



ONJ UPDATE 2018 OSTEONECROSI DELLE OSSA MASCELLARI (ONJ) DA BIFOSFONATI E ALTRI FARMACI: PREVENZIONE, DIAGNOSI, FARMACOVIGILANZA, TRATTAMENTO

TRATTAMENTO DELLA ONJ:
UPDATE DELLA LETTERATURA (2014-2018)
concentrati piastrinici

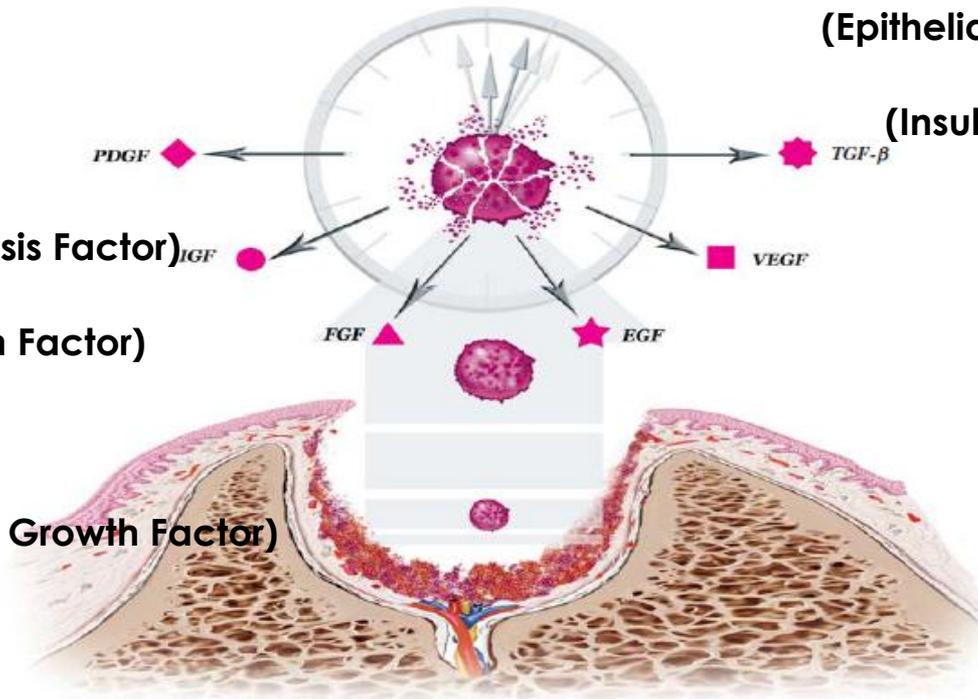
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AUTOLOGOUS PLATELET CONCENTRATES

- PF 4
(Platelet Factor 4)
- IL-1
(Interleukin-1)
- PDAF
(Platelet-Derived Angiogenesis Factor)
- VEGF
(Vascular Endothelial Growth Factor)
- EGF
(Epidermal Growth Factor)
- PDEGF
(Platelet-Derived Endothelial Growth Factor)



- ECGF
(Epithelial Cell Growth Factor)
- IGF
(Insulin-like Growth Factor)
- Oc
(Osteocalcin)
- On
(Osteonectin)
- Fg
(Fibrinogen)
- Vn
(Vitronectin)
- Fn
(Fibronectin)
- TSP-1
(Thrombospondin-1)

I CONCENTRATI PIASTRINICI RILASCIANO FATTORI DI CRESCITA CHE PROMUOVONO LA RIPARAZIONE TESSUTALE E INFLUENZANO LA BIOATTIVITÀ DELLE CELLULE ENDOTELIALI DURANTE L'ANGIOGENESI, DETERMINANDO UNA GUARIGIONE MIGLIORE E PIÙ RAPIDA.

Anitua E. Andia I. Ardanza B. Nurden P. Nurden AT.

Autologous platelets as a source of proteins for healing and tissue regeneration.

