Bisphosphonate-Related Osteonecrosis Of The Jaw Triggered By Dental Implants

-The Current Situation In Japan And Correspondence With Osteoporosis Patients When Getting Dental Implants-

KAORI YAGO[1)], HIDEKI KIZU[2)], HAYATO HASHIGUCHI[2)], SOICHIRO ASANAMI[3)]

1) Department of Oral Surgery, Mita Hospital, International Health and Welfare University, Tokyo, Japan
2) Department of Oral Surgery, Tachikawa Kyosai Hospital, Tokyo, Japan
3) Department of Oral Surgery, Sanno Hospital , Tokyo, Japan

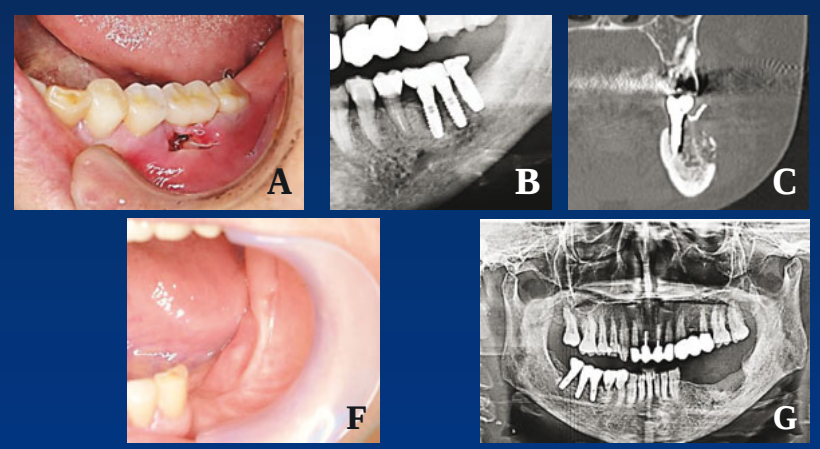
Purpose:

Japan is a super-aged society with the highest life expectancy in the world. The prevalence of osteoporosis drastically increases with age following menopause. It is said that 12.8 million patients in Japan suffer from osteoporosis and patients administered bisphosphonate , which is considered the top choice drug for osteoporosis according to the guidelines, have a high probability of undergoing implant treatment. Bisphosphonate (BP) is specifically incorporated into osteoclasts, thereby inducing apoptosis and suppressing bone resorption, and is therefore widely used for osteoporosis and cancer metastasis of the bone. However, cases of BP-related osteonecrosis of the jaw (BRONJ) are problematically increasing as a complication thereof. While dental extraction often triggers the onset thereof, dental implant treatment may also act as a trigger.There is still no treatment established for BRONJ, so once it occurs, it is intractable.
We herein report on our experience regarding cases in which good results were achieved by carrying out surgical treatment on patients in which BRONJ was triggered by dental implants. Moreover, we report on the current state and correspondence of implant treatment with respect to osteoporosis patients with some bibliographical considerations.

Patients:

