Case Report

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Successful Pregnancy in a Patient with IgA Nephropathy Treated with Telitacicept: A Case Report and Literature Review

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1. Abstract

IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritis, with complex pathogenic mechanisms involving abnormal B cell activation. As a novel biologic agent, Telitacicept inhibits both B-lymphocyte stimulator and a proliferation-inducing ligand, can reduce B cell-mediated autoimmune responses, suppressing the production of galactose-deficient IgA1 and thereby inducing disease remission. Women with IgAN are at a higher risk of adverse pregnancy outcomes such as preeclampsia and miscarriage, especially those with uncontrolled massive proteinuria and advanced chronic kidney disease. Therefore, IgAN disease control before and during pregnancy is essential. We report the case of a female patient who was effectively treated with Telitacicept and subsequently successfully conceived. This case report also reviews the characteristics and outcomes of pregnancy in patients with IgAN and explores the value of Telitacicept in women of childbearing age, suggesting effective and safe treatment options for women who wish to conceive.

2. Keywords:
Case report, IgA nephropathy, pregnancy, Telitacicept, long-lived plasma cells

3. Introduction

IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide. Its occurrence is closely related to autoimmune mechanisms, as abnormally activated B lymphocytes play a key role in disease onset and progression. B cell activation leads to the release of galactose-deficient IgA1 (Gd-IgA1), a crucial step in the development of IgAN(Chang and Li 2020). Elevated levels of circulating Gd-IgA1 and autoantibodies against it are associated with increased risk of disease progression(Cheungpasitporn et al. 2019). Currently, specific treatments for IgAN are lacking; targeting B cell activation to reduce Gd-IgA1 production may offer a new therapeutic approach. The incidence of IgAN in women is highest in those of reproductive age. Pregnant women with IgAN have a greater risk of adverse pregnancy outcomes, including miscarriage, a low birth weight infant, and preeclampsia than those without. Previous studies have suggested that proteinuria levels and chronic kidney disease (CKD) stage during pregnancy are closely related to adverse pregnancy outcomes(Liu et al. 2016). Therefore, stabilizing proteinuria and kidney function during pregnancy may reduce the risk of complications in women with IgAN. Telitacicept is a novel recombinant fusion protein consisting of the extracellular soluble portion of transmembrane activator and calcium modulator and cyclophilin ligand interactor receptor fused to the Fc portion of human IgG. It binds to and inhibits B-lymphocyte stimulator (BLyS/BAFF) and a proliferation-inducing ligand (APRIL)(Dhillon 2021), thus targeting two components of the B cell-mediated autoimmune response. This leads to inhibition of Gd-IgA1 production and suppression of disease activity and progression.

4. Case Presentation

A 32-year-old female was found to have 3+ urinary protein levels seven years prior to presentation, but no specific treatment was administered. A follow-up examination three years ago revealed 3+ urinary protein levels, 3+ urinary blood levels, and serum creatinine levels of 90 μmol/L. The outpatient physician prescribed the maximum tolerated dose of the renin-angiotensin-aldosterone system (RAAS) inhibitor valsartan (150 mg orally once a day). The patient was not seen again until September 2021, when she was hospitalized owing to proteinuria and hematuria. Laboratory analysis revealed serum creatinine levels of 93 μmol/L, an estimated glomerular filtration rate (eGFR) of 71.3 mL/min, 3+ urinary blood levels, and 3+ urinary protein levels. The patient's blood pressure was normal

and renal ultrasonography revealed no abnormalities. The patient had a history of pulmonary tuberculosis aged 15 years; however, chest CT during hospitalization showed no disease activity. Based on these results, a renal biopsy was performed, with the following immunofluorescence findings: IgA (++), IgM (-), IgG (+-), C3 (++), and C4 (-). Light microscopy revealed 23 intact glomeruli, 3 globally sclerosed glomeruli, 1 cellular crescent, and 1 small cellular crescent, all with segmental sclerosis, and 2 adhesions. Diffuse mild-to-moderate mesangial cell proliferation, severe focal segmental proliferation, increased mesangial matrix, and proliferation of endothelial cells in the segmental loop were observed. Focal tubular epithelial cell granulation, vacuolar degeneration, and atrophy, as well as protein casts, were visible. Interstitial fibrosis and inflammatory cell infiltration were observed. A few small arteries showed slight thickening of the vessel wall. Eosinophilic deposits were also observed in the mesangial area. The pathological diagnosis was IgAN (Lee classification, grade 3; Oxford classification, M1E1S1T0) (Figure 1).