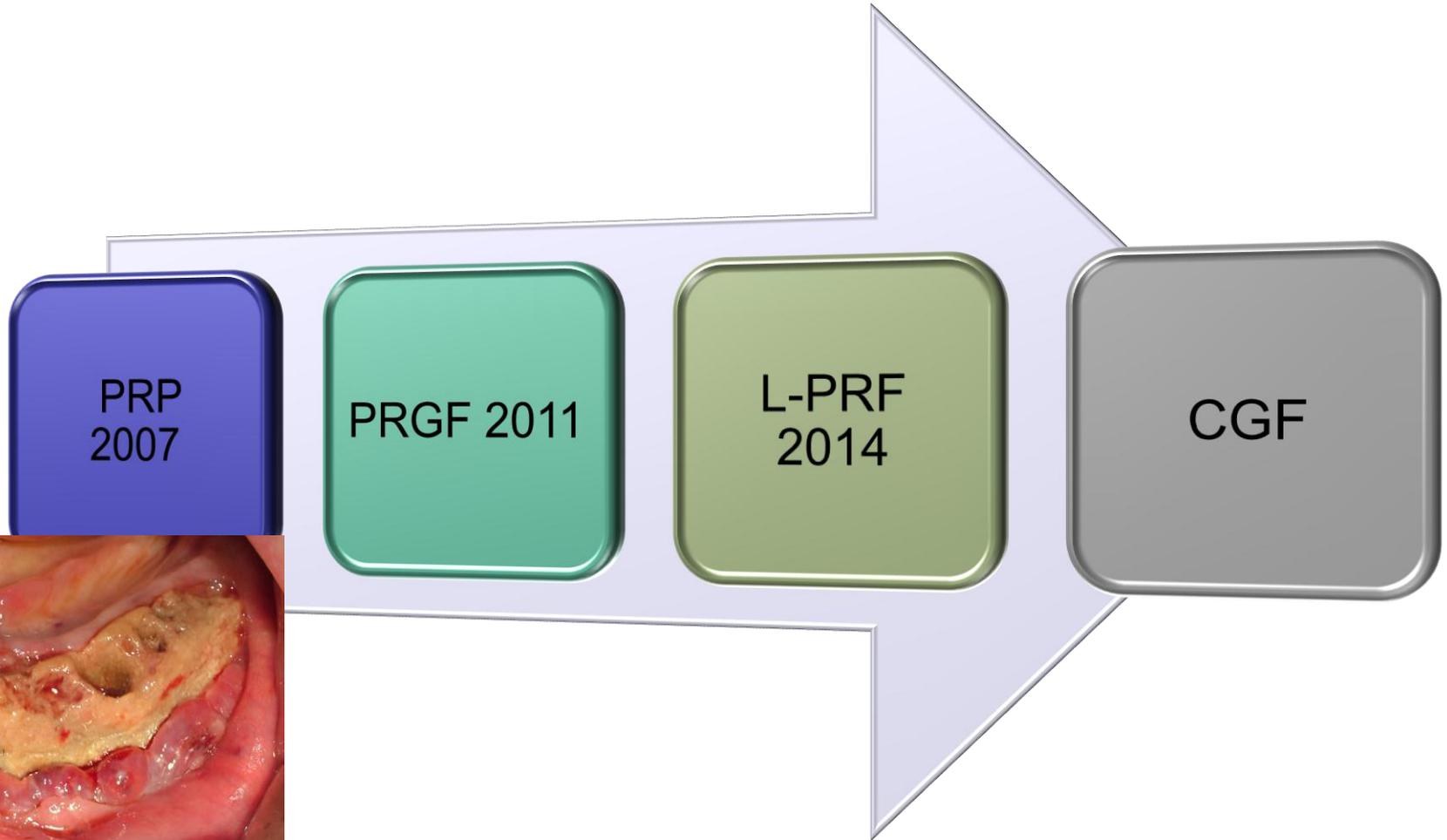
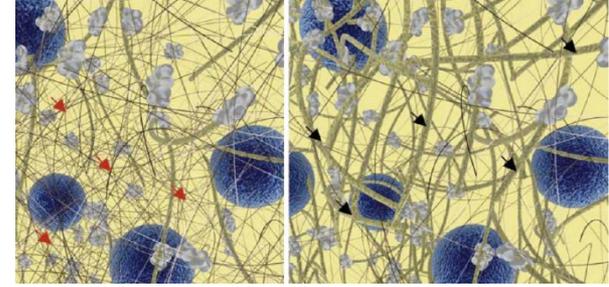
Thrombosis & Haemostasis. 91(1):4-15, 2004

JanPietrzak WS. Eppley BL.

