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Case Report

Incident Vertebral Fractures During Romosozumab Treatment in a Patient With a Pathogenic *LRP5* Variant

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Abstract

A defect in the canonical Wnt-β-catenin pathway may lead to reduced bone strength and increased fracture risk. Sclerostin is a key inhibitor of this pathway by binding to low-density lipoprotein (LDL) receptor–related protein *(LRP)-5/6*, thereby reducing bone formation. The effectiveness of romosozumab, a human monoclonal antibody that binds sclerostin and prevents this inhibitory effect, has been questioned in patients with inactivating genetic variants in *LRP5* or *LRP6*. We present a 67-year-old woman with severe osteoporosis with 4 grade 2 vertebral fractures due to a heterozygous pathogenic variant in *LRP5*. She was treated with romosozumab for 1 year, after which a routine follow-up spine x-ray revealed 5 new vertebral fractures, despite a strong increase in bone mineral density (BMD) (lumbar spine [LS] + 58%; femur neck [FN] + 23%), although overestimated at LS because of the vertebral fractures. This suggests that in patients with loss-of-function *LRP5* variants, romosozumab is able to increase BMD. However, it is unclear whether the progressive vertebral fractures are due to the severe osteoporosis in relation to the start of romosozumab or a diminished responsiveness related to her *LRP5* variant. Further evaluation is needed on the effect of romosozumab on BMD and fracture outcomes in patients with a likely defective *LRP5/6* receptor.

Key Words: *LRP5*, romosozumab, vertebral fracture BMD. Osteoporosis

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; FN, femoral neck; L, lumbar; LDL, low-density lipoprotein; *LRP*, LDL receptor–related protein; LS, lumbar spine; OPPG, osteoporosis-pseudoglioma syndrome; T, thoracic; TBS, trabecular bone score; TSH, thyrotropin.

Introduction

Osteoporosis is characterized by a low bone mineral density (BMD) and microarchitectural deterioration of bone tissue resulting in reduced bone strength and increased fracture risk [1]. The canonical Wnt-β-catenin pathway plays a significant role in bone homeostasis [2]. Defects in this pathway may lead to (severe) osteoporosis. Sclerostin is a key inhibitor of this pathway by binding to low-density lipoprotein (LDL) receptor–related protein *(LRP)-5/6*, leading to decreased bone formation. Loss-of-function *LRP5* variants modify the binding site of the *LRP5* receptor to Wnt signals, blocking the activation of the Wnt canonical pathway in preosteoblasts and osteoblasts, thus decreasing bone formation [2]. Romosozumab, a human monoclonal antibody that binds to sclerostin and prevents this inhibitory effect, has a strong anabolic and mildly antiresorptive effect, which results in a strong gain of BMD [3]. Clinical trials in postmenopausal women showed a superior effect of romosozumab, compared to placebo or alendronate, with respect to both increase in BMD and fracture prevention [4, 5]. It has been suggested that the anabolic actions of romosozumab may be diminished or absent in patients with loss-of-function variants in *LRP5* because they already lack the LRP5/Frizzled binding that sclerostin inhibits [6, 7]. However, research in *LRP5*-deficient mice showed that antisclerostin treatment does lead to an increase in bone formation, and trabecular and cortical bone mass [7]. Here we present a 67-year-old woman with severe osteoporosis due to a pathogenic heterozygous variant in *LRP5* who, during treatment with romosozumab, showed an increase in BMD, but developed several new vertebral fractures.

Case Presentation

A 67-year-old woman was referred from the general practitioner to our tertiary bone clinic because of severe osteoporosis with multiple vertebral fractures. She had a history of a subtotal thyroidectomy because of a goiter (>30 years earlier; no levothyroxine treatment needed afterward, and euthyroid at presentation), hypertension, and glaucoma. She experienced a wrist fracture 17 years earlier, and 2 years ago she developed back pain, after which she was diagnosed with multiple fractures of the thoracic (T) vertebrae, and osteoporosis of both the lumbar spine (LS [L2-L4]: T-score −4.6 SD) and the femur neck (FN [left]: T-score −3.4 SD) on a dual-energy x-ray absorptiometry (DXA) scan elsewhere. She was started on oral alendronate, but within 3 weeks she

