Abatacept Improves Intractable Protein-Losing Enteropathy Secondary to AA Amyloidosis in a Patient With Rheumatoid Arthritis

Masato Sawamura, MD, PhD; Naoki Sawa, MD; Hideomi Fujiwara, MD; Masayuki Yamanouchi, MD, PhD; Noriko Hayami, MD, PhD; Akinari Sekine, MD; Hiroki Mizuno, MD; Eiko Hasegawa, MD; Tatsuya Suwabe, MD, PhD; Junichi Hoshino, MD, PhD; Takeshi Fujii, MD, PhD; and Yoshifumi Ubara, MD, PhD

Abstract

A 71-year-old Japanese woman with a history of rheumatoid arthritis of 50 years' duration was admitted to our hospital with refractory diarrhea. Endoscopic biopsy revealed AA amyloid deposition in the large intestine. Although the patient had been prescribed 5 tumor necrosis factor inhibitors over the past 10 years, rheumatoid arthritis was poorly controlled, with a Disease Activity Score 28 using C-reactive protein score of 6.52 on admission. Treatment with tocilizumab (8 mg/kg every 2 weeks) was initiated, but this was ineffective. After 3 months, abatacept (cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin) was initiated (750 mg/mo) and the patient's diarrhea began to improve. After 3 months of abatacept treatment, serum albumin, C-reactive protein, and serum amyloid A levels had all decreased to within normal ranges. After 3 years of abatacept treatment, serum albumin, C-reactive protein, and serum amyloid A levels had all decreased to within normal ranges. Interleukin 6 is a key factor in AA amyloid formation, but this case suggests that T-cell activation increases the production of cytokines (including interleukin 6) via a mechanism involving cytotoxic T-lymphocyte-associated antigen 4, resulting in a second key factor of AA amyloid formation.
but these were also ineffective. At the age of 71 years, the patient tried certolizumab pegol again, but refractory diarrhea occurred (Figure 1).

On admission, the patient, a nonsmoker, was 154 cm tall and weighed 81.8 kg (body mass index, 40 kg/m^2) with a blood pressure of 136/72 mm Hg and a temperature of 36.7°C. Her hands, feet, and ankles were deformed and severely swollen bilaterally, with edema in the lower extremities.

Laboratory findings were as follows: white blood cell count, 10,300/µL(normal range, 3,300-8,600/µL); red blood cell count, 390×10^6/µL(normal range, 386 to 492×10^6/µL); hemoglobin level, 12.5 g/dL(normal range, 11.6 to 14.8 g/dL); total protein level, 2.9 g/dL(normal range, 6.6 to 8.1 g/dL); albumin level, 1.1 g/dL(normal range, 3.0 to 5.1 g/dL); serum urea nitrogen level, 19 mg/dL; serum creatinine level, 0.6 mg/dL(normal range, 0.4 to 0.8 mg/dL); erythrocyte sedimentation rate, 60 mm/h(normal range, 3 to 15 mm/h); C-reactive protein (CRP) level, 1.1 mg/dL(normal range, <0.14 mg/dL); rheumatoid factor, 20 U/mL (normal range, 0 to 15 U/mL); matrix metalloproteinase-3(MMP-3) level, 15 µg/mL(normal range, 4.1-5.1 g/dL); anti-cyclic citrullinated peptide antibody level, 175 U/mL (normal range, <4.5 U/mL); SAA level, 51.3 µg/mL (normal range, <8.0 µg/mL); IgG level, 192 mg/dL (normal range, 861-1,747 mg/dL); IgA level, 87.1 mg/dL (normal range, 93-393 mg/dL); and IgM level, 23.8 mg/dL (normal range, 50 to 269 mg/dL).

Urinary protein excretion was 0.3 g/d, and urinary sediment contained 11 to 30 erythrocytes per high power field.

