacizumab	-	Mandibular ONJ 2	Surgical

Table 1. Cont.

Author	Age	Sex	Diseases	Medication	Biological Therapies	Causal Factor	Mronj Stage	Mronj Treatment
Greuter et al. [28] (2008)	63	F	Breast cancer	Doxorrubicin	Bevacizumab	Tooth extraction	Maxillary ONJ 3	Surgical
Agostino et al. [29] (2010)	73	M	Renal carcinoma	-	Sunitinib, Temsirolimus y Bevacizumab	-	-	-
	76	M	Renal carcinoma	IL-2	Sorafenib, Sunitinib, Temsirolimus y Bevacizumab	-	-	-
	68	M	Renal carcinoma	IL-2	Sunitinib, Everolimus y Bevacizumab	-	-	-
	58	F	Renal carcinoma	IL-2	Sunitinib, Sorafenib, Temsirolimus y Bevacizumab	-	-	-
Bettini et al. [30] (2012)	57	F	Lung cancer	Chemotherapy, Gentamicine, Cisplatin, Corticosteroids, Lincomicine	Bevacizumab	-	Mandibular ONJ 2 mandibular	Surgical
Brunamonti et al. [31] (2012)	47	M	Adenocarcinoma	Epirubicin+Cisplatin	Bevacizumab	-	Mandibular ONJ 2	Surgical
Fusco et al. [32] (2014)	60	M	Rectal cancer, lung metastasis	Chemotherapy and radiotherapy	Bevacizumab	Tooth extraction	Mandibular ONJ 2	Conservative
Pakosch et al. [33] (2013)	53	F	Pancreas cancer	Gemcitabine, Folinic acid, Oxaliplatin, Paclitaxel	Erlotinib, Bevacizumab y Sorafenib	Poorly fitted prosthesis	Mandibular ONJ 2	Surgical
Santos-Silva et al. [34] (2013)	61	M	Renal carcinoma	Captopril, Hidroclorotiazide	Bevacizumab y Temsirolimus	-	Mandibular ONJ 2	Conservative
Serra et al. [35] (2009)	64	M	Lung adenocarcinoma	Cisplatin, Gemcitabine	Bevacizumab	-	Mandibular ONJ 2	Surgical
Tzermpos et al. [36] (2014)	69	M	Lung cancer	Chemotherapy (Carboplatin+ Docetaxel), Cortisone	Bevacizumab	Poorly fitted prosthesis	Mandibular ONJ 2	Surgical
Hopp et al. [37] (2012)	58	M	Retinal vascular thrombosis	-	Bevacizumab	-	Mandibular ONJ 2	Surgical

Table 1. Cont.