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Table 1. Laboratory and dual-energy x-ray absorptiometry scan results over time

	Reference range	At presentation	1 mo before starting romosozumab	1 mo after 1-y romosozumab
Serum				
Calcium	2.20-2.65 mmol/L	2.45 mmol/L	2.45 mmol/L	2.33 mmol/L
	8.82-10.62 mg/dL	9.82 mg/dL	9.82 mg/dL	9.34 mg/dL
Phosphate	0.80-1.40 mmol/L	1.36 mmol/L	1.25 mmol/L	1.05 mmol/L
	2.48-4.34 mg/dL	4.21 mg/dL	3.87 mg/dL	3.25 mg/dL
Albumin	35-50 g/L	43 g/L	39 g/L	39 g/L
	3.5-5.0 g/dL	4.3 g/dL	3.9 g/dL	3.9 g/dL
Creatinine	50-100 µmol/L	62 µmol/L	51 µmol/L	55 µmol/L
	566-1131 mg/dL	701 mg/dL	577 mg/dL	622 mg/dL
eGFR	>90 mL/min	90 mL/min	>90 mL/min	>90 mL/min
Alkaline phosphatase	<98 U/L	103 U/L	152 U/L	133 U/L
Bone alkaline phosphatase	<14.3 µg/L	15.8 µg/L		
P1NP	7.5-75.3 ng/mL	32 ng/mL		
β-C-terminal telopeptide	< 1.01 µg/L	0.41 µg/L		
25-OH vitamin D	50-120 nmol/L	76 nmol/L	65 nmol/L	41 nmol/L
	20-48 ng/mL	30.4 ng/mL	26 ng/mL	16.4 ng/mL
TSH	0.56-4.27 mU/L	2.69 mU/L		
DXA scan[a]				
Lumbar spine	T score	− 4.6 SD	− 5.4 SD	− 2.6 SD[b]
	Z score	−3.0 SD	−3.5 SD	−0.6 SD[b]
	BMD	0.643 g/cm^2	0.558 g/cm^2	0.884 g/cm^2[b]
Femur neck, left	T score	− 2.8 SD	− 3.7 SD	− 2.8 SD
	Z score	−1.2 SD	−2.0 SD	−1.1 SD
	BMD	0.645 g/cm^2	0.527 g/cm^2	0.647 g/cm^2
Total hip, left	T score	−2.9 SD	−3.6 SD	−3.2 SD
	Z score	−1.5 SD	−2.1 SD	−1.7 SD
	BMD	0.648 g/cm^2	0.556 g/cm^2	0.599 g/cm^2
Trabecular bone score	T score	−3.8 SD	−4.4 SD	−4.6 SD
	≥ 1.350	1.132	1.081	1.058

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; TSH, thyrotropin.
[a]All DXA scans were performed on the same GE-Lunar Prodigy Advance machine.
[b]Potentially overestimated due to lumbar vertebral fractures.

discontinued because of side effects of malaise; thereafter, she did not use any other antiosteoporotic medication. Except for smoking and a postmenopausal state, there were no secondary causes for osteoporosis. However, her family history revealed that her mother and 3 aunts had osteoporosis and kyphosis (fracture history unknown).

Diagnostic Assessment

A DXA scan at our hospital at referral showed a decreased BMD (LS [L2-L4]: T-score −4.6 SD, FN [left]: T-score −2.8 SD), as well as a decreased trabecular bone score (TBS [L2-L4]: T-score −3.8 SD) (Table 1 and Fig. 1). A spine x-ray showed 3 grade 2 vertebral fractures (T5-T7). Genetic testing, which was performed because of her very severe osteoporosis with multiple vertebral fractures combined with the positive family history, revealed a pathogenic heterozygous variant in *LRP5* (c.1828G > A p.[Gly610Arg]). On ophthalmologic examination there were no signs of osteoporosis-pseudoglioma syndrome (OPPG) or familial exudative retinopathy [8].

