Efficacy and safety of denosumab treatment in a prepubertal patient with cherubism

Haruka Kawamura[1], Satoshi Watanabe[1], Takeshi I[2], Izumi Asahina[2], Hiroyuki Moriuchi[1], and Sumito Dateki[1]

[1] Department of Pediatrics, Nagasaki University Hospital, Nagasaki, Japan
[2] Department of Oral and Maxillofacial Surgery, Nagasaki University Hospital, Nagasaki, Japan

Disclosure statement
The authors declare no conflict of interest.

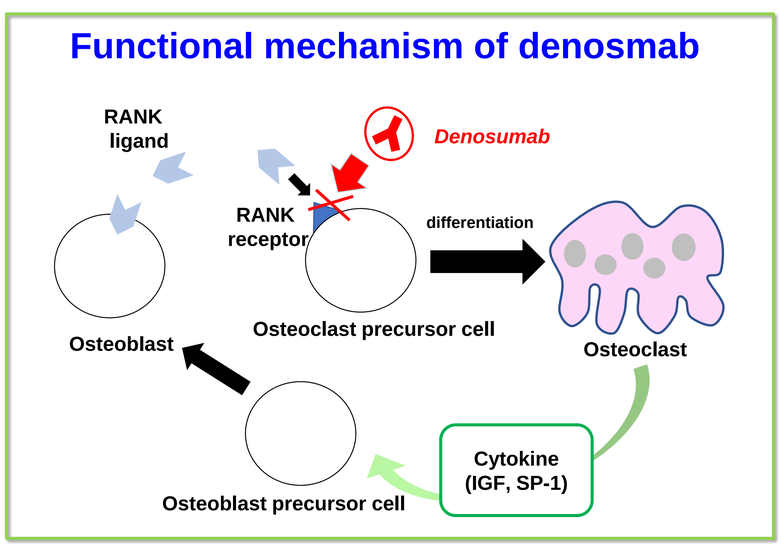
Introduction

☑ Denosumab is an inhibitor of receptor activator of nuclear factor kappa-B (RANK) ligand, which strongly suppresses the differentiation, proliferation, and activation of osteoclasts.

☑ Cherubism is caused by heterozygous mutations in the SH3 domain-binding protein 2 gene (*SH3BP2*) characterized by symmetrical swelling of the mandible and maxilla, excessive bone resorption with polycystic destruction of the bone structure, and tooth displacement (OMIM# 118400). The bone is replaced by a fibrous granuloma containing multinucleated giant cells that express RANK and differentiate into activated osteoclasts.

☑ We report a Japanese boy with cherubism, who demonstrated clinical improvement following a 6-month treatment course of denosumab.

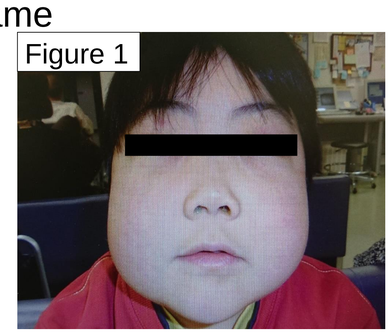
Functional mechanism of denosmab



Case report

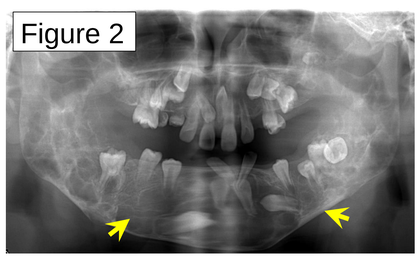
A Japanese male patient was diagnosed with cherubism at 4.5 years of age, because of characteristic facial features and radiographic findings, and a family history of the same disorder in his father.

Figure 1



At 9 years of age, he was referred to us because of progressive swelling of upper and lower jaws (Figure 1), and delayed permanent teeth eruptions.

Figure 2



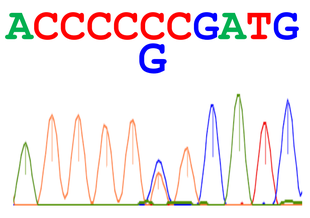
Panoramic radiographs and computed tomography (Figures 2, 3), revealed expansive multilocular osteolytic lesions of the mandible and maxilla, which were about to reach the orbit cavities and buried multiple permanent teeth (yellow arrows).

His height was 139.9 cm (+ 0.51 SD), weight 47 kg, BMI 24.0 (+1.77 SD), prepubertal (Tanner stage P1; testicular volume of 2 ml bilaterally).

Markers of bone resorption (urine NTx/Cr, 409.9 nmol BCE/mmol/Cr [13.0–66.2]) and formation (BAP, 126.4 μg/L [8.7–20.9]) were higher than the standard levels, while other laboratory results were normal.

Mutation analysis for the *SH3BP2* gene demonstrated a heterozygous hot spot mutation for cherubism.