We performed an endoscopic biopsy of the large intestine. Congo red staining was positive for the thickened walls of small arteries, muscularis mucosae, and surrounding tissues in the subserosal layer and revealed apple green birefringence under polarizing light. Immunohistochemical staining was positive for AA but negative for kappa and lambda chains, β2 microglobulin, and transthyretin (Figure 2A). Protein-losing enteropathy secondary to AA amyloidosis was diagnosed. Because RA was poorly controlled, with a Disease Activity Score 28 using CRP score of 6.52 on admission, we initiated treatment with TCZ (8 mg/kg every 2 weeks). Neither RA disease activity nor intractable diarrhea subsided, and SAA levels increased to 182 µg/mL. After 3 months, TCZ was discontinued after the development of a severe systemic allergic reaction. We then tried ABT (750 mg/mo). Intractable diarrhea began to improve (Figure 1B). After 3 months, serum albumin, CRP, and SAA levels had all normalized. A repeat biopsy of the large intestine 3 years since the initiation of ABT therapy revealed a marked reduction in amyloid deposition (Figure 2B). Cytokines (TNF-α and interleukin [IL] 6) also reflect disease activity and are improved (Figure 1A).

**DISCUSSION**

Gillmore et al\(^3\) reported that when SAA concentrations in the blood were controlled at less than 10 mg/L, amyloid deposits in the organs decreased and the 10-year survival rate was good (~90%), whereas in patients with SAA concentrations 10 mg/L or higher, the 10-year survival rate was approximately 40%. Inhibiting SAA production is therefore the most rational treatment of AA amyloidosis. Treatments of AA amyloidosis involving biologics have recently shown promise.\(^3\) Several studies and case reports\(^4-7\) have suggested that TCZ is useful in treating RA complicated by AA amyloidosis. Okuda et al\(^8\) conducted a nationwide survey of 199 Japanese patients with AA amyloidosis. Biologics were used to treat 97 patients (48.7%): TCZ was administered to 66 patients, with 95.5% exhibiting good responses; anti-TNF agents were administered to 27 patients, with 95.5% exhibiting good responses; and ABT was administered to 27 patients, with 74.1% exhibiting good responses; and ABT was administered to 4 patients, with 75% exhibiting good responses. The efficacy of TCZ was significantly better than that of TNF inhibitors (P=0.007). In addition, Hagiwara et al\(^9\) found that IL-6 is necessary for the synergistic induction of the SAA gene by IL-6, IL-1β, and TNF-α.

Only 1 study\(^10\) to date has examined the effectiveness of ABT for AA amyloidosis refractory to TNF inhibitors with or without TCZ. Nakamura et al reported that ABT was effective against AA amyloidosis secondary to RA in 2 patients. In one patient, refractory diarrhea occurred 5 years after initiating...
FIGURE 1. A, Entire clinical course of the patient. B, Clinical course over the past 3 years. ABT = abatacept; ADA = adalimumab; CRP = C-reactive protein (normal range, <0.14 mg/dL); CZP = certolizumab pegol; ETN = etanercept; GLM = golimumab; IL = interleukin; IL-1β (normal range, <10 pg/mL); IL-6 (normal range, <4.0 pg/mL); INF = infliximab; MTX = methotrexate; SAA = serum amyloid A (normal range, <8.0 μg/mL); sAlb = serum albumin (normal range, 4.1-5.1 g/dL); TNF-α = tumor necrosis factor-α (normal range, 1.5-12.0 pg/mL); TCZ = tocilizumab.
etanercept and endoscopic biopsy revealed AA amyloid deposition in the gastrointestinal tract. After ABT administration, disease activity of RA and diarrhea subsided and amyloid deposition was reduced after 1 year. In the other patient, renal dysfunction and proteinuria occurred and renal biopsy revealed AA amyloid deposition. Etanercept and TCZ were administered sequentially, but renal function continued to decline. After switching
to ABT, proteinuria decreased and renal function deterioration halted. After 2 years, a biopsy of the gastrointestinal tract revealed deposition of AA amyloid equal to that revealed by the first biopsy.9

Abatacept consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4. It inhibits T-lymphocyte activation by selectively binding to CD80 and CD86, thereby blocking interaction with CD28 and suppressing the production of cytokines such as interleukin (IL) 6 and tumor necrosis factor-α (TNF-α). APC = antigen presenting cell; IFN-γ = interferon-gamma; MHC = major histocompatibility complex; RANKL = Receptor activator of nuclear factor kappa-B ligand; SAA = serum amyloid A; TCR = T cell receptor.