Treatment

The patient was started on teriparatide, but after 10 months she discontinued because of side effects of nausea and malaise. We discussed romosozumab with her, but since she had experienced side effects both with alendronate and teriparatide, she opted for a wait-and-see policy without consolidation therapy. Approximately 1 year later her DXA-scan, performed on the same machine, showed a decrease of BMD (LS [L2-L4]: T-score −5.4 SD, FN [left]: T-score −3.7 SD, TBS [L2-L4]: T-score −4.4 SD), and a spine x-ray showed a new grade 2 fracture of lumbar (L) vertebral body L5. Treatment with romosozumab was strongly advised, and subsequently started for 1 year.

Outcome and Follow-up

During treatment, she did not experience any physical trauma nor an episode of new back pain, and she confirmed that she received her monthly romosozumab injections (dose: 210 mg per month). After 1 year of treatment with romosozumab,

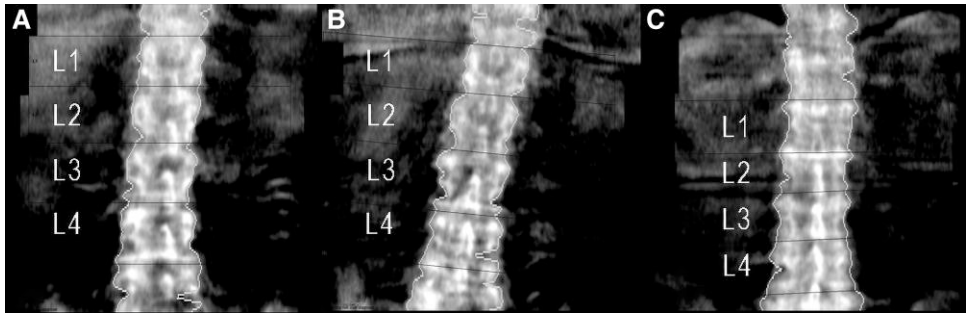

Figure 1. Dual-energy x-ray absorptiometry images of the lumber spine. A, At presentation at our outpatient clinic. B, One month before starting and C, 1 month after finishing 1-year treatment with romosozumab.