Author	Age	Sex	Diseases	Medication	Biological Therapies	Causal Factor	Mronj Stage	Mronj Treatment
Erovigni et al. [38] (2016)	79	M	Colon adenocarcinoma	Capecitabin, Oxaliplatin, Fluoracil, Folinic acid, Irinotecan, radiotherapy	Bevacizumab	Tooth extraction	Mandibular ONJ 2	Conservative
	60	M	Rectal cancer, lung and brain metastasis	Chemotherapy and radiotherapy	Bevacizumab	Tooth extraction	Mandibular ONJ 2	Conservative
Mawardi et al. [44] (2016)	43	M	Metastasis of colorectal carinoma	5-fluorouracil, Leucovorin, Irinotecan	Aflibercept	-	Mandibular ONJ 1	Surgical
	63	M	Gastrointestinal metastatic carcinoid	5-fluorouracil, Leucovorin and Oxaliplatin	Aflibercept	-	Mandibular ONJ 1	Conservative
	51	M	Esophageal carcinoma metastasis	-	Aflibercept	Tooth extraction	Mandibular ONJ 1	Conservative
Ponzetti et al. [45] (2016)	64	F	Metastasis of colorectal carinoma	5-fluoracil, Irinotecan and Levofolinic Acid	Aflibercept	-	Mandibular ONJ 1	Conservative
Zarringhalam et al. [46] (2017)	47	M	Intestine, liver, peritoneum and pelvis metastasis	-	Aflibercept	-	Mandibular ONJ 1	Conservative
Viviano et al. [47] (2017)	72	M	Gastrointestinal stromal tumor	-	Imatinib	Tooth extraction	Mandibular ONJ 2	Surgical
Owosho et al. [48] (2015)	52	M	Melanoma metastasis in the iliac region and pancreas	-	Ipilimumab	-	Mandibular ONJ 2	Surgical
Kim et al. [40] (2013)	52	M	Bone metastasis from thyroid cancer	Previous zoledronic acid treatment	Everolimus	-	Mandibular ONJ 2	Conservative
Yamamoto et al. [41] (2017)	80	F	Breast cancer	Capecitabine, Tamoxifen, Fulvestrant y Exemestan	Everolimus	-	Mandibular ONJ 2	Conservative
Jung et al. [42] (2017)	62	F	Renal carcinoma	-	Everolimus y Pazopanib	Implant surgery	Mandibular ONJ 2	Surgical
Giancola et al. [43] (2013)	64	M	Renal carcinoma metastasis	Previous zoledronic acid treatment	Everolimus	-	Mandibular ONJ 2	Surgical
Garuti et al. [51] (2017)	74	M	Hepatic cancer	-	Sorafenib	Tooth extraction	Mandibular ONJ 1	Conservative
Marino et al. [49] (2015)	51	F	Liver and lymph nodes metastasis from thyroid cancer	Levotiroxine, Calcitriol, Vitamin D3, Duloxetine, Propanolol, Lansoprazole y Loperamide	Cabozantinib	Tooth extraction	Mandibular ONJ 2	Surgical

Table 1. Cont.

Author	Age	Sex	Diseases	Medication	Biological Therapies	Causal Factor	Mronj Stage	Mronj Treatment
Mohamed et al. [39] (2018)	70	M	Renal carcinoma	-	Sunitinib, Everolimus, Pazopanib	Tooth extraction	Mandibular ONJ 1	Conservative
	53	F	Lung cancer	Carboplatin, Cisplatin, Vironelbine Zoledronic	Erlotinib, Afatinib y Denosumab	Tooth extraction	Maxillary ONJ 2	Surgical
	55	F	Lung cancer	Carboplatine, Vironelbine, Alimeta.	Bevacizumab	Tooth extraction	Maxillary ONJ 1	Conservative
	66	M	Multiforme glioblastoma	Temozolomide, Irinotecan	Bevacizumab	Trauma by intraoral radiography	Mandibular ONJ 2	Conservative
	74	F	Multiple myeloma	Cyclophosphamide, Thalidomide, Alkaran, Capecitabine, Oxaliplatin, Folfiri, Irinotecan, and Pamidronate	Bevacizumab y Cetuximab	Spontaneous	Mandibular ONJ 1	Surgical
	53	F	Leukemia	Citarabine and Vincristine	Nilotinib y Dasanitib	Gingival ulcer	Mandibular ONJ 2	Surgical
	81	F	Leukemia	Capecitabine, Alendronate	Trastuzumab, Imatinib y Denosumab	Tooth extraction	Mandibular ONJ 2	Surgical
Patel et al. [52] (2017)	67	M	Lung, brain, skin, hearth and pelvis metástasis from renal carcinoma	Amlodipine, Ramipril, Levetiracetam, Dexamethasone, Lansoprazole, Morphine, Metoclopramide, Amiodarone hydrochloride, and Cholecalciferol. Previous treatment Pazopanib and Nivolumab	Axitinib	-	Maxillary ONJ 1	Conservative
Antonuzzo et al. [53] (2016)	59	F	Metastatic colorectal cancer	-	Regorafenib	-	Maxillary ONJ 3	-
Preidl et al. [54] (2014)	36	F	Crohn disease	Steroids, Risedronate, Zoledronic acid, Prednisolone	Adalimumab	Tooth extraction	Mandibular ONJ 3	Surgical
Cassoni et al. [55] (2016)	63	F	Idiopathic arthritis	Salazopyrin	Adalimumab	Implant surgery	Mandibular ONJ mandibular	Surgical
Favia et al. [56] (2017)	49	F	Chron disease	-	Infliximab	Tooth extraction	Mandibular ONJ 3 mandibular	Surgical
Ekber et al. [50] (2013)	74	F	Rheumatoid arthritis and osteoporosis	Methotrexate, Prednisolone, Folic Acid, Ibuprofen, Pantoprazole, Calcium, Vit. D. Previous treatment with zoledronic acid.	Infliximab	Tooth extraction	Mandibular ONJ 3	Surgical
					Tocilizumab	Tarthrectomy	Mandibular ONJ 3	Surgical