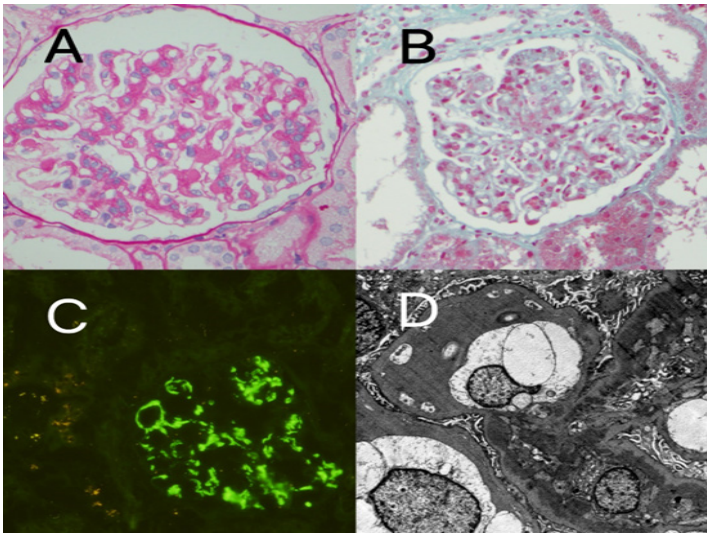

Figure 1: Pathological analysis of the renal biopsy tissue.
A Light microscopy with periodic acid-Schiff staining (magnification, ×400).
B Light microscopy with Masson's trichrome staining (magnification, ×400).
C IgA immunofluorescence microscopy (magnification, ×400).
D Electron microscopy (magnification, ×6000).

The patient was prescribed oral prednisone acetate (50 mg/day). In October 2021, the patient visited the outpatient clinic again, with an increased serum creatinine level (126 μmol/L), a 24-hour urinary protein level of 4.67 g, a urinary erythrocyte level of 1274/μL, urinary leukocytes (+), increased white blood cell counts in peripheral blood, and an elevated neutrophil percentage, indicating urinary tract infection. The patient was readmitted to hospital; changes in renal function and urine are presented in Table 1.

Table 1: Blood routine, renal function, and urinalysis results upon admission

Urinalysis parameter	Result	Reference range
WBC	10.9*109	3.5-9.5*109
GR% granulocyte	88.8	40.0-75.0
Creatinine	124	41-73
24-h urinary protein	4.67 g	0.0–0.15
Occult blood	3+	
LEU	1+	
Protein	3+	
Red blood cell count	1274/μL	0.0–17.6
Red blood cells per HPF	86	0.0–3.0

5. Treatment Course

Upon admission, the patient received antibiotics to control the infection, following which urine and renal function was re-examined. Urinary protein levels had decreased from 4.67 to 2.02 g, urinary erythrocyte levels had decreased from 1274 to 505/μL, while serum creatinine levels remained relatively stable. This indicated that treatment with valsartan and steroids had been ineffective. The patient expressed a strong desire to conceive and therefore hoped that the disease could be controlled as quickly as possible. On October 18, 2021, treatment with steroids combined with Telitacicept (subcutaneous injection once a week) was initiated, and the patient was advised to attend regular outpatient follow-up appointments. The patient's proteinuria, hematuria, and creatinine levels decreased significantly after one week, and since then, her 24-hour proteinuria has remained stable at less than 0.5 g. We adjusted the dosage of steroids and Telitacicept according to the patient's condition. Following successful reduction of the dose of prednisone acetate to 10 mg, the dosage was slowly tapered to 0. The treatment course is presented in Figure 2.

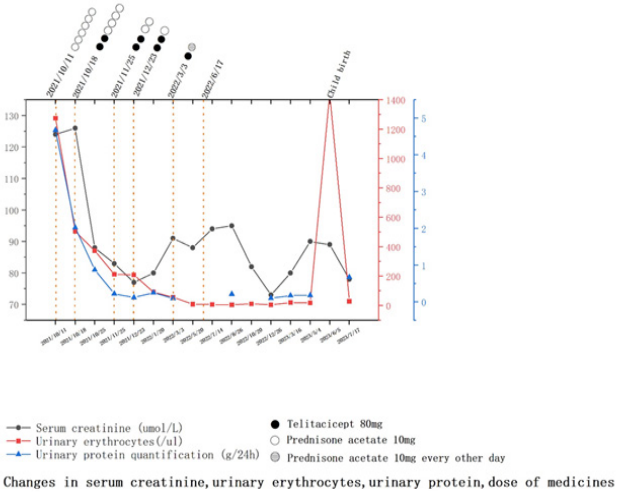

Figure 2: Changes in serum creatinine, urinary erythrocytes, and urinary protein levels, and medications administered.