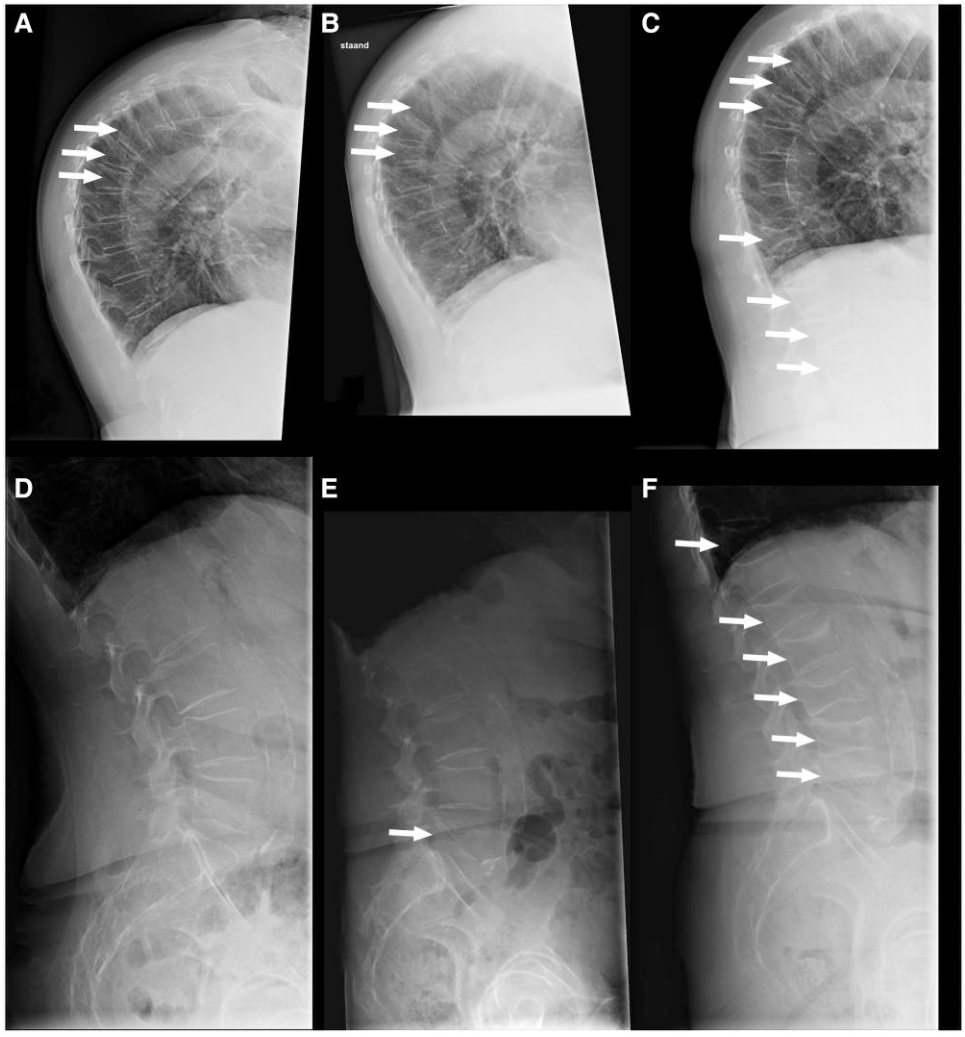

Figure 2. Spine x-rays of the A to C, thoracic and D to F, lumbar spine with arrows indicating the vertebral fractures. A and D, At presentation at our outpatient clinic. B and E, One month before starting and C and F, 1 month after finishing 1-year treatment with romosozumab.

a new DXA scan showed improvement of the BMD, but not of the TBS (LS [L2-L4]: T-score −2.6 SD, FN [left]: T-score −2.8 SD, TBS [L2-L4]: T-score −4.6 SD), while a routine spine x-ray showed 5 new (asymptomatic) vertebral fractures: T11 (grade 3) and L1 to L4 (grade 2) (Fig. 2). Therefore, it is likely that the increase in LS BMD was (partly) due to an overestimation because of the new vertebral fractures. Following completion of treatment with romosozumab, she received one infusion with zoledronate (5 mg) to see whether she could tolerate this. If so, we will suggest switching to denosumab to further increase her BMD.

Discussion

OPPG is a rare autosomal recessive disorder with severe juvenile osteoporosis and congenital blindness, caused by

homozygous loss-of-function variants in the *LRP5* gene [9, 10]. Heterozygous *LRP5* loss of function leads to a less severe phenotype, but can still cause early-onset osteoporosis. *LRP5* variants have been found in 8% to 20% of patients with early-onset osteoporosis [11-13]. In patients with OPPG due to biallelic *LRP5* variants, the response to bisphosphonate treatment is generally good, but not much is known about the treatment responses in those with heterozygous *LRP5* variants [10]. Osteoanabolic treatment with teriparatide showed an increased BMD both in humans and mice harboring *LRP5* loss-of-function variants [14-16], suggesting a treatment response. However, little is known about a treatment effect of romosozumab in patients with loss-of-function *LRP5* variants. On theoretical grounds, romosozumab may be less effective due to an already compromised binding of LRP5/Frizzled, which sclerostin inhibits [6]. However, in *LRP5*-deficient mice, a positive effect of antisclerostin treatment on bone formation, as well as on trabecular and cortical bone mass, has been observed [7].

The patient described in this report, harboring a known pathogenic heterozygous *LRP5* variant, was treated with romosozumab for 1 year because of severe osteoporosis with multiple vertebral fractures, and side effects of earlier bisphosphonate and teriparatide treatment. However, after 1 year of romosozumab, 5 new incident vertebral fractures were detected although her BMD had increased substantially. Recently, Marsman et al [17] described an 83-year-old woman who, during treatment with romosozumab, showed a decrease in BMD of the hip combined with multiple new vertebral fractures without a clear explanation. Unfortunately, it was not reported whether genetic testing was performed in this patient. Furthermore, data from the ARCH and FRAME trials showed that 0.5% to 4.0% of treated patients experienced a new vertebral fracture during treatment with romosozumab, but also here, no data on possible *LRP5* variants were provided [4, 5].