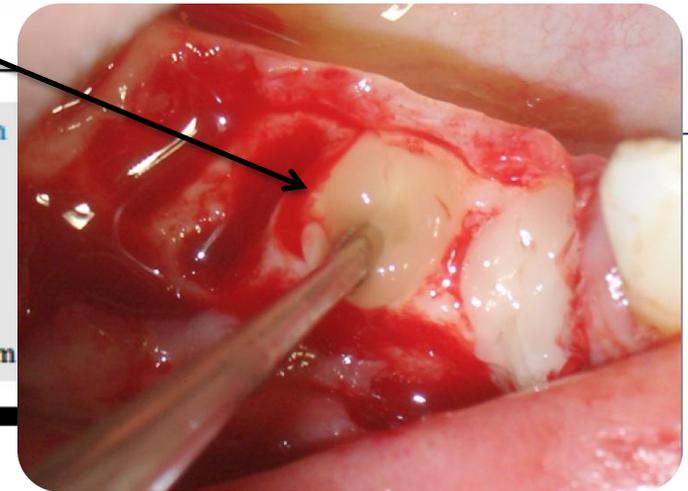
Platelet rich plasma: biology and new technology.

Journal of Craniofacial Surgery. 16(6):1043-54, 2005

Platelet Concentrates for MRONJ



APC



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journal homepage: www.ejcancer.com

Review

Autologous platelet concentrates for bisphosphonate-related osteonecrosis of the jaw treatment and prevention. A systematic review of the literature



Massimo Del Fabbro^{a,b,*}, Giorgia Galesio^c, Marco Mozzati^c

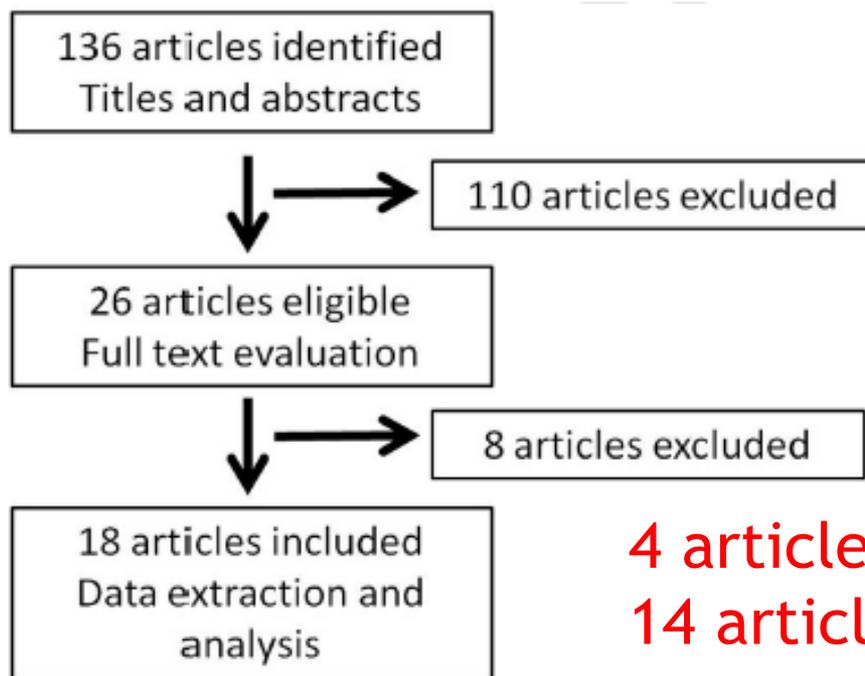
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Available online 6 November 2014



4 articles on MRONJ prevention
14 articles on MRONJ treatment

Fig. 1. Flowchart of the article selection process.

Table 1
Excluded studies and reason for exclusion.