CONCLUSION
We encountered a case of AA amyloidosis—related protein-losing enteropathy resulting in diarrhea and hypoalbuminemia, which was refractory to TCZ. Soon after the administration of ABT, diarrhea and hypoalbuminemia subsided. After 3 years, endoscopic biopsy confirmed that amyloid deposition in the large intestine had resolved. The IL-6 receptor antibody derivative TCZ can treat AA amyloidosis by markedly decreasing SAA by blocking IL-6, which may be a key factor in amyloidosis. However, the present case suggests that T-cell activation via a mechanism involving cytotoxic T-lymphocyte—associated antigen 4 increases the production of cytokines including IL-6, resulting in the second key factor of AA amyloid formation (Figure 3).
Abbreviations and Acronyms: ABT = abatacept; CRP = C-reactive protein; IL = interleukin; RA = rheumatoid arthritis; SAA = serum amyloid A; TCZ = tocilizumab; TNF = tumor necrosis factor.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Yoshifumi Ubara, MD, PhD, Nephrology Center, Toranomon Hospital, Kajigaya, 1-3-1, Takatsu, Kawasaki, Kanagawa 212-0015, Japan (ubara@toranomon.gr.jp).

ORCID
Masato Sawamura: https://orcid.org/0000-0002-4763-6124; Noriko Hayami: https://orcid.org/0000-0003-4461-9721; Tatsuya Suwabe: https://orcid.org/0000-0003-0825-2512; Junichi Hoshino: https://orcid.org/0000-0002-0444-101X; Yoshifumi Ubara: https://orcid.org/0000-0003-2322-8203

REFERENCES
1. Jensen LE, Whitehead AS. Regulation of serum amyloid A protein expression during the acute-phase response. Biochem J. 1998;334(pt 3):489-503.
2. Gillmore JD, Lovat LB, Penney MR, Payys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. Lancet. 2001;358(9275):24-29.
3. Okuda Y. AA amyloidosis—benefits and prospects of IL-6 inhibitors. Mod Rheumatol. 2019;29(2):268-274.
4. Hattori Y, Ubara Y, Surriya K, et al. Tocilizumab improves cardiac disease in a hemodialysis patient with AA amyloidosis secondary to rheumatoid arthritis. Amyloid. 2012;19(1):37-40.
5. Courties A, Grateau G, Philippe P, et al. Club Rhumatismes Inflammation and the REGATE Registry. AA amyloidosis treated with tocilizumab: case series and updated literature review. Amyloid. 2015;22(2):84-92.
6. Lane T, Gillmore JD, Wechalekar AD, Hawkins PN, Lachmann HJ. Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature. Clin Exp Rheumatol. 2015;33(6 suppl 94):S46-S53.
7. Okuda Y, Yamada T, Ueda M, Ando Y. First nationwide survey of 199 patients with amyloid A amyloidosis in Japan. Intern Med. 2018;57(23):3351-3355.
8. Haghara K, Nishikawa T, Isobe T, Song J, Sugamata Y, Yoshizaki K. IL-6 plays a critical role in the synergistic induction of human serum amyloid A (SAA) gene when stimulated with proinflammatory cytokines as analyzed with an SAA isofrom real-time quantitative RT-PCR assay system. Biochem Biophys Res Commun. 2004;314(2):363-369.
9. Nakamura T, Kumon Y, Hirata S, Takaoka H. Abatacept may be effective and safe in patients with amyloid A amyloidosis secondary to rheumatoid arthritis. Clin Exp Rheumatol. 2014;32(4):501-508.
10. Adams AB, Ford ML, Larsen CP. Costimulation blockade in autoimmunity and transplantation: the CD28 pathway. J Immunol. 2016;197(6):2045-2050.
11. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001;344(12):907-916.
12. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford). 2012;51(suppl 5):vi3-v11.