It might be that the progressive vertebral fractures are due to the severe osteoporosis in relation to the start of romosozumab. Further, the BMD (measured on the same machine) increased significantly both at the LS and FN (LS +0.326 g/cm^2 [+58%]; FN [left] + 0.120 g/cm^2 [+23%]), but the BMD at the lumber spine was most likely overestimated because of the new fractures at L1 to L4. On the other hand, the BMD increase of 23% of the FN is larger than would be expected based on the ARCH and FRAME trials, which both showed an increase of around 6% [4, 5]. In contrast, the TBS remained virtually stable after 1 year of treatment with romosozumab (−0.023 [−2%]). Earlier studies on the effect of romosozumab on TBS were mixed showing either a significant increase or no effect [18, 19]. Therefore in our patient, we cannot make conclusions as to whether an absence of an increase in TBS on romosozumab was related to a decreased effect on bone quality due to the presence of a loss-of function *LRP5* variant. At different visits, serum alkaline phosphatase was increased, but at the initial visit this was only minimally (103 U/L; normal range < 98 U/L), and other bone turnover markers were either normal or slightly elevated (see Table 1). This suggests a relationship with either recent vertebral fractures and/or with osteoanabolic treatment, while the presence of osteomalacia is less likely. The initial spine x-ray also revealed calcifications in the abdominal aorta, which over time slightly progressed but remained stable during treatment with romosozumab. Therefore, it is not very likely that these calcifications contributed substantially to the gain in LS BMD. The ARCH trial showed an increase in cardiovascular events with romosozumab compared to alendronate (2.5% vs 1.9%, respectively) [5]. Therefore, according to the US Food and Drug Administration, romosozumab should not be used in case of stroke or myocardial infraction within the last year; the European Medicines Agency advises against use in case of any history of stroke or myocardial infraction. In our patient, we decided for romosozumab treatment because of her severe osteoporosis combined with multiple vertebral fractures, which is known to have a substantial effect on quality of life [20], side effects of alendronate and teriparatide, and the fact that risk factors for the development of cardiovascular diseases are not a contraindication for romosozumab treatment.

In conclusion, we describe the case of a female patient with a pathogenic heterozygous *LRP5* variant having severe osteoporosis with multiple vertebral fractures, who developed 5 new vertebral fractures during 1-year treatment with romosozumab despite a substantial increase in BMD. However, it is unclear whether the progressive vertebral fractures are due to the severe osteoporosis in relation to the start of romosozumab, or whether there is a true diminished antifracture effect of romosozumab caused by the *LRP5* variant. This case suggests that in patients with loss-of-function *LRP5* variants, romosozumab is able to increase BMD, despite the decrease of the LRP5/Frizzled binding that sclerostin inhibits, but it is unclear whether this increase in BMD results in similar fracture prevention as in patients with a normally functioning *LRP-5/6* receptor. Further information is needed on the effect of romosozumab both on BMD and fracture outcomes in other patients with genetic variants in *LRP5* or *LRP6*.

Learning Points

- The canonical Wnt-β-catenin pathway plays an important role in bone homeostasis, and defects in this pathway may lead to (severe) osteoporosis.
- Sclerostin is a key inhibitor of the canonical Wnt-β-catenin pathway by binding to *LRP-5/6*, while romosozumab, a human monoclonal antibody that binds to sclerostin, prevents this inhibitory effect.
- In our patient with a loss-of-function *LRP5* variant, romosozumab was able to increase BMD, despite the decrease of the LRP5/Frizzled binding that sclerostin inhibits. However, it is unclear whether this increase in BMD results in similar fracture prevention as in patients with a normally functioning *LRP-5/6* receptor.

Contributors

E.V.V., M.W., G.M., and M.C.Z. were involved in the analysis and treatment of the patient. E.V.V. wrote the initial draft of the manuscript. All authors reviewed and revised the manuscript to improve its intellectual and technical content.