Study	Reason for exclusion
Badr and Oliver [50]	Letter to the Editor, not an outcome study
Cetiner et al. [51]	Technique description through a case report, not an outcome study
Marx [52]	Review of surgical approaches to treat BRONJ, not an outcome study
Lee et al. [56]	Literature review plus description of 13 cases of BRONJ associated with actinomycosis, without a specific outcome. Does not report treatment results
Mozzati et al. [57]	Redundant publication (see Mozzati et al. [62])
Mozzati et al. [63]	Redundant publication (see Mozzati et al. [67])
Albanese et al. [64]	Literature review. No clinical cases presented
Gonzalez-Garcia et al. [66]	One single BRONJ case treated with a mixture of marrow MSCs, β -TCP, anorganic bovine bone and PRP. The role of PRP in healing is unclear

β -TCP, beta-Tricalcium phosphate; MSCs, mesenchymal stem cells; BRONJ, bisphosphonate related osteonecrosis of the jaw; PRP, platelet-rich plasma.

4 ARTICLES ON MRONJ PREVENTION

Table 2

BRONJ prevention. Summary of studies in which patients under bisphosphonates underwent oral surgery procedures in combination with APC.

Study ID	Study design	Treatment (APC type)	Setting	N. of patients (AE)	M/ F	N. of sites treated (AE)	Reason for taking BP	BP type	Admin Route	Follow-up (months)	Risk of bias
Scoletta et al. [58]	PCS	Tooth extraction (PRGF)	Univ.	65 (5)	20/ 45	220 (5)	MM, prostatic, breast, prostate, ovarian, rhinopharynx, lung carcinoma, lymphoma, osteoporosis, Paget disease, rheumatoid arthritis	Zol (57), Pam (2), Zol + Pam (5)	i.v.	4-24	High
Mozzati et al. [62]	PCC	Tooth extraction (PRGF)	Univ.	PRP: 91 (0) CTR: 85(5)	36/ 55	275 (0) 267(5)	MM, prostatic, breast, lung, ovarian carcinoma	Zol	i.v.	24-60	Low
Scoletta et al. [68]	PCS	Tooth extraction (PRGF)	Univ.	63 (1)	18/ 45	202 (2)	MM, prostatic, breast, lung carcinoma, lymphoma, osteoporosis	Zol (54), Pam (4), Iba (4)	i.v.	>4	High
Torres et al. [49]	CR	Implant placement (PRP)	Private	1 (0)	0/1	6 (0)	Osteoporosis	Ale	oral	36	High

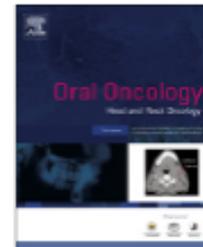
AE, adverse events; Ale, Alendronate; APC, autologous platelet concentrate; BP, bisphosphonate; CR, case report; F, female; Iba, Ibandronate; i.v., intravenous administration; M, male; MM, multiple myeloma; Pam, Pamidronate; PCC, prospective case-control; PCS, prospective case series; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; Univ., University; Zol, Zoledronate; BRONJ, bisphosphonate related osteonecrosis of the jaw.



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MRONJ PREVENTION

Tooth extraction in patients on zoledronic acid therapy

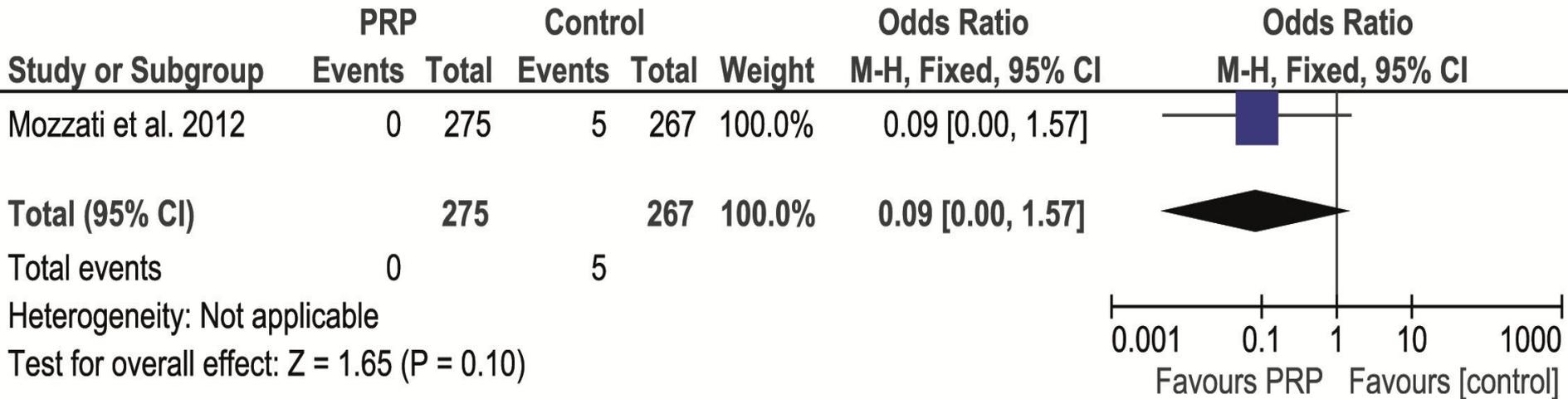
Marco Mozzati, Valentina Arata, Giorgia Galesio*

