Siglec-15-Targeting Therapy Increases Bone Mass in Rats and Is a Potential Therapeutic Strategy for Juvenile Osteoporosis

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Introduction

- There is no consensus on the treatment of osteoporosis in children. [1]
- The possible adverse effects of the long-term use of antiresorptive therapies on skeletal growth in children is of particular concern. [2]
- Sialic acid-binding immunoglobulin-like lectin 15 (Siglec-15) is an immunoreceptor that regulates osteoclast development and bone resorption.
- Its deficiency suppresses bone remodeling in the secondary spongiosa, but not in the primary spongiosa, due to a compensatory mechanism of osteoclastogenesis. [3]

Objective

- In the current study, we investigated the efficacy and safety of anti-Siglec-15 therapy as juvenile osteoporosis medications by using growing rats.

Materials and Methods

Material

- Rat anti-Siglec-15 rat antibody (anti-Siglec-15 Ab) was provided by Daiichi Sankyo Co., Ltd. (Tokyo, Japan).

Study Design :

- Male F344/Jcl rats at 6 weeks of age (N=10/group)
  - ✓ Control (Ctl)
  - ✓ Siglec-15 0.25 anti-Siglec-15 Ab 0.25 mg/kg/3 weeks s.c.
  - ✓ Siglec-15 1 anti-Siglec-15 Ab 1 mg/kg/3 weeks s.c.
  - ✓ Siglec-15 4 anti-Siglec-15 Ab 4 mg/kg/3 weeks s.c.
  - ✓ ALN 0.028 Alendronate (ALN) 0.028 mg/kg/2 times per week s.c.
  - ✓ ALN 0.14 ALN 0.14 mg/kg/2 times per week s.c.

Treatment period : 6 weeks (from 6 to 12 weeks of age)

Longitudinal evaluations

(weeks of age)	6	9	12
Body length, Femoral length	+	+	+

Post-mortem evaluations

- Bone mineral density (BMD) in the distal femur
- Micro CT images of the tibia and femur
- Biomechanical test of the distal femur
- Histology of tibia

Results

- Anti-Siglec-15 Ab did not result in adverse effect on skeletal growth, whereas ALN impaired skeletal growth. (Fig. 1)
- Anti-Siglec-15 Ab did not cause growth retardation and morphological abnormalities, whereas ALN resulted in these negative outcomes. (Fig. 2)
- Anti-Siglec-15 Ab did not decrease in the osteoclasts in primary spongiosa, whereas ALN decreased in the osteoclasts in primary spongiosa. (Fig. 2)
- Both anti-Siglec-15 Ab and ALN increased bone mass and mechanical properties of long bone. (Fig. 3)

Conclusion

- Anti-Siglec-15 therapy increased bone mass without adverse effects on skeletal growth, whereas ALN increased bone mass but was associated with the development of morphological abnormalities, as well as growth retardation.
- Anti-Siglec-15 therapy could be an alternative antiresorptive therapy, having an ideal safety profile, for juvenile osteoporosis.

