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Research Article

Gastric but not Renal Amyloid Deposition is Removed by Biologics Therapy in AA Amyloidosis Patients with Rheumatoid Arthritis

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Abstract

Objectives: Several biologics therapy reportedly regress gastric amyloid deposition in AA amyloidosis patients, but it is uncertain whether they can also regress renal amyloid deposition. We carried out serial renal biopsy to clarify the regression of amyloid deposition in kidney by biologics.

Methods: After the diagnosis of AA amyloidosis was determined by gastric biopsy to rheumatoid arthritis (RA) patients, renal biopsy was carried out. The patients who had inadequate response by conventional oral medicines for RA were treated with tocilizumab or etanercept for more than two years. After biologics treatment, gastric and renal biopsy was carried out.

Results: Six AA amyloidosis patients received biologics and the disease activities of RA were improved significantly. By renal biopsy, four patients were diagnosed with glomerular type and two patients with vascular type. After biologics treatment, amyloid deposition of gastroduodenal tracts was markedly regressed in all six patients. However, amyloid deposition of kidney did not regress significantly in two patients with vascular type whereas four patients with glomerular type could not be carried out renal biopsy due to renal failure.

Conclusions: Amyloid deposition of kidney, unlikely to gastric tract, may not regress significantly in AA amyloidosis patients with RA by biologics therapy.

ABBREVIATIONS

RA: Rheumatoid Arthritis; AA: Amyloid-A; SAA: Serum AA; TNF: Tumor Necrosis Factor; IL-6: |Interleukin 6; DMARDs: Disease Modifying Anti-Rheumatic Drugs; DAS28: 28-joint Disease Activity Score; BUN: Urea nitrogen; CRP: C - reactive protein

INTRODUCTION

Amyloidosis forms a group of diseases characterized by extracellular deposition of proteins in characteristic amyloid fibrils. During fibril formation, elements such as glycosaminoglycans interact with the amyloid protein [1-3], promote the structural-shift process, and favor the deposition of fibrils in these organs. Amyloid deposition leads to organ dysfunction, organ failure, and eventually death [3].

Secondary amyloidosis, which develops secondary to chronic inflammatory conditions such as rheumatoid arthritis (RA), is now called amyloid-A (AA) amyloidosis because a major factor in the protein deposition process involves the precursor protein AA, a cleaved product of the acute phase protein serum AA (SAA) [4-6]. AA amyloidosis occurs in a proportion of patients with chronic inflammatory diseases, including RA, ankylosing spondylitis, juvenile rheumatoid arthritis, and Crohn's disease [7]. Patients with RA represent about 50% of the thousands of patients suffering from AA amyloidosis [7,8]. AA amyloid proteins can be broadly distributed in several vital organs, such as kidneys, heart, and gastrointestinal tract [4], owing to the overproduction of SAA under such inflammatory conditions [9].

Several studies have reported the beneficial effects of combination therapy with corticosteroid and cytotoxic reagents

for AA amyloidosis with RA [10-13], but this condition is often unresponsive to these therapies once organ dysfunctions have become apparent and progressive, leading to end stage renal disease, severe infection, or intractable diarrhea with high mortality rates [4,5,7], suggesting that amyloid fibrils hardly remove once it have deposit in the organ.

However, recent studies have indicated that anti-tumor necrosis factor-α (anti-TNF) or anti-interleukin 6 (anti-IL-6) agents reportedly regress the amyloid deposition in gastrointestinal tract by suppressing the levels of SAA significantly [14-16].

In kidney, however, the regression of amyloid deposition is poorly understood. Because it is generally accepted that in amyloidosis patients renal function retards progressively irrespective of the disease activity [7,17], which makes serial renal biopsy difficult.

We classified renal amyloidosis into two groups, glomerular type and vascular type [17]. In patients with glomerular involvement, renal function deteriorated rapidly regardless of disease state; most patients received hemodialysis within 10 years after diagnosis. In patients with purely vascular involvement, however, renal function did not deteriorate significantly, suggesting that serial renal biopsy can be carried out only in vascular type.