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 Department of Biomedical Sciences and Human Oncology, Dentistry Section, University of Turin, Turin 10126, Italy

ARTICLE INFO SUMMARY

Tooth extraction-per tooth analysis-APC vs control

Received in revised form 12 March 2012

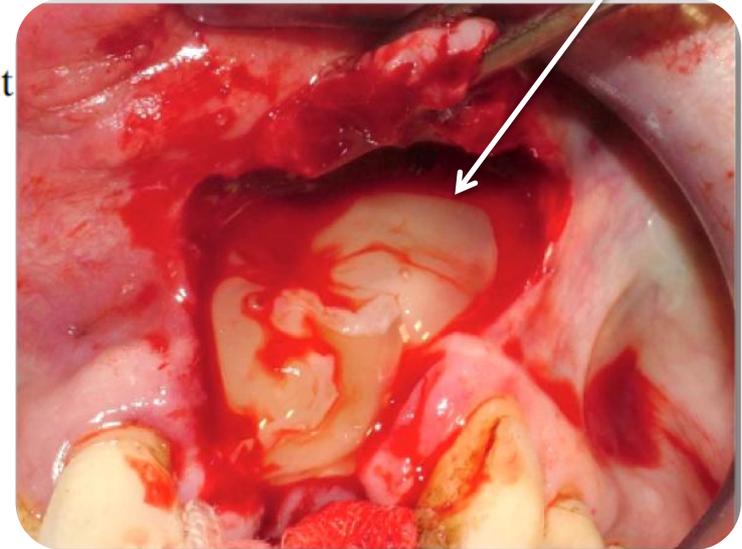


14 ARTICLES ON MRONJ TREATMENT

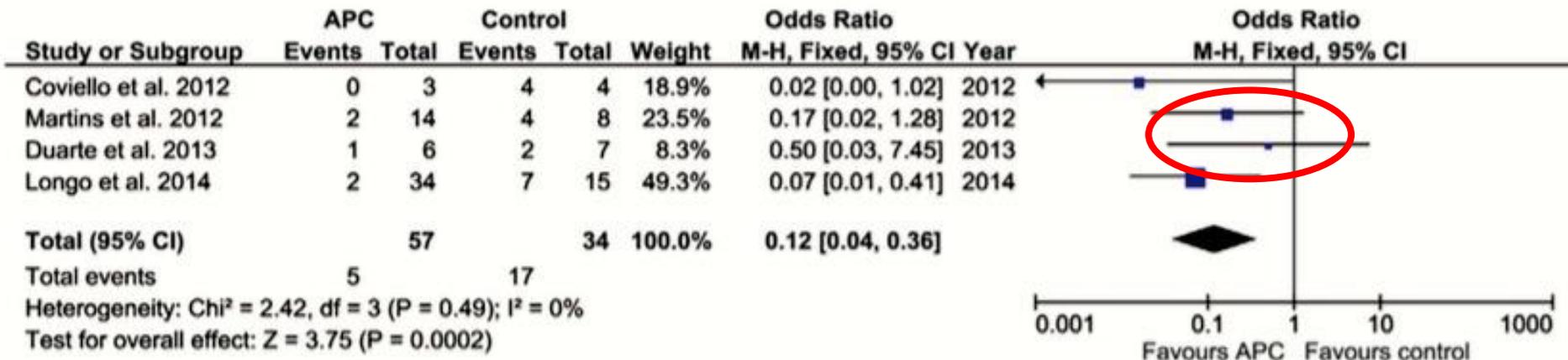
Autologous platelet concentrates for bisphosphonate-related osteonecrosis of the jaw treatment and prevention. A systematic review of the literature

Massimo Del Fabbro ^{a,b,*}, Giorgia Galesio ^c, Marco Mozzati ^c

14 articles: surgical debridment + APC (11 PRP, 2 PRGF, 1 PRF)
Only 4 comparative studies...