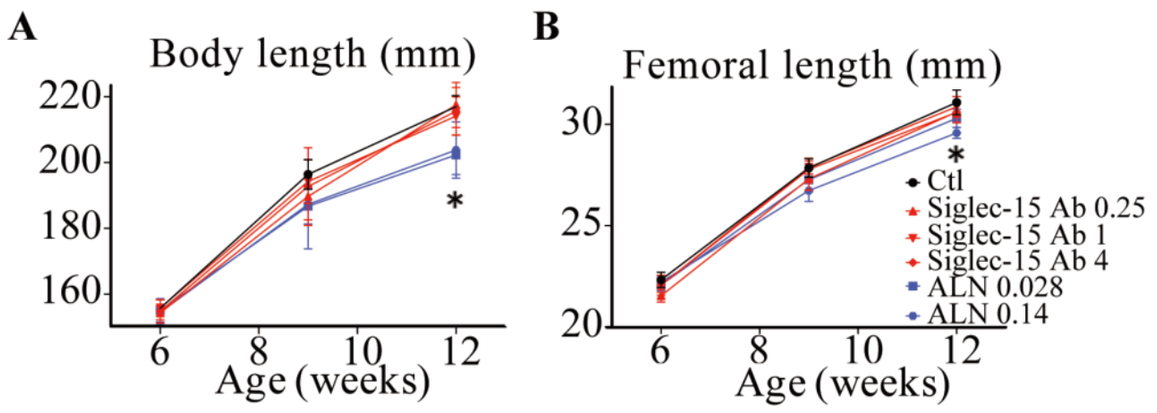

Fig. 1. Effects of anti-Siglec-15 Ab on skeletal growth in growing rats

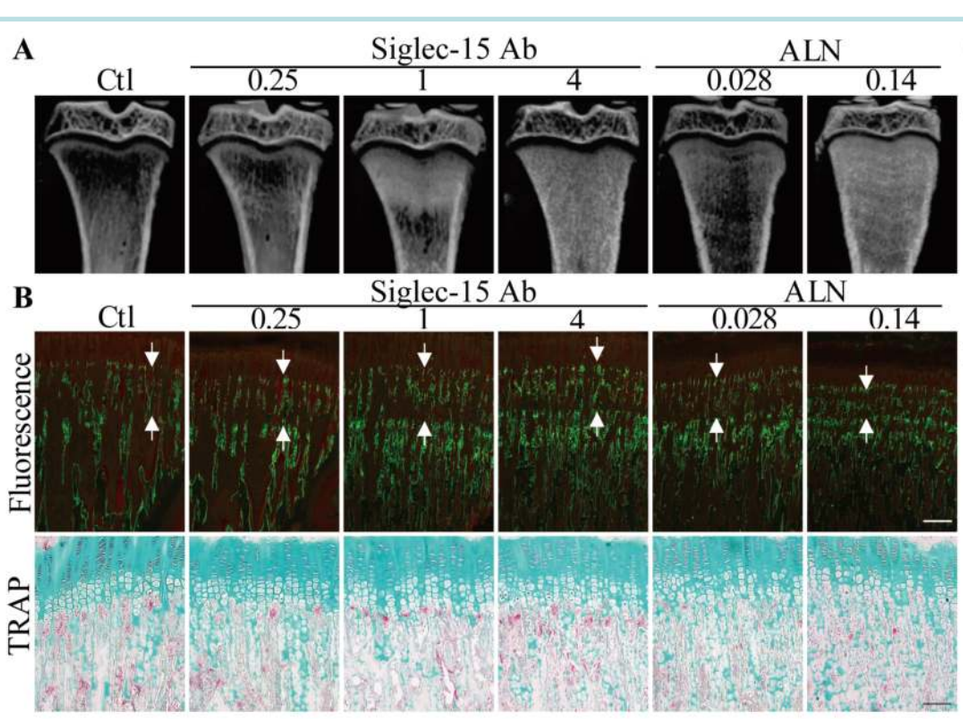

Fig. 2. Effects of anti-Siglec-15 Ab on endochondral ossification in growth plates of long bones in growing rats

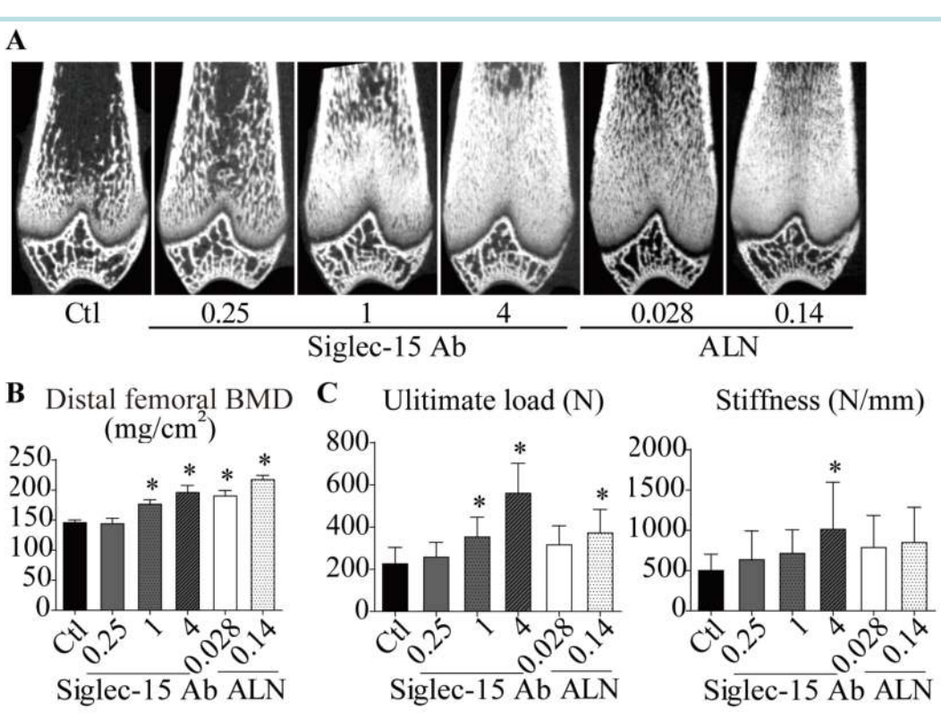

Fig. 3. Effects of anti-Siglec-15 Ab on bone mass and mechanical properties of long bones in growing rats

References
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