The present study was carried out to clarify whether the amyloid deposition in kidney was regressed by biologics therapy or not. We treated amyloidosis patients with RA by biologics; etanercept or tocilizumab. Etanercept is a fusion protein produced by recombinant DNA which treats autoimmune diseases by interfering with TNF by acting as a TNF inhibitor. Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody that binds both soluble and membrane-expressed IL-6, inhibiting IL-6-mediated pro inflammatory activity. Both biologics have promising effects for RA and reduce joints inflammation, limit erosive damage, decrease disability, and improve quality of life.

PATIENTS AND METHODS

Patients

We examine RA patients who fulfilled the 2010 American College of Rheumatology /European League against Rheumatism classification criteria for RA [18] and were treated at Higashiosaka City General Hospital. After informed consents were obtained, we carried out gastroduodenal biopsy for active RA patients who had inadequate response to conventional disease modifying anti-rheumatic drugs (DMARDs) and the deposition of amyloid was confirmed by the positive green birefringence under polarized light in sections with Congo red staining [19] and anti-AA antibody [20].

At first, the RA patients with AA amyloidosis were treated with low dose methotrexate (4~8mg/week) and 5mg of prednisolone. Six patients who could not have achieved adequate response with methotrexate and prednisolone were treated with tocilizumab infusion (8mg/kg, every 4 weeks) or etanercept injection (25mg, twice a week) to control the disease activity of RA, and the patients who had achieved clinical remission were enrolled in the present study.

Follow-up examination of clinical course

The disease activity of RA was determined by 28-joint Disease Activity Score (DAS28) score and active RA was determined by DAS28 score over 4.0. At the diagnosis of AA amyloidosis, age at onset of RA, disease duration, radiological staging, and drugs taken till were studied in each patient. Radiological staging was based on the criteria by Steinblocker [21].

After the diagnosis of AA amyloidosis, we followed the clinical course of the patients at least for two years. Blood and urine samples were taken occasionally to examine the serum creatinine, urea nitrogen (BUN) and C-reactive protein (CRP) and urinary protein.

Follow-up examination of gastroduodenal and renal biopsy

Gastroduodenal and renal biopsies were carried out before and after two years of biologics treatment and the regression of amyloid deposition in kidney and gastroduodenal tract were compared. We classified renal amyloidosis into two groups, glomerular type and vascular type [17] according to the patterns of amyloid deposition in kidney. In patients with purely vascular involvement, renal function did not deteriorate significantly, which enabled us to re-examine renal biopsies. In the other type of renal amyloidosis, glomerular type, renal biopsy could not be re-examined because renal function deteriorates rapidly.

RESULTS

Classification of renal amyloidosis patients into vascular and glomerular type

We carried out gastroduodenal biopsy for active RA patients who had inadequate response to conventional DMARDs, and ten patients were diagnosed AA amyloidosis. Among them, six patients were eligible for renal biopsy and the renal biopsy was carried out. Amyloid deposition was also found in kidney in all six patients. In two patients amyloid deposition was found selectively around blood vessels (vascular type, Case 1 and 2), and in four patients amyloid deposition was found predominantly in the glomerulus (glomerular type, Case 3-6) as shown in (Figure 1).

Comparison of clinical courses of RA before and after biologics therapy between two groups

At the diagnosis of AA amyloidosis, all patients showed inadequate response to prednisone and methotrexate and the disease activity was high. The mean DAS28 score of glomerular type and vascular type was 4.8 and 4.7 respectively. Other clinical features such as the mean age, disease duration, and radiological stage did not differ significantly as shown in (Table 1).

We prescribed either tocilizumab or etanercept to all six patients and were enrolled in the present study. Four patients were prescribed tocilizumab and two patient's etanercept. After prescribed biologics treatment, all patients achieved clinical remission in less than six months, and the biologics therapy were continued for more than two years. The clinical assessments before and after two years of biologics treatment were summarized in Table 1. DAS28 score of all patients were decreased fewer than 2.6 and the levels of CRP were also decreased, suggesting that the disease activity of RA were well controlled by these biologics.

