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論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Name	山田知絵子
論文題名 Title	Clinical and Genetic Characterization of Osteogenesis Imperfecta in Japanese Patients: Outcomes of Sequential Bisphosphonate Therapy（日本人骨形成不全症患者の臨床的・遺伝学的特性の解析：逐次的ビスホスホネート療法の臨床アウトカム）

論文内容の要旨

〔目　的(Objective)〕

Although novel drug development and clinical trials are ongoing, bisphosphonates remain the standard treatment of osteogenesis imperfecta (OI). This study aimed to evaluate clinical effects of bisphosphonate therapy across clinical subtypes and genetic variants of OI, and to explore treatment outcomes of sequential bisphosphonate therapy in patients with severe disease.

〔方法ならびに成績(Methods/Results)〕

This retrospective analysis was conducted using clinical data from patients with genetically confirmed OI. Bone mineral density (BMD), trabecular bone score (TBS), height, and fracture incidence were analyzed in patients undergoing pamidronate (PAM) treatment and in those who switched from PAM to zoledronate (ZOL).

A total of 83 patients with genetically confirmed OI (40 females and 43 males from 66 unrelated families; median age, 14.80 years [IQR, 7.62–20.40]) were included, of whom 51 (type I: n=36; type III: n=9; type IV: n=5; type V: n=1) with a history of PAM treatment were selected for subgroup analysis.

COL1A1, *COL1A2*, and *IFITM5* variants were found in 63, 18, and 2 patients, respectively. Variant types included glycine substitution (25.9%), splice site (32.1%), frameshifts (22.2%), nonsense (12.3%), other missense (2.5%), entire gene deletions (3.7%), and in-frame insertions (1.2%). In *COL1A1*, splice sites (34.9%) and frameshifts (28.6%) were most frequent, whereas in *COL1A2*, glycine substitutions (66.7%) were predominant. Clinically, 65 patients were classified as Sillence type I, 11 as type III, and 5 as type IV. Among patients with *COL1A1* glycine substitutions, 66.7% were Sillence type III, whereas 83.3% of those with *COL1A2* glycine substitutions were Sillence type I.

Analysis of up to 5 years of PAM treatment demonstrated a significant overall increase in BMD accompanied by a reduction in the annualized fracture rate. However, BMD improvement was significantly attenuated in patients with type III compared with those with other types (years 2–4, $p < 0.001$). Although BMD significantly increased in both groups following PAM initiation, the glycine-substitution group showed lower BMD than the haploinsufficiency group. Type III patients who switched from PAM to ZOL demonstrated increased BMD Z-scores and reduced fracture incidence.

〔総　括(Conclusion)〕

Switching from PAM to ZOL appears to be associated with improved outcomes in severe cases. These results suggest that clinical classification, alongside genotype information, may help inform prognosis and guide treatment strategies.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本研究では、遺伝学的に診断された日本人骨形成不全症(OI)83例を対象に、臨床像、遺伝子型、ビスホスホネート治療の臨床成績を後方視的に解析した。*COL1A1*グリシン置換は重症III型と関連し、*COL1A2*グリシン置換ではI型が多く遺伝子型と臨床的重症度との関連が示された。Pamidronate(PAM)治療により全体として骨折率は有意に低下したが、III型やグリシン置換例では骨密度(BMD)低値が持続した。また、PAMからZoledronate(ZOL)へ切り替えた重症例は、BMD ZスコアおよびBMD身長補正Zスコアが上昇し、骨折率も有意に減少した。以上より、OIでは臨床分類と遺伝子型を踏まえた重症度評価や経過予測が治療戦略の検討に有用であり、PAM治療で効果が不十分である重症例では、ZOLへの切り替えが治療選択肢となる可能性が示唆された。本研究成果を学位に値すると考える。