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The patient did not undergo quantitative urine protein testing on 05/20/2022, 07/14/2022, 10/20/2022, or 06/5/2023 because routine urinalysis suggested only trace amounts of protein were present. The patient had elevated urinary erythrocyte levels on 06/05/2023, which were considered to be labor-related.

In early June 2022, the patient stated that she planned to become pregnant because of her stable condition. She received her last dose of Telitacicept on June 17, 2022, at which time prednisone acetate was also discontinued; in accordance with the manufacturer's guidelines, we recommended that the patient wait four months from the date of Telitacicept discontinuation before attempting to become pregnant. However, the patient became pregnant only three months after drug discontinuation, and on June 5, 2023, delivered a healthy baby boy with Apgar scores of 9 at 1 minute and 10 at 5 minutes. The patient's last follow-up was on July 17, 2023, with a 24-hour urinary protein level of 0.67 g and a serum creatinine level of 78 μmol/L; urinary erythrocyte levels were not measured. The patient did not relapse following discontinuation of drug treatment, indicating significant disease control. Our research center is conducting a study on Elabela combined with Bayesian Stochastic Modelling in assessing the prognosis of IgAN(The Second Hospital of Jilin University, No. 2022LC116). We evaluated patients with this model and found that the prognosis of the disease was significantly improved with the application of Telitacicept.

6. Discussion

In the present case, the patient did not achieve complete remission after treatment with valsartan, and experienced urinary tract infection after oral corticosteroid treatment. However, when treatment with Telitacicept was introduced, proteinuria, hematuria, and serum creatinine levels significantly decreased within a short period, and successful conception was achieved after drug discontinuation. No disease relapse occurred during the pregnancy; sustained remission of IgAN was achieved. This provides a new treatment approach for women who wish to become pregnant, as it may cause rapid improvement of the disease and therefore reduce the risk of adverse pregnancy outcomes. IgAN is the most common cause of primary glomerulonephritis globally, with up to 40% of patients with IgAN progressing to end-stage kidney disease within 20 years(Floege and Barratt 2021). There is a lack of specific therapeutic drugs targeting IgAN, and supportive treatment is mainly adopted in clinical practice. For patients with persistent proteinuria (>0.75–1 g/day) despite three months of optimized treatment, steroid therapy is recommended. However, the efficacy of steroid and conventional immunosuppressive therapy in patients with IgAN remains controversial. The STOP-IgA study demonstrated that immunosuppressive regimens did not significantly improve disease prognosis compared to supportive treatment but led to more adverse reactions(Rauen et al. 2015). A recent study in patients with IgAN showed that although rituximab therapy depleted B cells, the serum levels of Gd-IgA1 and autoantibodies against it, which increase with the risk of disease progression, did not decrease(Lafayette et al. 2017). Although the pathogenesis of IgAN remains unclear, targeting Gd-IgA1 production and autoantibody formation may offer a new direction for IgAN treatment.