Surgical removal of necrotic bone – per pt. analysis – APC vs ctr



Conclusion of the 2015 systematic review

Autologous platelet concentrates for bisphosphonate-related osteonecrosis of the jaw treatment and prevention. A systematic review of the literature



Massimo Del Fabbro^{a,b,*}, Giorgia Galesio^c, Marco Mozzati^c

Though the results of this review must be cautiously interpreted, due to the low evidence level of the studies included, and the limited sample size, they are **suggestive for possible benefits of APC** when associated with surgical procedures for treatment or prevention of MRONJ.

To confirm such indication, prospective comparative studies with large sample size are urgently needed.

FURTHER EVIDENCE FROM LITERATURE REVIEWS



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Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com



Medication-related osteonecrosis of the jaw: Is autologous platelet concentrate application effective for prevention and treatment?
A systematic review

JCMFS 2016

Pia Lopez-Jornet ^{a, *}, Arturo Sanchez Perez ^b, Rui Amaral Mendes ^c, Aurelio Tobias ^d

There are no published scientific data to sufficiently support any specific treatment protocol, including the use of APC together with surgical debridement, for the management of MRONJ. RCTs of the use of APC are needed

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Review)

Rollason V, Laverrière A, MacDonald LCI, Walsh T, Tramèr MR, Vogt-Ferrier NB



**Cochrane
Library**

Cochrane Database of Systematic Reviews

“There is lack of good quality scientific evidence to decide how best to treat BRONJ, high quality trials are needed”

Rollason V, et al, Cochrane Database Syst Rev. 2016

It is **ALWAYS** possible to perform a **systematic review** of the literature on any topic!

However,

- 1) The strength of the outcomes depends on the quality of the retrieved studies
- 2) Comparing different studies may be hindered by a number of heterogeneities in **AIM, DESIGN, METHODS (TREATMENTS, OUTCOME VARIABLES, SAMPLE SIZE, INCLUSION CRITERIA, etc.)**

Recent evidence (prevention) - PRGF and implants

Failure Risk Estimates After Dental Implants Placement Associated With PRGF-Endoret in Osteoporotic Women Under Bisphosphonate Therapy: Retrospective Study on 235 Patients and 1267 Implants

Marco Mozzati, DDS,* Valentina Arata, DDS,† Maurizio Giacomello, DDS,‡
Massimo Del Fabbro, BSc, PhD,§ Giorgia Galesio, DDS,* Carmen Mortellaro, MD, DDS,||
and Laura Bergamasco, PhD¶

risk for developing BP-related osteonecrosis of the jaws (BRONJ). The American Association of Oral and Maxillofacial Surgeons recommends that dental implants should be avoided in oncologic patients treated with intravenous BPs. Conversely, for patients receiving oral BPs, dental implant placement is not explicitly contraindicated even if a cautious approach is suggested. The aim of the current study was to assess the risk level as related to adverse events such as implant failure and BRONJ in a large cohort of osteoporotic patients submitted to implant placement and concomitant application of PRGF-Endoret. The study included 235 middle-aged women under oral BPs therapy for osteoporosis, who underwent positioning of 1267 dental implants. The implants were always positioned in the maxilla. The outcomes were implant failure and BRONJ. The distribution was based on personal risk factors distribution was analyzed. Sixteen implants were lost in 16 patients during follow-up, leading to a survival of 98.7% and 98.7% on patient basis, respectively. No cases of BRONJ were observed. In line with the current literature, the present study supports the use of PRGF-Endoret for preventing the developing BRONJ associated to dental implant placement for patients receiving oral BPs. The use of PRGF-Endoret to enhance and support healing, such as platelet concentration, is recommended.

