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Targeted therapies and dental implants: A literature review

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Abstract

Targeted drugs and dental implants are respectively, gold standard into oncology and edentulism treatment. It thus raises the question of impact on dental implant success in patient under targeted therapies, because this drug can affect biological pathways needed to implant integration. Through this original literature review, clinical trials in animal model and patient case report suggest, to have a particular attention for anti-angiogenic treatment which had a negative effect on osseointegration and, particular attention when they are combined with anti-resorptive at the ONJ risks. The recommendations are backed up on treatment half-life, to realize implant placement distanced of the latest injection. Moreover, these precautions could be completed by many others, like specials implant coating, or by embedded implant. However, the lack of clinical human study in the scientific literature, cannot permit to confirm that.

Introduction

According to French Oncology National Institute (INCA), targeted cancer therapies are drugs aiming to block the growth and / or the spread of tumor cells by specifically addressing some of their abnormalities. Their main mode of action consists of an inhibition of oncogenesis mechanisms with high specificity for cancer cells or their microenvironment.

These may be intracellular inhibitors (e.g., small chemical molecules, including protein kinase inhibitors) or extracellular inhibitors (e.g., biological drugs, including monoclonal antibodies) (Figure1). Their main objective of these targeted therapies is to treat cancer with more precision hence potentially fewer side effects [1].

Unlike the conventional chemotherapies, they can be used for many years. With the scientific advances in the field of implantology, the patient's number under target therapies who could be candidate to dental implant increase.

To enlightenment drugs names, the Figure 1 provides clues to the type of agent with the stem and the cellular target by substems, the prefix remaining variable [2].

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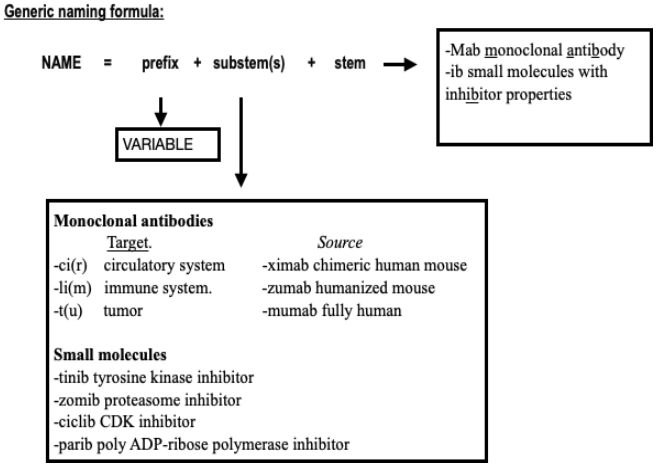

Figure 1: Naming Targeted Therapies (TT).

Dental implantology has been modernised and is expanding since few decades to reach a success rate exceeding 95% in healthy population and becomes the edentulism gold standard treatment [3].

This/theses advancements is/are due to a better understanding of the failures' causes. Failure is identified when one or more of the following signs are observed [4]:

1) Pain on function,

2) Implant mobility,

3) Radiographic bone loss greater than half of the implant length,

4) Exudate uncontrolled and / or

5) The implant is no longer in the mouth.

Esposito *and al*. [5] explained biological failures are defined as the inability of the host tissues to establish or maintain osteointegration. According to the chronological criterion, they are divided into early or primary failures (failures to accomplish osteointegration) and late or secondary failures (failures to maintain osteointegration).

Early failures occur from few weeks to few months after implantation, during the burial period or are detected when the implant is loaded prosthetically. Late failures are encountered after loading the implants. They are characterized by a loss of osteointegration; this can be progressive or can manifest itself quickly.

Immediately after surgery, implant surface is surrounded by blood. Healing occurs for several weeks after intervention. During this time, a new bone is formed from blood clot which contains growth factors to permit activation of osteoblastic cells.

In this representation, coatings with hydroxyapatite and calcium phosphate develop a positive bone interaction and induce the growth of bone tissue (Figure 2).

In figure 2, coatings with hydroxyapatite $Ca_5(PO_4)_3(OH)$ and calcium (Ca^{2+}), phosphate (PO_4^{3-}) develop positive bone interaction, inducing bone tissue growth thanks to ionic transfer, permitting nucleation sites for bone-like carbonated hydroxyapatite formation on bone-implant surface.