Clinical case–control studies have shown that serum BLyS/BAFF levels in patients with IgAN are positively correlated with mesangial IgA deposition density and serum IgA1 levels, indicating that increased BLyS/BAFF levels induce excessive IgA1 production and promote disease progression(Li et al. 2014). BLyS/BAFF transgenic mice exhibit increased serum IgA levels and glomerular IgA deposition, suggesting the possible involvement of BLyS/BAFF in IgAN pathogenesis(McCarthy et al. 2011). Kim et al. reported that antibody-targeting of APRIL resulted in decreased proteinuria, serum IgA levels, and glomerular IgA deposition in a mouse model of IgAN(Kim et al. 2015). Additionally, Muto et al. reported that APRIL expression was significantly increased in the tonsils of patients with IgAN; patients with APRIL overexpression responded well to tonsillectomy, which reduced serum Gd-IgA1 levels, confirming the involvement of APRIL in IgAN progression(Muto et al. 2017). Through dual-target inhibition of BLyS/BAFF and APRIL, Telitacicept interferes with B cell maturation, differentiation, and function, reduces IgA1 and Gd-IgA1 production, inhibits the formation of anti-Gd-IgA1 autoantibodies, reduces immune complex deposition in the glomerular mesangial area, and slows the progression of IgAN. A phase II clinical trial of Telitacicept in patients with IgAN experiencing persistent proteinuria showed that four weeks of treatment with 240 mg/week Telitacicept decreased 24-hour urinary protein levels 49% from baseline levels; 160 mg/week Telitacicept treatment caused a 25% decrease. Telitacicept treatment at either dose resulted in a significant increase in the eGFR, and a decrease in serum IgA, IgG, and IgM levels, compared with placebo(Lv et al. 2023). Telitacicept is currently approved for the treatment of systemic lupus erythematosus (SLE) in China(Shi et al. 2021). Its potential use in rheumatoid arthritis, multiple sclerosis, myasthenia gravis, and Sjögren's syndrome is also under investigation(Ding et al. 2021, Fan et al. 2022). Clinical trials, although still ongoing, have demonstrated the potential of this drug for treating B cell-mediated autoimmune diseases.

Treatment of IgAN is challenging in women of childbearing age; this is also the age at which it most frequently occurs. Previous research has focused mainly on the impact of pregnancy on kidney function, with little investigation into adverse pregnancy events in patients with IgAN. A recent large meta-analysis found no significant differences in kidney outcomes between pregnant and non-pregnant women with IgAN. However, a higher incidence of adverse pregnancy outcomes has been observed in patients with IgAN, even those with preserved kidney function. An analysis of 820 pregnancies in 557 women revealed that 88.3% resulted in live births, 14.2% in preterm births, 13.1% in low birth weight infants, 8.6% in preeclampsia, and 49.1% in cesarean sections(Wang et al. 2019). A prospective cohort study by Liu et al. suggested that elevated levels of proteinuria during pregnancy may be a significant risk factor for adverse pregnancy outcomes in women with IgAN(Liu et al. 2016). A study by Dvořák et al. in pregnant women with CKD found that higher pre-pregnancy creatinine and proteinuria levels were associated with shorter

pregnancies and lower birth weight infants; analysis of lupus nephritis and IgAN subgroups revealed that this association was more pronounced in patients with IgAN(Dvořák et al. 2021). A retrospective study by Suetsugu et al. revealed a close association between the histological severity of kidney disease, urinary protein levels, renal function, and the occurrence of preeclampsia(Suetsugu et al. 2011). Piccoli et al. reported a significant increase in the risk of preeclampsia in patients with IgAN(Piccoli et al. 2017).

Additionally, excessive proteinuria leads to maternal hypoalbuminemia, which reduces uteroplacental blood flow, resulting in inadequate placental perfusion, compromised fetal oxygenation, limited fetal growth, and perinatal death. Therefore, stabilizing kidney function and reducing urinary protein levels before and during pregnancy are critical. Comprehensive guidelines suggest that pregnancy should be postponed in patients with proteinuria until treatment reduces urinary protein levels to <1 g/24 h for at least six months(Blom et al. 2017, Hladunewich et al. 2017, Hladunewich et al. 2016). Pregnancies in patients with CKD stage 3 or higher have a greater risk of adverse outcomes and should be considered on a case-by-case basis(Cabiddu et al. 2016, de Jong et al. 2022). However, few drugs have been proven safe for use in pregnancy. Discontinuation of drugs that treat IgAN, such as RAAS inhibitors, is recommended before and in the early stages of pregnancy because of the risk of severe congenital defects and oligohydramnios. Drugs including cyclophosphamide, mycophenolate mofetil, methotrexate, azathioprine, and leflunomide are known teratogens, and their use should be discontinued for at least 3–6 months before conception(Cabiddu et al. 2016, de Jong et al. 2022). The use of rituximab during pregnancy remains controversial because it can cross the placenta and potentially reduce the number of fetal B cells in the late stages of pregnancy(Chakravarty et al. 2011). Immunosuppressants considered safe during pregnancy include glucocorticoids, hydroxychloroquine, azathioprine, and calcineurin inhibitors. However, these drugs have significant limitations such as low complete remission rates, long treatment cycles, and potential infection or teratogenic risks. Additionally, immune-mediated kidney disease may recur during or after pregnancy. Therefore, there is a need for a drug that can achieve significant disease remission before pregnancy, allows patients to conceive during remission, and maintains clinical remission during pregnancy.

