

First report of membranous nephropathy and systemic lupus erythematosus associated with abatacept in rheumatoid arthritis

Sirs,

Abatacept is a soluble fusion protein that consists of the extracellular domain of human CTLA-4 linked to IgG1, which selectively modulates the CD80/CD86:CD28 costimulatory signal.

Treatment with abatacept is efficacious in patients with rheumatoid arthritis (RA) (1) and overlap syndrome between RA and systemic lupus erythematosus (SLE) (2). Moreover, abatacept treatment has been explored for its efficacy in lupus nephritis and primary glomerulonephritis (3, 4).

However, here we described the first case of a patient with RA who developed membranous nephropathy (MN) and SLE after treatment with abatacept.

A 60-year-old Asian woman with an 11-year history of disabling seropositive RA had been previously unsuccessfully treated with bucillamin and sulfasalazine. She also had Sjögren's syndrome (SS) and primary biliary cirrhosis (PBC), but was on a stable course. Other past history included type 2 diabetes mellitus, bronchiolitis and lumbar canal stenosis. She also had a prior infection with human hepatitis B virus (HBV), but HBV-DNA in sera repeatedly tested negative.

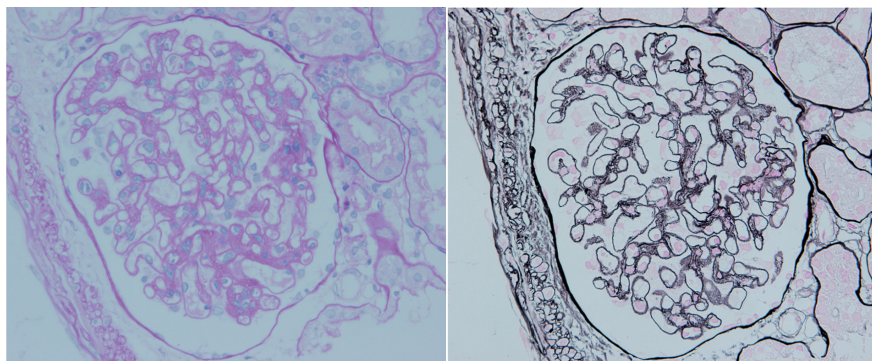
At the age of 59, abatacept was started with informed consent of the patient. At the start of abatacept treatment, ANA titer was 80 IU/ml (normal <80 IU/ml). At month 6, she achieved a moderate response according to EULAR response criteria, nevertheless she still complained of RA symptoms, in which DAS28-ESR was high at 5.31.

After 7 months of abatacept therapy, she exhibited general fatigue and proteinuria. Even after discontinuation of abatacept, she developed significant proteinuria, hypoalbuminaemia, and oedema. She was admitted to our hospital with the diagnosis of nephrotic syndrome.

Laboratory investigations showed the following: ESR of >160 mm/h, lymphopenia, normocytic anemia (Hb 10.6 mg/dl) without autoimmune haemolytic anaemia, elevated CRP (4.44 mg/dl, normal: 0.0-0.3), and low complement levels; urinalysis 4+, hyaline casts, granular casts, waxy casts, no growth; 24 h urine total protein 12.58 g/day, creatinine clearance 85 ml/min.

ANA titer increased to 1:1280, and antibodies to double-stranded (ds) DNA was positive at 20.5 IU/ml (normal: <12.0IU/ml). HBV-DNA was not detected. Chest x-ray and abdominal CT revealed no lesion.

Finally, a diagnosis of SLE was made according to the 1997 ACR revised criteria for classification of SLE.



A.

B.

Fig. 1. Renal histology.

A. Light microscopy showed thickening of glomerular basement membranes in PAS staining. (x 400).

B. Spike formation was observed in the basement membrane in PAM staining. (x 400).

After she started methylprednisolone (0.5g/day for 3 days) with moderate-dose prednisolone (0.8 mg/kg/day) therapy, her proteinuria and other laboratory data, such as low complement levels and lymphopenia improved. The antibodies to dsDNA also disappeared.

She underwent renal biopsy before prednisone treatment, which revealed subepithelial and subendothelial immune deposits on the glomerular basement membrane (GBM) with GBM thickening (Fig. 1A and B). However immunofluorescence analysis showed only the immune deposits of IgM and IgA, but without IgG, C3c, and C1q. The results were incompatible with lupus nephritis but supported other secondary MN due to comorbidity.

Abatacept is generally well tolerated with rare adverse events such as lupus-like syndrome and glomerulonephritis in RA (1). To our knowledge, abatacept might induce mesangial IgA glomerulonephritis in patients with RA (5). In that case report, abatacept was switched after secondary failure of TNF inhibitors, which might be related with disease progression in IgA glomerulonephritis, whereas our patient is bio-naïve RA patient except for abatacept.

Although our patient is characterised by additional complications, such as SS and PBC, which might be associated with secondary MN (6), we found the only efficacy of abatacept in SS (7). According to PBC, the therapeutic effect of CTLA4-Ig was also reported on a murine model (8).

Since a similar case has never been demonstrated before, it is unclear which factor accelerated lupus syndrome and MN in RA. Hence physicians should exercise caution, paying attention to any symptoms associated with SLE and MN during the course of treatment when using abatacept to treat RA patients.

Y. ASAMI, MD, PhD^{1,3}

H. ISHIGURO, MD²

A. UEDA, MD, PhD³

H. NAKAJIMA, MD, PhD³

¹Department of Rheumatology, and

²Department of Nephrology, Yokosuka City Hospital, Japan;

³Department of Haematology and Clinical Immunology, Yokohama City University School of Medicine, Japan.

Address correspondence to:

Dr Yukiko Asami, 3-9 Fukuura, Yokohama, Kanagawa, 236-0004 Japan.

E-mail: daiichinaika2005@yahoo.co.jp

Competing interests: none declared.

References

- BATHON J, ROBLES M, XIMENES A C *et al.*: Sustained disease remission and inhibition of radiographic progression in methotrexate-naïve patients with rheumatoid arthritis and poor prognostic factors treated with abatacept: 2-year outcomes. *Ann Rheum Dis* 2011; 70: 1949-56.
- IKEDA K, SANAYAMA Y, MAKITA S *et al.*: Efficacy of abatacept for arthritis in patients with an overlap syndrome between rheumatoid arthritis and systemic lupus erythematosus. *Clin Dev Immunol* 2013; 2013: 697525.
- ASKANASE AD, BYRON M, KEYES-ELSTEIN LL *et al.*: Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. *Arthritis Rheum* 2014; 66: 3096-104.
- GARIN EH, REISER J, CARA-FUENTES G *et al.*: CTLA4-IgG1 therapy in minimal change disease and focal segmental glomerulosclerosis. *Pediatr Nephrol* 2015; 30: 469-77.
- MICHEL M, HENRI P, VINCENT FB, LEON N, MARCELLI C: Mesangial immunoglobulin (Ig) A glomerulonephritis in a patient with rheumatoid arthritis treated with abatacept. *Joint Bone Spine* 2013; 80: 660-3.
- SINICO RA, MEZZINA N, TREZZI B, GHIGGERI GM, RADICE A: Immunology of membranous nephropathy: from animal models to humans. *Clin Exp Immunol* 2016; 183: 157-65.
- MEINERS PM, VISSINK A, KROESE FGM *et al.*: Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). *Ann Rheum Dis* 2014; 73: 1393-96.
- DHIRAPONG A, YANG GX, NADLER S *et al.*: Therapeutic effect of cytotoxic T lymphocyte antigen 4/immunoglobulin on a murine model of primary biliary cirrhosis. *Hepatology* 2013; 57: 708-15.