Key Words: Bisphosphonate, BRONJ, tooth extraction, implant, PRGF, platelets

The Journal of
Craniofacial Surgery

JCFS 2016

Retrospective study
235 W patients
1267 implants
PRGF at placement
>24 mo follow-up
16 imp. failures (1.3%)
98.7% imp. survival
No MRONJ cases



Platelet Concentrates for TREATMENT OF MRONJ (2007-)

AUTHOR	TYPE	Year	Journal
M. M. Curi	PRP	2007	J Oral Maxillo fac Surg
M. M. Curi	PRP	2011	J Oral Maxillo fac Surg
M. A.T. Martins	PRP	2012	Oral Oncology
S.Bocanegra-Perez	L-PRP	2012	Int.J. Oral Maxfac.Srg
Mozzati M.	PRGF	2012	Oral Oncol.
Octavian Dincă	L-PRF	2014	R. J Morph Embry
J.-W. Kim	L-PRF	2014	B J. Oral Maxfac.Srg
Pelaz A.	L-PRF	2014	M Or.Patol Or.Cir.Bucal.
Longo F.	L-PRP	2014	Int.J .Dentistry
Jin-Woo Kim	L-PRF	2014	B J. Oral Maxfac.Srg
S.E. Nørholt	L-PRF	2016	Int.J. Oral Maxfac.Srg
Jung-Hyun Park	L-PRF	2017	J Oral Maxillo fac Surg



Alternative treatments for oral bisphosphonate-related osteonecrosis of the jaws: A pilot study comparing fibrin rich in growth factors and teriparatide



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Comparative case series (pilot) 9 PATIENTS: 4 PRF, 5 TERIPARATIDE FOLLOW-UP: 6 MONTHS

PRF showed better results (resolution)
than TERIPARATIDE in the treatment
of recurrent BRONJ.

Very few cases....
Short follow-up....

PRF 2014

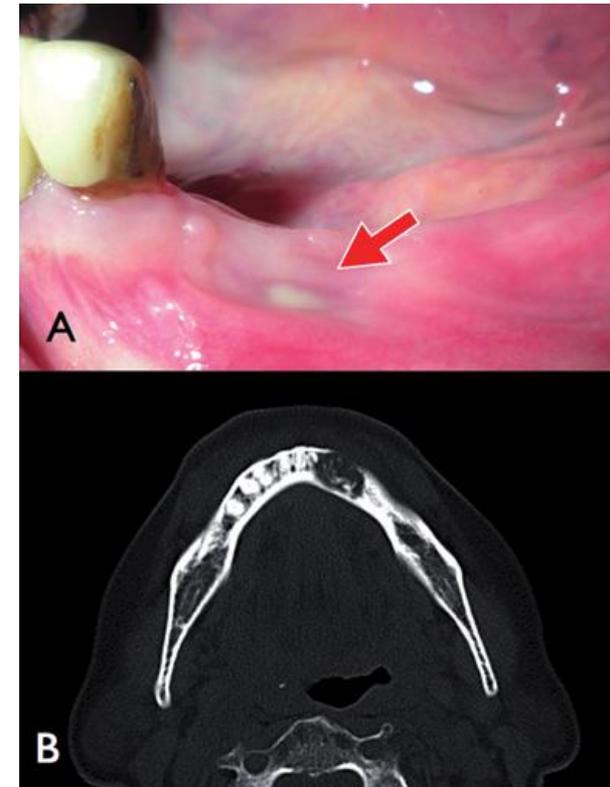


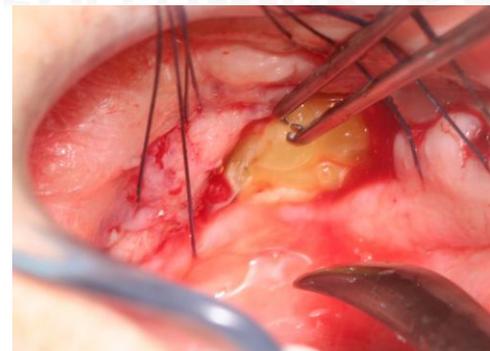
Fig. 2. Case A4. Mandibular BRONJ with purulent sinus tract highlighted with an arrow (A). Computed tomography (B) shows the osteolytic pattern affecting the incisive mandibular area.

Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study

Jin-Woo Kim, Sun-Jong Kim[†], Myung-Rae Kim

- ### CASE SERIES
- 34 PATIENTS
 - FOLLOW-UP: 4 MONTHS

- ❖ 77% complete resolution
- ❖ 18% delayed resolution
- ❖ 6% no resolution



- ❖ It is feasible to use L-PRF for the treatment of BRONJ, but the effectiveness cannot be judged with this study design!!!

