Denosumab Response in Glucocorticoid-Induced Osteoporosis Resistant to Bisphosphonate Therapy in an Adolescent with Childhood Onset Minimal Change Disease

Abstract

Glucocorticoid induced osteoporosis is difficult to treat in patients with nephrotic syndrome. The efficacy and safety of denosumab in pediatric population is unknown. We report the successful use of denosumab in a child who was non responsive to conventional measures and bisphosphonates.

Keywords: *Denosumab, Nephrotic syndrome, Biphosphonates*

Introduction

Children with nephrotic syndrome (NS) are usually treated with steroids[1] and are risk of side effects.[2] Glucocorticoid-induced osteoporosis (GIOP) is one of the most dreaded complications of long-term steroids. Treatment for GIOP poses a challenge, especially in the pediatric population.

Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand (RANKL). Glucocorticoids are known to alter the expression of both RANKL and osteoprotegrin. Preclinical data suggests the use of this monoclonal antibody in GIOP. However, even though safe in adult population, there are potential safety considerations and sparse data to guide its use in children and adolescents.[3] Its safety and efficacy for GIO in pediatric population is yet to be explored comprehensively, and remains undocumented in children with NS.

Case Report

We report a 16-year-old boy diagnosed with NS at the age of 2.5 years. He was steroid responsive initially and achieved complete remission (CR) but had frequent relapses (FR), and needed multiple courses of steroids for frequently relapsing nephrotic syndrome (FRNS). Later on, he developed secondary steroid-resistance and was deemed steroid nonresponder at four years of age. Native kidney biopsy was done in view of steroid resistance. Renal biopsy findings were consistent with minimal change disease. He was subsequently treated with steroids and tacrolimus at 0.1 mg/kg in two divided doses for six months. He achieved only partial remission. Therefore, mycophenolate mofetil (MMF) was added along with CNI. He remained on dual therapy till he was ten years old along with intermittent courses of steroids. Repeat biopsy was performed for creeping rise in serum creatinine that showed histological changes consistent with CNI toxicity. Treatment was changed to to rituximab and MMF. He has been in clinical remission for the last four years.

He developed multiple treatment-related complications inlcuding posterior capsular cataract, short stature, cushingoid facies, and abdominal striae. On screening for GIOP, his bone mineral density (BMD) was found to be reduced (Z score = −2.9, significantly lower than normal limit for age and sex) on a DEXA scan of the spine (L1–L4). Calcium and vitamin D supplementation was commenced as an adjunctive supportive therapy. He was given a single dose of zoledronate (4 mg) in March 2022, to which he developed an infusion reaction. A repeat DEXA scan in September 2022 showed no significant improvement in BMD (Z score = −1.5, significantly lower than normal for age and sex). In view of the infusion reaction to bisphosphonates (BPN), he was administered with three doses of denosumab 60 mg subcutaneous in September 2022, March 2023, and September 2023. Serial BMD assessments over last one year have shown improvement.

Discussion

To the best of our knowledge, we report the first Indian case of efficacy of denosumab in GIO for INS. The efficacy and safety of denosumab in GIOP can be assessed from the randomized controlled trial (RCT) by Saag *et al.*[4] in adult population, where the drug is compared with risedronate in GIOP. However, they had not specially addressed pediatric patients with glomerular disease. In another RCT,[5] denosumab was compared to alendronate in GIO with glomerular disorder, and was found superior in increasing BMD. However, the pediatric population was excluded in the study. The overwhelming response to denosumab in GIO in adult population prompted us to use the drug in our patient. Over the first few years of FRNS, the child had received multiple courses of steroids for inducing remission. Loss of vitamin D binding globulin due to persistent nephrotic state contributes to osteoporosis. In view of the prolonged and repeated course of steroids, the possibility of GIOP remains high. Furthermore, the child had several other steroid-related side effects.

The role of BPN in management of GIO in INS is controversial. BPN (such as pamidronate) have causal association with focal segmental glomerulosclerosis (FSGS). For the trial of BPN, zoledronic acid was attempted in this case. However, the child developed infusion reaction. The lack of significant improvement in BMD at six months led us to consider denosumab, a monoclonal antibody against RANKL. We also want to highlight that there were

no serious adverse effects reported in follow-up by the patient.

We hope that this report encourages the use of denosumab in GIOP, and pediatricians and pediatric nephrologists should consider this drug in their armamentarium for GIOP. This report also highlights the suggestion of screening for GIOP in children with FRNS, steroid-dependent NS, and steroid-resistant NS.[6]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Gulati S, Chauhan S. Denosumab Response in Glucocorticoid-Induced Osteoporosis Resistant to Bisphosphonate Therapy in an Adolescent with Childhood Onset Minimal Change Disease. Indian J Nephrol. doi: 10.25259/IJN_474_2024

Received: 18-08-2024; **Accepted:** 11-09-2024; **Online First:** 25-10-2024; **Published:** ***

DOI: 10.25259/IJN_474_2024