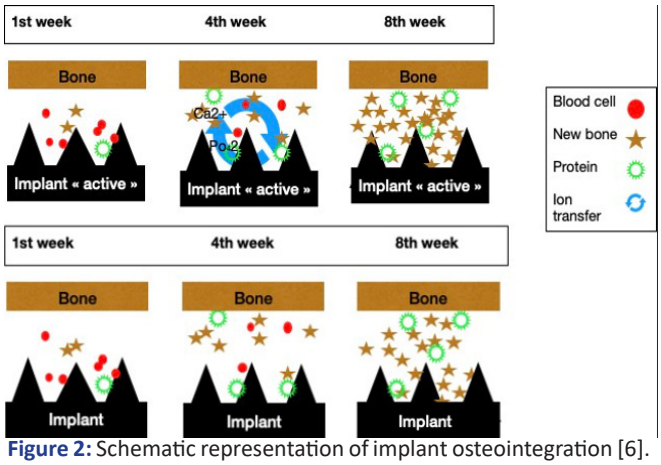

Figure 2: Schematic representation of implant osteointegration [6].

Thus, the aim of this review was to analyze current scientific knowledge on implantology in patients treated with targeted therapies.

Materials and methods

Research Strategy

A comprehensive analysis of literature was performed using databases such as PubMed, Elsevier and CoChrane to document this literature review. The MeSH keywords used were « Dental or Oral » and « Therapies or Drugs ».

Selection of articles

Duplicate and irreverent articles were eliminated. Studies were selected according to the following inclusion criteria: studies reporting implant placement procedures in animals or patients. Selection was refined according to the following exclusion criteria: studies concerning other drugs and, implantation of medical device in patients other than in the oral sphere.

After reading titles and abstracts, articles were referenced in a table by « include », « exclude» or « ? ». No restriction on study origin or publication year interfered in the article selection.

Information extraction

For each included study, full text was reviewed to extract all informations, namely, target, principal diseases treated, Osteonecrosis of the Jaw (ONJ) risks, half-life, bone effect, and results.

Results and discussion

Search results

In total, 350 articles were vetted, 126 of them were found on PubMed, 59 on Elsevier and 165 on Cochrane. After analyzing titles and results and eliminating irrelevant articles, 15 were selected (Figure 3) The research strategy is detailed in Figure 3.

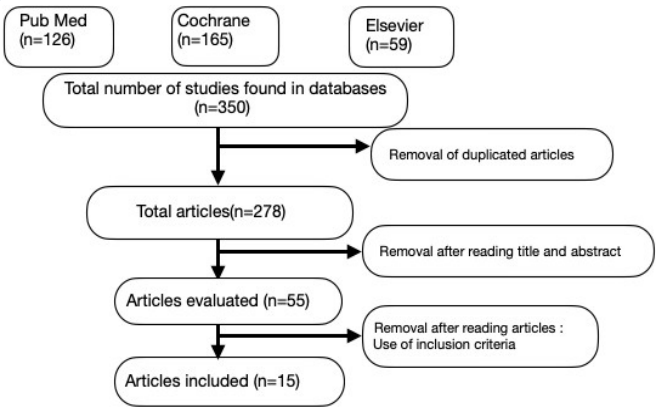

Figure 3: Selection of flowchart for articles referring to targeted therapies and dental implants.

All selected articles were published between 2010 and 2021. Articles dealing with in vivo studies has been described by target (anti-angiogenic, anti-resorptive, and anti-inflammatory) and starting by animals' models then terminating by case reports for each target. All patient/animal studies are summarized in Table 1.

Two articles focused on anti-angiogenic bone effects in rabbit model. Four weeks following implant insertion, osteointegration of the implants was measured using microcomputer tomography and histomorphometry evaluation. Both showed less osteointegration, thus inhibition of angiogenesis may negatively affect implant osteointegration [7,8].

On the other hand, a case report discussed a 8-years follow-up of implant treatment administered during the remission phase of chronic myelogenous leukemia maintained using Nilotinib. Two implants were embedded; after 8 years it was still a success [9].