An increasing body of research indicates that long-lived plasma cells (LLPCs) play a crucial role in the chronicity, refractoriness, and recurrence of autoimmune diseases(Chang et al. 2019, Hiepe et al. 2011). Unlike short-lived plasmablasts, LLPCs do not respond to conventional immunotherapy or targeted B cell therapy. The CD20 antibody rituximab targets the early stages of B cell genesis, indirectly reducing the numbers of plasmablasts and short-lived plasma cells; however, its effect on LLPCs is limited. This may explain why Gd-IgA1 levels and the levels of autoantibodies against it do not decrease significantly after rituximab treatment(Lafayette et al. 2017). LLPCs, especially those in the bone marrow, are independent components of immune memory and as such can sustain chronic inflammation through the continuous production of antibodies without requiring antigen stimulation or help from B or T cells(Hiepe and Radbruch 2016). Reports suggest that the survival time of LLPCs depends on the bone marrow microenvironment rather than on intrinsic cellular characteristics. In addition, contact with bone marrow stromal cells that provide signals necessary for long-term survival is dependent on BLyS/BAFF or APRIL (Cornelis et al. 2021). However, several studies have shown the redundancy of BLyS/BAFF and APRIL; blocking both cytokines is therefore necessary to impair LLPC survival(Benson et al. 2008, Cornelis et al. 2021). Ingold et al. reported that inhibiting both BLyS/BAFF and APRIL also prevented the formation of new bone marrow plasma cells after immunization(Ingold et al. 2005). These findings suggest that either BLyS/BAFF or APRIL is required for the survival of both newly formed plasma cells and LLPCs. As an inhibitor of both BLyS/BAFF and APRIL, Telitacicept may achieve long-term disease control and clinical stability, and delay disease progression, by affecting the survival of LLPCs.

In terms of safety and tolerability, Telitacicept is metabolized by cells rather than by the liver and kidneys, and is associated with fewer side effects than conventional drugs(Dhillon 2021). In a phase II study of Telitacicept for the treatment of IgAN, there was no significant difference in the occurrence of adverse reactions between the Telitacicept and placebo groups; all adverse reactions were mild-to-moderate(Lv et al. 2023). In a phase III clinical study of Telitacicept for the treatment of SLE in China, the incidence of adverse events was similar between the Telitacicept and placebo groups, and the incidence of serious adverse events was lower in the Telitacicept group than that in the placebo group32. The most common adverse events were infections and injection site adverse reactions. Our research center is also conducting an observational study on the safety and efficacy of Telitacicept for the treatment of IgAN (The Second Hospital of Jilin University, No. 2023YX0070). In addition, Telitacicept has shown a favorable safety profile in clinical trials for the treatment of rheumatoid arthritis, Sjögren's syndrome, and myasthenia gravis(Ding et al. 2021, Fan et al. 2022). No clinical trials have been conducted to examine the effects of maternal and neonatal exposure to Telitacicept in pregnant women during pregnancy; therefore, we recommend that Telitacicept is not taken during pregnancy unless the benefits outweigh the risks. A Phase IIb clinical trial in patients with SLE treated with Telitacicept reported 11 pregnancies in the Telitacicept-treated group and none in the placebo group, with 1 pregnancy progressing to term and the remaining 10 women opting for termination(Wu 2019, October). Further data are needed regarding the effect of Telitacicept on pregnancy outcomes, especially because IgAN predominantly affects women of childbearing age.

7. Conclusions

The patient in our case achieved rapid improvement with Telitacicept treatment, successfully conceived three months after Telitacicept discontinuation, and achieved long-term disease remission. Telitacicept may be a potential treatment option for women with IgAN who want to

become pregnant, providing rapid disease remission before pregnancy and maintaining this remission during pregnancy, thereby reducing the risk of adverse pregnancy events resulting from disease progression or recurrence. This offers a potential therapeutic option for patients who wish to conceive; however, further research is required to confirm this finding.

7.1. Author Contributions

Xinru Du and Geng Tian contributed to manuscript writing, data collection and data analysis. Xinyu Gao contributed to histopathological assessment and manuscript editing. Xuehong Lu contributed to study design and manuscript editing. All authors have read and agreed to the published version of the manuscript.

7.2. Ethics approval

The study was approved by the Ethics Committee of The Second Hospital of Jilin University (No. 2021174) and adhered to the Declaration of Helsinki.

7.3. Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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