Figure 2. Percentage of oral complications related to biological therapy. MRONJ is the most common oral complication registered, followed by mucosal lesion, infection, and exudative erythema multiforme.

Among them, it can be observed that there are more cases of osteonecrosis in the mandible (83.58%) than in the maxilla, as well as a higher frequency in men, with 53.73%. Regarding the treatment carried out for osteonecrosis, it can be observed that a surgical treatment was carried out in 55.22% of the cases, which consists in the majority of them in a mandibular sequestrectomy or resection. Conservative treatment consists mainly of antibiotic therapy, antimicrobial rinses, strict oral hygiene measures, as well as modifications in biological therapy.

4. Discussion

Although osteonecrosis is the most studied complication due to its severity, there are also references to other complications at the oral level. Although these complications do not involve such a high risk for the patient, they require treatment to control and improve their quality of life.

These drugs can be difficult to identify clinically by their brand names. A table (Table 2) is presented with the drugs and their most common commercial name to facilitate their identification for the professional, as well as a series of recommendations on the management of patients with biological therapy.

Table 2. Biological therapies associated with oral complications and trade name. Most common biological therapies and trade name related to oral complications are shown.

Drug	Trade Name	Category
Adalimumab	Humira	MAB
Afatinib	Giotrif	TKI
Aflibercept	Zaltrap, Eylea	Fusion protheine
Axitinib	Inlyta	TKI
Bevacizumab	Avastin	MAB
Cabozantinib	Cometriq, Cabometyx	TKI
Dasatinib	Sprycel	TKI

Table 2. *Cont.*

Drug	Trade Name	Category
Denosumab	Xgeva, Prolia	MAB
Erlotinib	Tarceva	TKI
Everolimus	Afinitor	mTOR inhibitor
Imatinib	Gleevec	TKI
Infliximab	Remicade	MAB
Ipilimumab	Yervoy	MAB
Lenvatinib	Lenvima	TKI
Nilotinib	Tasigna	TKI
Pazopanib	Votrient	TKI
Regorafenib	Stivarga	TKI
Rituximab	Erbitux, Rituxan	MAB
Sorafenib	Nexavar	TKI
Sunitinib	Sutent	TKI
Tacrolimus	Advagraf	mTOR inhibitor
Temsirolimus	Torisel	mTOR inhibitor
Tocilizumab	Actembra	MAB
Trastuzumab+Pertuzumab	Herceptin + Perjeta	MAB

TKI: tyrosine-kinase inhibitor, MAB: monoclonal antibody, mTOR: mammalian target of rapamycin.

4.1. 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 [57].

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 [58] suggests that the withdrawal of BPs would not reduce the risk of developing adverse effects after surgery such as osteonecrosis [59]. 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 [60,61].

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.

4.2. 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).

Dysesthesia: 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 3)

Table 3. 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 [2,62].

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].

4.3. 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.

5. Conclusions

The biological drugs that, according to the literature described, have the greatest relationship with adverse events in the dental field are bevacizumab, denosumab and sunitinib. The main adverse event is osteonecrosis of the jaws (MRONJ), resolved in most of the cases described with surgical treatment.

It is necessary to take into account the oral complications associated with these therapies and the importance of monitoring by the dentist from the beginning, in order to prevent or reduce the appearance of these.

Despite the reported cases, more studies are needed to describe in a more exhaustive way the appearance of complications that could be related to these treatments.

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