A new osteoporosis treatment, romosozumab, tested in animal conclude to a systemic administration of Scl-Ab promoted bone and cemental regeneration, while local, low dose delivery did not heal periodontal osseous defects [10].

Another case report related the osteonecrosis of the jaw (ONJ) associated with the used of bisphosphonates (BPs) and denosumab as osteoporosis treatment. The case reported injuries around dental implants at 5 years [11].

Last case report deals with adalimumab-related dental implant surgical-site infection. A 55-year-old woman patient with a twice-weekly adalimumab subcutaneous injections history for ulcerative colitis. She experienced intraoral purulent drainage from all 5 dental implant sites with submental and submandibular space infections 2 weeks after surgery [17].

All the patient/animal studies are summarized in Table 1.

Table 1: Selection of flowchart for articles referring to targeted therapies and dental implants.

Targeted drugs	Biological target	Principal diseases concerned	Patient/animal	Bone effects	Half-life	ONJ	Success	Ref.
Sunitinib	Tyrosine Kinase Receptor (TKR)	Kidney advanced cancer	Animal (14)	↘	3-4 days	✗	✓	(7)
Bevacizumab	Tyrosine Kinase Receptor (TKR)	Metastasis cancer breast/kidney	Animal (14)	↘	20 days	✗	✓	(8)
Nilotinib	Tyrosine Kinase Receptor (TKR)	Myeloid Leukemia	Patient (1)	✗	17 hours	✗	✓	(9)
Romosozumab	Scl-Ab	Osteoporosis	Animal	↗	12,8 days	✗	✓	(10)
Denosumab	RANKL	Osteoporosis	Patient (1)	✗	28 days	✓	✗	(11)
Adalimumab	TNF alpha	Auto immune diseases	Patient (1)	✗	10-20 days	✗	✗	(17)

✗ No data, ONJ : osteonecrosis of the jaw, Scl-Ab : Sclerostin antibody

Bone effect

Tyrosin kinase receptors implications: Tyrosine Kinase Receptors (TKR) have a major role into angiogenesis and vasculogenesis. Sunitinib is an inhibitor of platelet growth factor receptors (PDGFR alpha and PDGFRß), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT) and colony-stimulating factor receptor (CSF-1R).

Raines et al. indicated VEGF-A has two roles in osteointegration: enhanced angiogenesis and an autocrine/ paracrine role in maturation of osteoblast-like cells in response to titanium surface properties [13].

TKR inhibition by drugs slowed down osteointegration but there was no more complications when anti-angiogenic are used without bisphosphonates (BPs) [7-9].

Today there is no case reported of the ONJ with single anti-angiogenic treatment; Nevertheless, association of Zoledronate and Becavizumab (BVZ) increases this one. Moreover, hemorrhagic majored risk is described when BVZ is used even lonely [16].

Osteoporosis treatments

BPs attach to hydroxyapatite binding sites on bony surfaces, especially the surfaces undergoing active resorption. When osteoclasts begin to resorb the bone impregnated with bisphosphonate, bisphosphonate released during resorption impairs osteoclasts ability to form the ruffled border, to adhere to the bony surface, and to produce the protons necessary for continued bone resorption.

The very important half-life (over 10 years) and thus the lack of therapeutic window is the main issue of BPs.

Unlike BPs, Denosumab and Romosozumab are binding RANKL and Sclerostin these differences in mechanism influence both the onset and reversibility of treatment (Figure 4). Their average half-life are 28 days for Denosumab and 12.8 days for Romosozumab.

Receptor activator of NF-kB (RANK) and its ligand (RANKL) play a main role in bone remodeling regulation; by binding to RANK, RANKL stimulates osteoclastogenesis and bone resorption, whereas its cognate decoy receptor osteoprotegerin (OPG) blocks this process by interacting with RANKL ; the Denosumab have a same action as OPG.

Sclerostin is a small protein expressed by the SOST gene in osteocytes, bone cells responding to mechanical stress applied to bone and appears to play an important role in the bone remodeling regulation. When sclerostin binds to its receptors like Wingless-type (Wnt) on osteoblasts cell surface, a downstream cascade of intracellular signaling is initiated, with the ultimate effect of inhibiting osteoblastic bone formation [19].