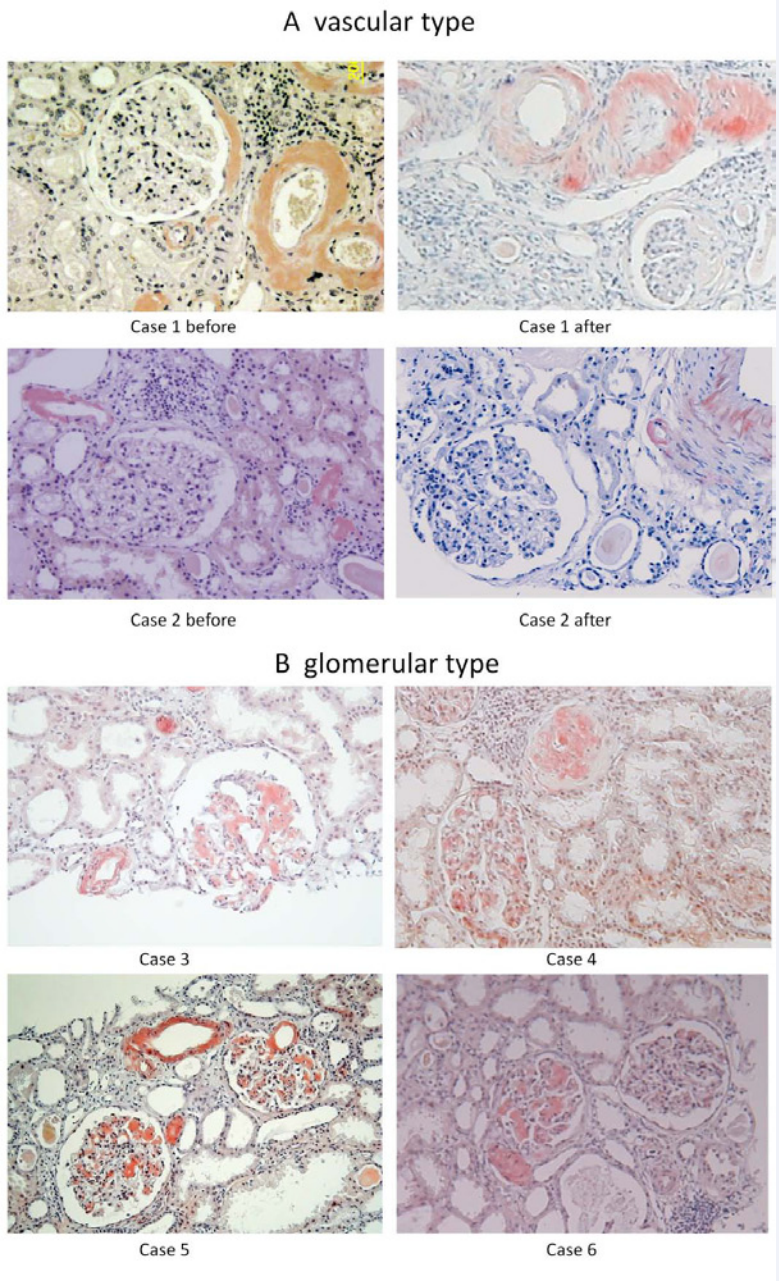

Figure 1 Results of renal biopsy before and after biologics therapy. A, In case 1 and case 2, amyloid deposits were observed selectively around blood vessels. Poor regression of amyloid protein deposits was seen in renal blood vessels after biologics treatment. B, In case 3-6, massive amyloid protein was observed in the glomerulus. Re-renal biopsy was not applicable due to deterioration of renal function (Congo red stained; original magnification × 200). Amyloid deposits were pointed out by red arrows.

Comparison of renal clinical courses between two groups before and after biologics therapy

We compared the renal function in these patients to clarify the effects of biologics therapy. In glomerular type of patients, the levels of creatinine and BUN were advanced (creatinine > 2.5 mg/dl) and proteinuria was deteriorated in two years (Table 2). But those of vascular type were not advanced significantly. Next, we compared the clinical course of renal insufficiency between glomerular type and vascular type by typical examples (Figure 2). In both groups of patients, the disease activities of RA such as CRP and DAS28 were stabilized in six months and the condition continued throughout the observation. In glomerular type, the creatinine levels were deteriorated gradually, and one patient was introduced hemodialysis in two years. In vascular type, however, the renal function did not deteriorate significantly by biologics therapy.