Surgical treatment of osteonecrosis of the jaw with the use of platelet-rich fibrin: a prospective study of 15 patients

*International Journal of
Oral &
Maxillofacial
Surgery*



Table 1. Patient characteristics.

Patient number	Age, years	Sex	Diagnosis	Anti-resorptive drug treatment	Duration of anti-resorptive drugs, months	Location of ONJ	Stage of ONJ	Anti-resorptive drugs stopped	Outcome	Follow-up, months
1	63	M	Osteoporosis	Alendronate (L)	240	17	2	Yes	Cured	20
2	66	F	Breast cancer	Denosumab (H)	72	23, 45	3	Yes	Cured	17
3	68	F	Osteoporosis	Alendronate (L)	84	36, 37	2	No	Cured	17
4	83	F	Breast cancer	Ibandronate (H)	17	43	2	Yes	Cured	16
5	82	F	Myeloma	Pamidronate (H)	24	43, 44	2	Yes	Cured	14
6	59	F	Osteoporosis	Denosumab (L)	72	26, 27	2	No	Cured	13
7	73	M	Renal cancer	Zoledronate (H)	15	47	2	Yes	Cured	12
8	75	F	Osteoporosis	Denosumab (L)	170	35, 36	2	No	Cured	12
9	54	F	Breast cancer	Zoledronate (H)	18	36	2	Yes	Cured	11
10	74	M	Osteoporosis	Alendronate (L)	48	36	2	No	Cured	10
11	70	F	Osteoporosis	Alendronate (L)	180	43, 44	2	No	Cured	10
12	68	F	Breast cancer	Zoledronate (H)	73	15, 16	2	Yes	Cured	8
13	69	M	Prostate cancer	Denosumab (H)	20	45, 46	2	Yes	Cured	7
14	61	F	Renal cancer	Zoledronate (H)	31	35, 46	3	Yes	Exposed	7
15	63	F	Osteoporosis	Alendronate (L)	91	36	2	No	Cured	7

ONJ, osteonecrosis of the jaw; M, male; F, female; L, low-dose; H, high-dose.

Does the Addition of Bone Morphogenetic Protein 2 to Platelet-Rich Fibrin Improve Healing After Treatment for Medication-Related Osteonecrosis of the Jaw?

Jung-Hyun Park, DDS, PhD, *Jin-Woo Kim, DDS, PhD, † and Sun-Jong Kim, DDS, PhD ‡

Purpose: To investigate the effect of the addition of bone morphogenetic protein 2 (BMP-2) to leukocyte-rich and platelet-rich fibrin (L-PRF) on the treatment of medication-related osteonecrosis of the jaws (MRONJ), this study compared the healing outcome of combined use of BMP-2 and L-PRF with single use of L-PRF.

Patients and Methods: Of 55 patients who were diagnosed with MRONJ, 25 were treated with L-PRF alone and 30 were treated with L-PRF and recombinant human BMP-2. For each patient, surgical sites were evaluated postoperatively at 4 and 16 weeks. Associations between the treatment method and the resolution of MRONJ were analyzed with the adjustment of patient-specific factors that may influence the treatment outcome.



controlled study

55 PATIENTS

- 25 L-PRF
- 30 L-PRF+BMP-2

FOLLOW-UP: 16 WEEKS

rationale: absence of BMPs within L-PRF

Table 2. TREATMENT RESULTS OF BOTH GROUPS

	L-PRF (n = 25)	L-PRF Plus BMP-2 (n = 30)
Complete resolution, n	9 (36.0%)	18 (60.0%)
Delayed resolution, n	13 (52.0%)	11 (36.7%)
No resolution, n	3 (12.0%)	1 (3.3%)

Abbreviations: BMP-2, bone morphogenetic protein 2; L-PRF, leukocyte-rich and platelet-rich fibrin.

- ❖ The combined treatment leads to the early resolution of MRONJ
- ❖ Patients who need to continue antiresorptive therapy may benefit from the combined regimen

CONCLUSIONS

Autologous platelet concentrates may represent a beneficial tool for the management of MRONJ

however...

more evidence-based clinical studies are needed to draw stronger conclusion and determine the true effect of such adjunct

Acknowledgements

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