***SH3BP2*: c.1253C>G,p.Pro418Arg**

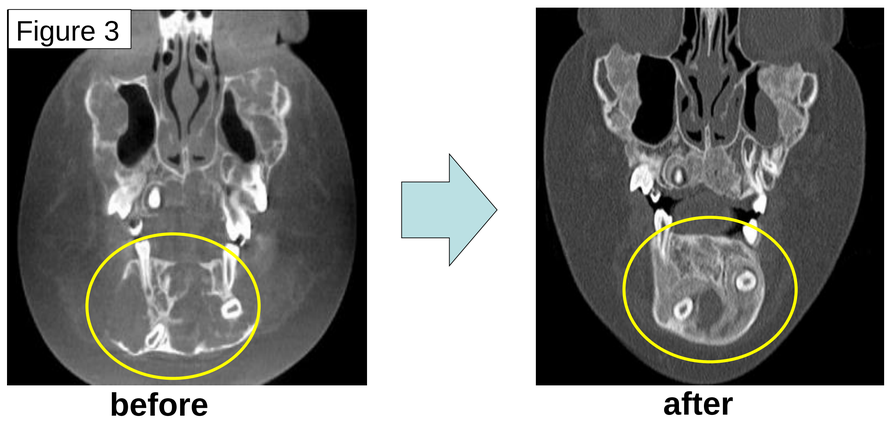


Denosumab treatment

Denosumab (Ranmark®) was injected subcutaneously (120 mg/dose) at days 0, 7, and 28, and then every 4 weeks thereafter for 6 months, based on the previously reported protocol for giant cell granuloma (1).

Gnathic bone computed tomography

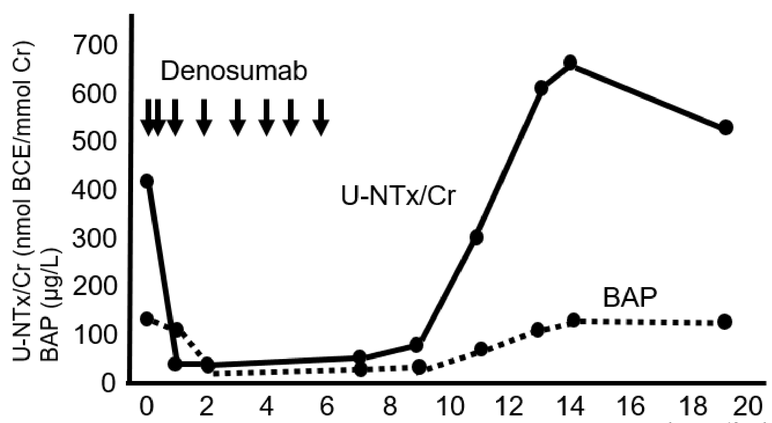
Figure 3



before **after**

The 6-month treatment course of denosumab resulted in dramatic ossification of the osteolytic legions and suppression of their expansion.

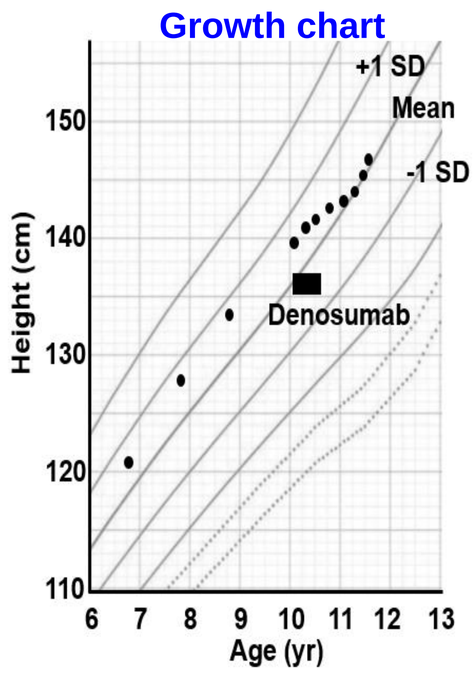
Treatment course and the levels of bone turnover markers.



U-NTx/Cr had decreased during the treatment, rebounded to a higher level than the baseline at 6 months after discontinuation of the denosumab treatment.

Temporal hypocalcemia at the initiation of the denosumab treatment, the patient exhibited mild hypercalcemia after the discontinuation of denosumab.

Growth chart



A transient decrease in growth rate for a period from 2 months after the initiation of the treatment to 5 months after the discontinuation.

The timing and duration of the growth retardation roughly matched those of low levels of bone turnover markers in this case, implying that the affected bone modeling and remodeling mediated by denosumab were responsible for his growth retardation.

Conclusion

☑ This is the first report demonstrating the therapeutic potential of denosumab for treatment of cherubism.

☑ Growth retardation may occur in prepubertal patients during denosumab treatment.

☑ Further studies are needed to establish a safe and effective protocol for denosumab treatment of prepubertal children.

Reference
1) Naidu A,et al. *J Oral Maxillofac Surg* 72: 2469-2484, 2014.