Recent evidence suggests that Wnt signaling pathways are implicated in angiogenesis in a variety of organs in normal and pathological conditions. Wnt signaling, appears to be essential in vascular endothelial cells and functions through a variety of regulators. Transcriptional regulation of VEGF by Wnt/β-catenin signaling has been demonstrated [18].

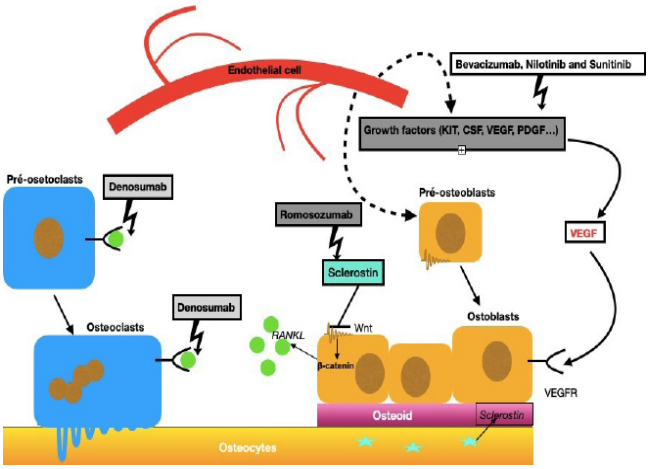

Figure 4: Schematic representation of different targeted therapies effects in bone turn over [14].

ONJ risks

The ONJ occurs when the jawbone is exposed and begins to starve from a lack of blood. Most osteonecrosis of the jaw cases happen after a dental extraction. The ONJ is associated with cancer treatments (including radiation), infection, steroid use, or antiresorptive medications used for osteoporosis.

The ONJ is much more common in those patients using these medications for bone cancer treatment. When used for osteoporosis in much lower doses, it is very rare.

As indicated *Guarneri et al.* in a retrospective analysis, 16% of the ONJ incidence was reported in patients receiving bisphosphonates with anti-angiogenic therapy (bevacizumab or sunitinib) for bone metastases from breast, colon, or renal cell cancers. Against 1-6% for BPs alone.

But in this study, ONJ incidence with bevacizumab for locally recurrent or metastatic breast cancer there is 0.9-2.4%. Thus, no more than BPs alone [15].

Conclusion and guidelines

Therapeutic window

All analyzed studies demonstrated physiological and cellular changes in patients and animal models after treatment by targeted therapies. Indeed, there was a decrease of osteointegration by anti-angiogenic treatments. It would be necessary to respect a delay of at least 5 weeks between the last injection of bevacizumab and invasive surgery, and a delay of 4 weeks between surgery and the initiation of bevacizumab treatment [16].

This recommendation is backed up on the long and variable Bevacizumab half-life (about 20 days) and variable.

It seems that the only solution, considering the lack of human trial, is consisting in consulting drug's half-life and keeping distance from the last injection (Figure 1).

Denosumab and Romosozumab unlike BPs, can offer a therapeutic window, like the anti-angiogenic, because they have a short half-life. Cases of ONJ are reported with Denosumab, even if the riskier procedure remains dental extraction; implant placement could be a trigger factor, that's why it is necessary to observe a delay between injection and surgery. Same with Adalimumab, which creates an immunodepression and majored infection risks.

Material and technique choice

In unfavorable cases such as patient under targeted drugs, the implant choice could help to approach the healthy conditions notably with « active » implant (Figure 1) with a coating of hydroxyapatite and calcium could create an ion transfer between implant and bone thus provide a better osteointegration.

Many other coats exist, as antibacterial, or various surface treatment. The results with local administration of Romosozumab [10] are not efficient because there is no maintenance of a minimal inhibitor concentration.

Similarly, it seems that embedded implants are less risky than tissue level implants because they are submitted to better conditions if they were exposed in oral cavity.

Follow up

Regular checks must be realized in patient under targeted therapies to prevent the onset of dental infection.

There is no absolute counter-indications to implant procedures, even if associated with BPs, since long time, cumulative dose increase the ONJ risks, benefits/risks ratio should be measured on case-by-case basis.

Failures can be immediate or many years later, hence the need of regular checks is recommended [11,17].