Histological assessment of renal biopsy before and after biologics therapy in vascular type

In glomerular type, renal functions were deteriorated gradually, so re-renal biopsy was not applicable. In vascular type,

Table 1: Patient characteristics before and after biologics treatment.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender/Age	M/52	F/65	F/47	F/71	M/60	F/74
Stage/Class*	III/II	IV/III	III/II	IV/II	II/II	IV/III
Cr(mg/dl)	1.7	1.1	1.2	1.5	1.1	1.4
BUN(mg/dl)	30.1	29.4	25.8	30.6	21.3	32.6
U-pro(mg/dl)	15	36	++	+	+/-	+
Type†	vascular	vascular	glomerular	glomerular	glomerular	glomerular
DAS28	5.2	4.4	5.6	4.8	5.9	4.6
CRP(mg/dl)	1.6	2.5	2.7	0.8	1.3	0.9
Treatment	TCZ	ETA	TCZ	ETA	TCZ	TCZ

*Radiological stage and functional class are reported as Steinblocker's classification.
†The types of renal amyloidosis are reported.
Abbreviations: F: Female; M: Male; Cr: Creatinine; BUN: Blood Urea Nitrogen; U-pro: Urinary Protein; DAS28: 28-joint disease activity score; CRP: C-reactive protein; TCZ: Tocilizumab, ETA: Etanercept.

Table 2: Clinical courses of disease activity and renal function before and after biologics treatment.

	Vascular type(n=2)		Glomerular type(n=4)	
	Before	2 years after	Before	2 years after
Cr(mg/dl)*	1.4	1.5	1.3	4.6
BUN(mg/dl)*	29.4	28.0	26.6	53.3
U-pro(mg/dl)*	42	29	158	247
DAS28*	4.8	2.3	4.7	2.2
CRP(mg/dl)*	2.0	0.08	1.9	0.09
SAA(μg/ml)	102	11	114	10

Abbreviations: Cr: Creatinine; BUN: Blood Urea Nitrogen; U-pro: Urinary Protein; DAS28: 28-joint Disease Activity Score; CRP: C-reactive pProtein; SAA: Serum Amyloid A.

however, renal function did not deteriorate significantly, which enabled us to re-examine renal biopsy. The typical results of renal biopsy before and after two years treatments were shown in Figure 1. When we compared the amyloid deposition before and after biologics treatment (case 1, 2), the amyloid deposits around blood vessels, particularly the small vessels, did not regress significantly in the kidney either in tocilizumab or in etanercept (Figure 1A). In case 2, the amount of renal amyloid was smaller but definitely remained after tocilizumab treatment (Figure 1A, case 2). These results show that the amyloid deposition of kidney is not regressed by biologics therapy in these patients.

Histological assessment of gastric biopsy before and after biologics therapy

The patients who achieved clinical remission by tocilizumab or etanercept were re-examined gastric biopsy in two year's interval. Typical examples of the gastric biopsy were shown in Figure 3. Before starting biologics therapy, all biopsy specimens from the antrum of the stomach and first portion of the duodenum showed marked deposition of amyloid fibrils (Figure 3 A,B). After two years treatments, however, amyloid deposits had significantly regressed at different parts of the stomach and the duodenum (Figure 3 C,D) in all patients. These results show that amyloid deposits were regressed by either etanercept or tocilizumab in gastroduodenal tract as reported.

DISCUSSION

AA amyloidosis develops secondary to chronic inflammatory conditions since a major factor in the protein deposition process involves the precursor protein AA, a cleaved product of the acute phase protein SAA [4-6]. AA amyloidosis occurs in a proportion of patients with chronic inflammatory diseases, including RA, ankylosing spondylitis, juvenile rheumatoid arthritis, and Crohn's disease [7]. AA amyloid proteins can be broadly distributed in several vital organs, such as kidneys, heart, and gastrointestinal tract [4], owing to the overproduction of SAA under such inflammatory conditions [9].

