

Case Report

Successful renal transplantation in Muckle–Wells syndrome treated with anti-IL-1 β -monoclonal antibody

Birgit Kortus-Götze and Joachim Hoyer

Department of Internal Medicine, Division of Nephrology, University Hospital of Giessen and Marburg, Marburg, Germany

Correspondence and offprint requests to: Birgit Kortus-Götze; E-mail: Kortusgo@med.uni-marburg.de

Abstract

We report the first case of a 32-year-old woman with Muckle–Wells syndrome and biopsy-proven systemic AA amyloidosis and end-stage renal disease. She was treated with canakinumab 150 mg subcutaneously every 8 weeks and underwent renal transplantation. Fourteen months after renal transplantation, the patient had no flares of Muckle–Wells syndrome and no evidence of amyloidosis in the renal transplant under an excellent graft function and therapy with canakinumab.

Keywords: amyloidosis; canakinumab; Muckle–Wells syndrome; renal transplantation

Background

The Muckle–Wells syndrome (MWS) is assigned to the family of periodic fever syndromes and belongs to the sub-group of the cryopyrin-associated periodic syndromes (CAPS).

It causes recurrent fever attacks, urticarial rash, myalgia, arthralgia, headache, sensorineural deafness and severe fatigue syndrome. MWS is an autosomal-dominant-inherited disease, which is caused by a mutation of the CIAS1 gene on chromosome 1q44 [1], leading to a permanent and excessive activation of the interleukin (IL)-1 receptor. So far, there have been >50 heterozygous mutations reported [2] leading to different phenotypes, i.e. different clinical manifestations of MWS [3]. The exact incidence of the CAPS is unknown. In the literature, there are currently ~100 case reports [4]. However, it is understood that the prevalence is higher than currently assumed [5].

The prognosis of MWS is determined by the development of systemic AA amyloidosis, especially renal amyloidosis with severe renal impairment up to end-stage renal disease. But, only little is known about the treatment of patients with MWS and renal impairment. Over decades, treatment has been ineffective due to a lack of specific drugs. Recently, new therapeutic strategies are targeting the IL-1 receptor and IL-1 β directly.

There are few case reports about successful treatment with anakinra, an IL-1 receptor antagonist, before and after

renal transplantation [6, 7]. In 2009 canakinumab, a human anti-IL-1 β -monoclonal antibody was approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of MWS.

Case report

A 32-year-old woman with MWS and systemic amyloidosis underwent renal transplantation in 2010 after 7 years of being on haemodialysis.

In detail, the patient developed all of the typical symptoms of MWS, starting in her earliest childhood. The diagnosis of MWS was made by the detection of a mutation in the CIAS1 gene on chromosome 1q44 Exon 3 with the variant R260W when the patient was 27 years old.

Her grandmother and mother died of sudden cardiac death due to systemic amyloidosis and end-stage renal disease. The brother, the aunt, three uncles and two cousins are also affected by MWS, three of them with renal impairment as well.

A renal biopsy confirmed the diagnosis of renal AA amyloidosis in 2001. Furthermore, a cardiac amyloidosis was found on MRI as well as a biopsy-proven AA amyloidosis in the adipose tissue and thyroid gland. Due to rapid progression of renal amyloidosis, the patient developed renal impairment with beginning haemodialysis in 2002. The orthotopic amyloid kidneys were anuric since 2005.

From 1995 to 2006, the patient was treated symptomatically with colchicine without any success. In 2006, the therapy with anakinra at a dosage of 100 mg subcutaneously every other day was started and showed a very good clinical and biochemical response. The important inflammatory markers C-reactive protein and serum amyloid decreased within 2 weeks to normal levels. Thereafter, the specific therapy was switched to canakinumab 150 mg subcutaneously once every 8 weeks because of better pharmacokinetic features and persistent suppression of IL-1 β with a sustained remarkable response of clinical symptoms and inflammatory markers.

In February 2010, our patient received a cadaveric kidney transplant. The initial immunosuppressive therapy consisted of cyclosporine A, mycophenolate mofetil and prednisolone. Immediately after renal transplantation, the patient had a very

good graft function. The creatinine decreased to 121 $\mu\text{mol/L}$ and the creatinine clearance increased to 48 mL/min at the time of discharge from our hospital 1 month after kidney transplantation. The patient was free of any rejection episodes. The therapy with canakinumab has been continued with the same dosage after renal transplantation with no flares of MWS despite improved renal clearance. No severe bacterial or viral infections or any other adverse events have occurred up to now. Fortunately, we did not observe any pharmacological interactions between canakinumab and the immunosuppressive therapy. A renal biopsy was performed 14 months after renal transplantation. No sign of amyloid deposition was found in the transplanted kidney at this time. One and half years after renal transplantation, the patient has an excellent graft function with a creatinine of 86 $\mu\text{mol/L}$ and a creatinine clearance of 75 mL/min. Furthermore, the patient has no proteinuria.

Discussion

The anti-IL-1 β -monoclonal antibody canakinumab has been recently introduced as a specific treatment option in patients with MWS with normal and impaired renal function. Lachmann *et al.* [8] reported about the successful treatment with canakinumab once every 8 weeks in patients with CAPS.

Little is known about the feasibility of renal transplantation in MWS patients and its impact on MWS activity under a specific treatment. As shown in our patient, we believe that under the immunomodulatory effect of canakinumab with direct and highly specific blockade of IL-1 β , there is no interference with the immunosuppressive therapy after renal transplantation. So far, the immunological challenge after renal transplantation and the triple immunosuppressive therapy had no negative impact on activity of MWS in our patient. It can be postulated that canakinumab can be used with a very good clinical response in patient with normal renal function as well as in patients with renal replacement therapy, either haemodialysis or renal transplantation.

In the future, the growing experience with canakinumab in the treatment of patients with MWS will demonstrate whether it is possible to prevent under the therapy the development of AA amyloidosis as a severe and life-threatening

complication of MWS with canakinumab treatment. In the case of our patient, we have had no recurrence of AA amyloidosis in the kidney transplant at the present time. The limitation is that the observation period of one and a half years is very short. Further evaluations will be performed in order to confirm the positive effect of canakinumab.

In our opinion, treatment with the anti-IL-1 β -monoclonal antibody canakinumab in patients with MWS and renal replacement therapy is feasible, safe and without severe side effects.

Conflict of interest statement. Both authors participated in previous clinical trials with canakinumab NCT00487708 and NCT0068537 and participate in the ongoing trial NCT0068537. The authors report receiving no consulting payment and there are no conflicts of interests.

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Received for publication: 11.8.11; Accepted in revised form: 22.8.11