Declarations

Author Contributions: E.C. wrote the manuscript and designed the figures and tables. S.B., B.P., L.C., and M.D. supervised manuscript preparation and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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References

1. https://www.e-cancer.fr/Professionnels-de-sante/Les-therapies-ciblees/Medecine-de-precision-les-therapies-ciblees
2. Abramson, R. Overview of Targeted Therapies for Cancer. My Cancer Genome. 2018. https:// www.mycancergenome.org/content/molecular-medicine/overview-of-targeted-therapies-for- cancer/ (Updated May 25).
3. Beschnidt SM, Cacaci C, Dedeoglu K, et al. Implant success and survival rates in daily dental practice: 5-year results of a non-interventional study using CAMLOG SCREW-LINE implants with or without platform-switching abutments. Int J Implant Dent. 2018; 4: 33.
4. Misch C, Perel M, Sammartino G, Schwartz-Arad D, et al. Implant success, survival, and failure: The International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference. Implant Dent. 2008; 17: 5–15.
5. Esposito M, Hirsch J-M, Lekholm U, Thomson P. Biological factors contributing to failures of osseointegrated oral implants. I. Success criteria and epidemiology. Eur J Oral Sci. 1998; 106: 527-551.
6. https://www.researchgate.net/publication/351962966_Innovative_Coatings_of_Metallic_Alloys_Used_as_Bioactive_Surfaces_in_Implantolog y_A_Review
7. Al-Jandan B, Marei HF, Abuohashish H, Zakaria O, Al-Mahalawy H. Effects of sunitinib targeted chemotherapy on the osseointegration of titanium implants. Biomed Pharmacother. 2018; 100: 433-440.
8. B. Al-Jandan, Effect of antiangiogenic targeted chemotherapy on the osseointegration of titanium implants in rabbits, British Journal of Oral and Maxillofacial Surgery. 2019; 57.
9. Morita K, Tsuka H, Kuremoto KC, Tsuga K. Oral Implant Treatment for a Patient Undergoing Molecularly Targeted Drug Therapy for Chronic Myelocytic Leukemia: A Case Report. Int J Prosthodont. 2020; 33: 111-115.
10. Yao Y, Kauffmann F, Maekawa S, Sarment LV, Sugai JV, Schmiedeler CA, Doherty EJ, Holdsworth G, Kostenuik PJ, Giannobile WV. Sclerostin antibody stimulates periodontal regeneration in large alveolar bone defects. Sci Rep. 2020; 10: 16217.
11. de Sales Lima MV, Rizzato J, Gracindo Marques DV, et al. Denosumab Related Osteonecrosis of Jaw: a Case Report. J Oral Maxillofac Res. 2018; 9: e5.
12. Walter, C., Al-Nawas, B., Wolff, T. et al. Dental implants in patients treated with antiresorptive medication – a systematic literature review. Int J Implant Dent. 2016; 2: 9.
13. Raines AL, Berger MB, Patel N, Hyzy SL, Boyan BD, Schwartz Z. VEGF-A regulates angiogenesis during osseointegration of Ti implants via paracrine/autocrine regulation of osteoblast response to hierarchical microstructure of the surface. J Biomed Mater Res A. 2019; 107: 423-433.
14. Zhang C, Zhang T, Geng T, Wang X, Lin K. Dental Implants Loaded With Bioactive Agents Promote Osseointegration in Osteoporosis: A Review. Front Bioeng Biotechnol. 2021; 9: 591796.
15. Guarneri V, Miles D, Robert N, Diéras V, Glaspy J, et al. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Res Treat. 2010; 122: 181-8.
16. Bevacizumab et actes invasifs: Recommandations pratiques - 10/03/09 Doi: RMR-02-2009-26-2-0761-8425-101019-200900752
17. Joseph E Cillo, Nicholaus Barbosa, Adalimumab-Related Dental Implant Infection, Journal of Oral and Maxillofacial Surgery. 2019; 77: 6.
18. Olsen JJ, Pohl SÖ, Deshmukh A, Visweswaran M, Ward NC, et al. The Role of Wnt Signalling in Angiogenesis. Clin Biochem Rev. 2017; 38: 131-142.
19. Lewiecki EM. Role of sclerostin in bone and cartilage and its potential as a therapeutic target in bone diseases. Ther Adv Musculoskelet Dis. 2014; 6: 48-57.