In the present study, we provide evidence that renal but not gastric amyloid deposition does not regress by biologics therapy (tocilizumab and etanercept).

In the digestive tracts, most of histological follow-up studies have revealed the reduction of amyloid deposits in the duodenal or colorectal mucosa after treatment by biologics in AA amyloidosis patients not only with RA but also with other chronic inflammatory arthritis patients [14-16]. Our present results are well in accordance with these observations.

In the kidney, however, regression of amyloid deposition by biologics therapy in RA patients has remained quite uncertain. Several indirect observations that the improvements of renal functions after biologics therapy suggest the resolution of

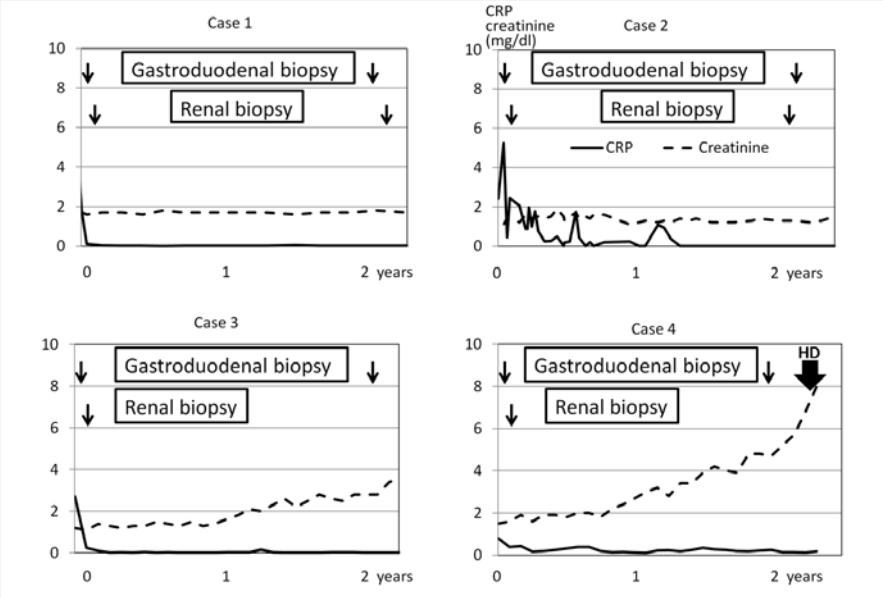

Figure 2 Typical clinical course and times of renal and gastroduodenal biopsies. The CRP and creatinine levels and the time of the renal and gastroduodenal biopsy were shown in case 1-4. The day of the renal or gastroduodenal biopsy was shown by arrows.