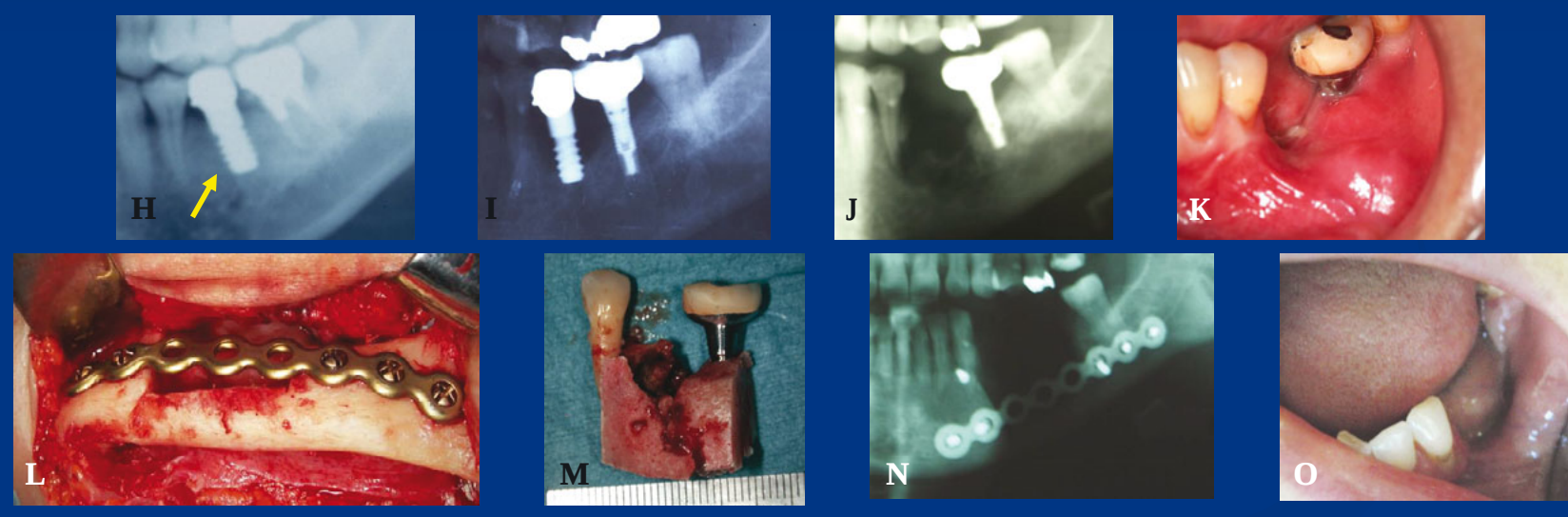
<Case 1 of BRONJ>

The case pertains to a 74-year-old woman taking Alendronate for treating osteoporosis. She had three dental implants in teeth number 36 and 37 at a local dentist during the three years that she had been taking Alendronate. Swelling and pain occurred at the same site of the gum after approximately 5 years and the patient visited our hospital due to aggravating pain and hypaesthesia of the lower lip (A～C). She was diagnosed with BRONJ and marginal resection of the mandible was carried out under general anesthesia (D, E). Currently, at 3 years following surgery, the prognosis is good, with no bone exposure or pain (F, G).



<Case 2 of BRONJ>

The case pertains to a 60-year-old woman taking zoledronate for treating bone metastasis from breast cancer. Implants were placed in 35 sites approximately 8 years prior by a local dentist (H); however, the implant was removed due to agitation (I, J). The patient visited our hospital through referral due to subsequent acute pain at the same site as well as hypaesthesia of the lower lip (K). Marginal resection of the mandible was carried out under general anesthesia (L～N), her pain disappeared, and the prognosis was good (O); however, the patient died due to the primary disease



Discussion

1. BRONJ With Dental Implants

Study#1 : (The Japanese Society of Oral and Maxillofacial Surgeons)
- According to the investigation in 2014 by the Japanese Society of Oral and Maxillofacial Surgeons, there were 4,797 BRONJ cases within approximately 3 years. Although predominantly more cases lead to osteonecrosis of the jaw due to Intravenous BP (IV BP) in reports from overseas countries, half of all osteoporosis cases were undergoing oral BP administration in Japan (fig 1).
- In about half the cases, ONJ developed following tooth extraction, while the percentage of cases in which it developed following a dental implant was about 1% (fig 2).

Study#2: (MATSUO A,YAGO K,et al. Jpn J Maxillofac Impl 2014; 13:29-39.)
- The incidence of BRONJ in patients with a dental implant placement was 17 cases from July, 2003 to March, 2013 in Japan.
- 10 of 17 cases had a history of oral BP use (59%).
- Average age of patients was 67.5 yrs.
- Gender : Male 1 (5.9%) Female 16 (94.1%)
- Location : Manbible 15 (88.2%) Maxilla 2 (11.8%)
- For the treatment method, there were 14 cases in which a surgical procedure was performed. For the outcomes, there were 8 cases of a cure, 4 cases of remission, and 1 case each of invariance, progression, death from the same illness, death from a different illness, and unclear.

Study#3（Lazarovici TS, et al. J Oral Maxillofac Surg 2010; 68 : 790-796）
- Among 145 BRONJ patients, 27 persons (18.6%) had implant related ONJ.
- Oral BP 11 (41%), IV BP 16 (59%)
- Duration of administration until the onset of BRONJ: Alendronate 68 months, zoledronate 16.4 months
- Period from the time after implant placement until the onset of BRONJ: Average 16.2 months
- There were six cases (26.1%) of the onset of BRONJ within six months after the implant placement.

Study#4 Meta-analysis (Holzinger D,et al.J Oral Maxillofac Surg 2014;72 : 1936)
- Among 138 BRONJ patients, 13 persons (9.4 %) had implant-related ONJ.
- There was a tendency for those in the injection group to end up with BRONJ.
- The patients administered BP before implant placement end up with ONJ earlier than the patients who started BP after the placement.
- The longer the duration of BP oral medication is, the earlier the onset of ONJ.