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References

1. van der Burgh AC, de Keyser CE, Zillikens MC, Stricker BH. The effects of osteoporotic and non-osteoporotic medications on fracture risk and bone mineral density. *Drugs*. 2021;81(16):1831-1858.
2. Marini F, Giusti F, Palmini G, Brandi ML. Role of Wnt signaling and sclerostin in bone and as therapeutic targets in skeletal disorders. *Osteoporos Int*. 2023;34(2):213-238.
3. Appelman-Dijkstra NM, Oei HLDW, Vlug AG, Winter EM. The effect of osteoporosis treatment on bone mass. *Best Pract Res Clin Endocrinol Metab*. 2022;36(2):101623.
4. Cosman F, Crittenden DB, Adachi JD, *et al*. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-1543.
5. Saag KG, Petersen J, Brandi ML, *et al*. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377(15):1417-1427.
6. Stringer F, Sims NA, Sachithanandan N, Aleksova J. Severe osteoporosis with pathogenic LRP5 variant. *JCEM Case Rep*. 2024;2(3):luae021.
7. Kedlaya R, Veera S, Horan DJ, *et al*. Sclerostin inhibition reverses skeletal fragility in an Lrp5-deficient mouse model of OPPG syndrome. *Sci Transl Med*. 2013;5(211):211ra158.
8. Campos-Obando N, Oei L, Hoefsloot LH, *et al*. Osteoporotic vertebral fractures during pregnancy: be aware of a potential underlying genetic cause. *J Clin Endocrinol Metab*. 2014;99(4):1107-1111.
9. Gong Y, Slee RB, Fukai N, *et al*. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell*. 2001;107(4):513-523.
10. Makitie O, Zillikens MC. Early-onset osteoporosis. *Calcif Tissue Int*. 2022;110(5):546-561.
11. Caetano da Silva C, Ricquebourg M, Orcel P, *et al*. More severe phenotype of early-onset osteoporosis associated with recessive form of LRP5 and combination with DKK1 or WNT3A. *Mol Genet Genomic Med*. 2021;9(6):e1681.
12. Sturznickel J, Rolvien T, Delsmann A, *et al*. Clinical phenotype and relevance of LRP5 and LRP6 variants in patients with early-onset osteoporosis (EOOP). *J Bone Miner Res*. 2021;36(2):271-282.
13. Rocca MS, Minervini G, Di Nisio A, *et al*. Identification of rare LRP5 variants in a cohort of males with impaired bone mass. *Int J Mol Sci*. 2021;22(19):10834.
14. Iwaniec UT, Wronski TJ, Liu J, *et al*. PTH stimulates bone formation in mice deficient in Lrp5. *J Bone Miner Res*. 2007;22(3):394-402.
15. Arantes HP, Barros ER, Kunii I, Bilezikian JP, Lazaretti-Castro M. Teriparatide increases bone mineral density in a man with osteoporosis pseudoglioma. *J Bone Miner Res*. 2011;26(12):2823-2826.
16. Homaei A, Chegini V, Saffari F. Clinical response to treatment with teriparatide in an adolescent with osteoporosis-pseudoglioma syndrome (OPPG): a case report. *Int J Endocrinol Metab*. 2022;20(2):e121031.
17. Marsman AF, de Jongh RT, Teunissen BP, Lems WF. Bone loss and new vertebral fractures during treatment with romosozumab: a case-report. *Arch Osteoporos*. 2024;19(1):10.
18. Jeong C, Kim J, Lim Y, Ha J, Kang MI, Baek KH. Effect of romosozumab on trabecular bone score compared to anti-resorptive agents in postmenopausal women with osteoporosis. *J Bone Metab*. 2021;28(4):317-323.
19. Hong N, Shin S, Lee S, Rhee Y. Romosozumab is associated with greater trabecular bone score improvement compared to denosumab in postmenopausal osteoporosis. *Osteoporos Int*. 2023;34(12):2059-2067.
20. Al-Sari UA, Tobias J, Clark E. Health-related quality of life in older people with osteoporotic vertebral fractures: a systematic review and meta-analysis. *Osteoporos Int*. 2016;27(10):2891-2900.