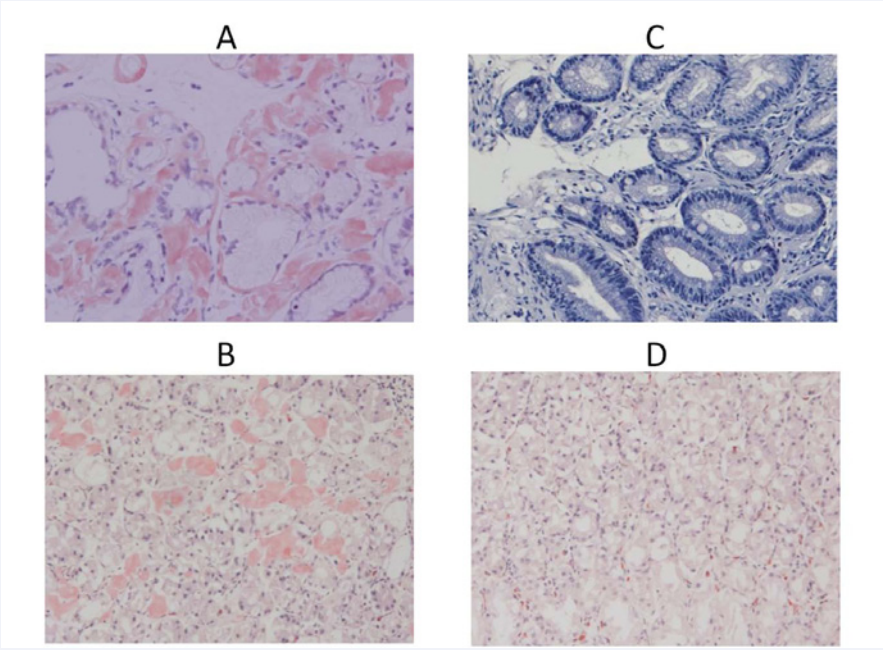

Figure 3 Results of gastroduodenal biopsy before and after biologics therapy. A, B, Massive amyloid A protein deposits were observed in duodenal mucosa and submucosa before the start of biologics therapy. C, D, Disappearance of amyloid A protein deposits was seen in duodenal mucosa and submucosa after biologics treatment (Congo red stained; original magnification × 200). Amyloid deposits were pointed out by red arrows.

amyloid deposition in the kidneys were reported [22-29], but this has not been proven using repeated renal biopsies, particularly in AA amyloidosis patients with RA.

In these situations, we suggest that renal amyloid deposition is not regressed by biologics therapy in AA amyloidosis patients with RA.

In RA patients, few cases were reported about repeated renal biopsy. Besides RA patients, a few cases were reported. Simsek *et al.*, reported no regression of amyloid mass in a patient with TRAPS by two years interval of etanercept treatment [30]. In their title, they suggest that no regression of the amyloid deposition occurred on the basis of follow-up renal biopsy, but they conclude that the treatment with etanercept was associated with remission of the nephrotic syndrome but amyloid deposition was noted to be more pronounced on the second renal biopsy. Moreover, their kidney specimen fits in glomerular type by our definition [17]. In glomerular type, it is quite natural that amyloid deposition is

increased even when the disease activity is well-controlled by DMARDs or biologics therapy as we reported. Verschueren *et al.,* also reported no regression of amyloid deposition in a patient with juvenile spondyloarthropathy by infliximab treatment [31]. Indeed, the four-month period of infliximab treatment was extremely short, but their findings are in accordance with our present observation. In the present study, we followed RA patients for more than two years. At the same time, however, they did not examine the regression of amyloid deposition in gastroduodenal tracts. There have been no reports comparing the regression of amyloid deposition between the gastroduodenal tracts and kidney at the same time. Our results suggest that amyloid depositions in the gastroduodenal tracts but not kidney were regressed significantly, which are in accordance with most of observations reported [14-16].

Taken together, amyloid deposition in the gastroduodenal tracts are regressed by biologics therapy. In the kidney, however, we showed poor regression of amyloid deposition by biologics therapy. Thus, clear evidence showing the regression of renal amyloid mass in RA patients has remained sparse but we believe that amyloid deposition in the kidney is not regressed by biologics therapy.

As to the regression of amyloid deposition, we show a discrepancy between the gastroduodenal tracts and kidney in the same patients. These results suggest that amyloid deposition is differently regulated between the gastroduodenal tracts and kidney. The mechanisms underlying the discrepancy are quite uncertain at present but several possibilities could be postulated.

As we also showed in the present study, the serum levels of SAA were decreased more drastically by biologics treatment than by the conventional DMARDs [14,15]. The decrease of SAA levels seem to be critical in regression of amyloid deposition [9,32]. The metabolic turnover of the tissue might explain the difference of the extent of regression; the turnover of the gastric mucosa is rapid, but the kidney turns over more slowly [33]. Therefore, amyloid deposition might be regressed in the gastroduodenal tracts but not in the kidney. However, the precise mechanism remains to be clarified.

Thus, we suggest that amyloid deposition of kidney, unlikely to gastric tract, does not regress significantly in AA amyloidosis patients with RA by biologics therapy.

CONCLUSION

Amyloid deposition of kidney, unlikely to gastric tract, may not regress significantly in AA amyloidosis patients with RA by biologics therapy.

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