Fig. 1 BRONJ in Japan
Route of administration of BP

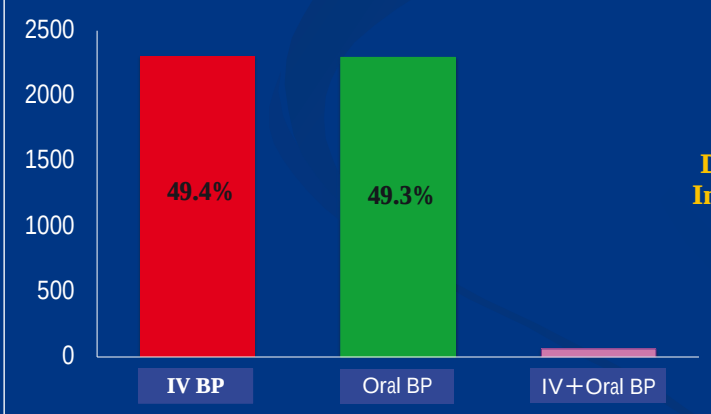
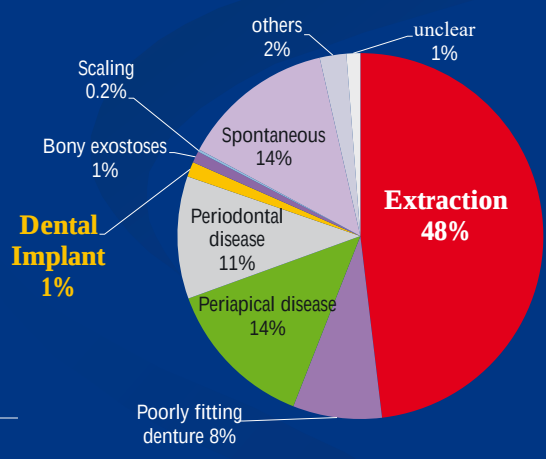


Fig. 2 Triggering factors



2. Points to help the implant treatment of patients receiving Oral BP succeed

1) *Cessation of BP*
Oral administration has less accumulation in the bone compared to injections because it has a lower gastrointestinal tract absorption rate (0.7%).
Therefore, as the precursor osteoclastic populations are not significantly affected, the cessation of BP makes it possible to recover so as to reach a state close to that of normal bone metabolic turnover.

2) *Considering the risk factors*
Consult with the BP prescribing doctor if a patient has received BP for more than four years or has risk factors even within four years (such as concomitant use of corticosteroids or angiogenesis inhibitors, diabetes mellitus etc.), and if there is a low risk of bone fractures,cease taking BP for two months before the operation and until the confirmation of the osseointegration after the operation (poor scientific basis).

3) *Administration of prophylactic antibiotics*
Administer the antibacterial drug (penicillin , macrolide etc.) for four days from one day before the operation.

4) *Surface texture*
Because BP is deposited on the hydroxyapatite selectively, the apatite coating implant may cause ONJ, as in case 2.

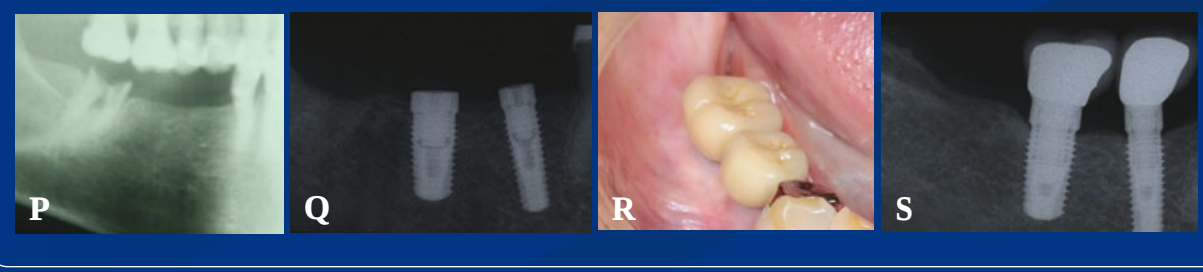
5) *Considerations for preventing peri-implantitis (distance between implants, compatibility of the superstructure etc.)*
When the distance between implants is short and the compatibility of the superstructure is poor, peri-implantitis may arise and ONJ may develop.

6) *In order to reduce the risk of bacterial infection*
select the two stage method to close the wound.

7) *Patient education*
Because there is the possibility of implant problems if the BP use takes place over a longer duration, as in case 1, explain to the patient the importance of regular, long term dental checkups, and maintaining good oral hygiene.

<Good prognosis case>

The case pertains to a 76-year-old woman who has been taking Risedronate for approximately 1 year and 5 months for treating osteoporosis. She desired implant treatment instead of dentures for missing teeth numbers 45 and 46 (P). She went off Risedronate for approximately 2 months and azithromycin was administered prior to surgery for two CAMLOG implants (Q). Risedronate was re-administered 1 month following installation of the superstructure. Approximately 7 and a half years have passed since getting the implants, with no occurrence of osteonecrosis of the jaw and a good prognosis (R, S).



Conclusion

Implant treatment should be avoided in cancer patients being administered BP; however, implant treatment should be given careful consideration when there is a strong demand from osteoporosis patients being administered BP. Dentists should explain to patients the onset risk of osteonecrosis of the jaw, obtain their consent, and consider the advisability while taking into consideration the administration period of BP and the risk factors of such patients.

Contact : KAORI YAGO, Department of Oral Surgery, Mita Hospital, International Health and Welfare University, Tokyo, Japan, 1-4-3 Mita Minato-ku Tokyo 108-8329, Japan Tel : ＋81-3-3451-8121, Fax : ＋81-3-3454-0067, E-Mail : k-yago@iuhw.ac.jp