Aspirin and Eicosapentaenoic Acid May Arrest Progressive IgA Nephropathy: A Potential Alternative to Immunosuppression

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Abstract

Immunoglobulin (Ig) A nephropathy is a prevalent form of primary glomerulonephritis, which leads to end-stage renal failure in a significant proportion of patients. Immunotherapy, including steroid use, is widely used to induce disease remission; however, it can cause serious side effects. We herein report 3 cases of progressive IgA nephropathy and their successful treatment with a combination of aspirin and eicosapentaenoic acid (EPA) without the use of steroids. The precise mechanism responsible for the combination therapy is still unknown; however, aspirin may potentiate the production of anti-inflammatory lipid mediators derived from EPA. Further clinical trials are required to substantiate this treatment regimen.

Key words: IgA nephropathy, aspirin, eicosapentaenoic acid, steroids

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Introduction

Immunosuppressive therapy is widely used to treat autoimmune diseases; however, it often causes serious side effects. Overcoming these limitations requires the development of new therapeutic strategies. Immunoglobulin (Ig) A nephropathy is the most common form of primary glomerulonephritis, and 15-40% of patients progress to end-stage renal disease (ESRD) within 10-20 years (1). Severe proteinuria (>1 g/dL), reductions in estimated glomerular filtration rates (eGFR), and hypertension at presentation predict the patient progression to ESRD (2, 3). In contrast, the long-term prognosis for patients with IgA nephropathy who present with minor urinary abnormalities and normal renal function is favorable (4), and they do not require aggressive immunotherapy. Immunosuppressive therapy for IgA nephropathy should be determined according to the risk stratification, because the treatment aims to prevent ESRD or death (5, 6). Steroids are widely used to induce disease remission; however, their use is limited due to their detrimental side effects, especially in elderly patients with comorbidities such as atherosclerosis, diabetes, thrombosis, and infection (7). In this report, we present the clinical features and treatment courses of 3 patients with IgA nephropathy successfully treated with the combination of aspirin and eicosapentaenoic acid (EPA) without the use of steroids in The Tokyo University Hospital.

Case Reports

Case 1

A 53-year-old Japanese woman presented with hematuria and proteinuria that had persisted since 2005. Her urinary abnormalities had been progressive, with deterioration in her renal function noted during routine health checkups. Her medical history included hypercholesterolemia, which had been treated with pitavastatin; however, she did not have hypertension or diabetes. Upon admission, the patient’s blood...
pressure was 120/54 mmHg. A urinalysis detected hematuria [21-50 red blood cells (RBCs)/high-power field (HPF)], proteinuria (2+), and her urinary protein/creatinine (Cr) ratio was 2.55 g/g Cr. Her eGFR was 41.7 mL/min/1.73 m². Blood tests revealed the patient’s serum creatinine (1.09 mg/dL), triglyceride (TG, 162 mg/dL), low-density lipoprotein cholesterol (LDL-C, 123 mg/dL), C-reactive protein (CRP, 0.02 mg/dL), and IgA (264 mg/dL) levels; however, hypocomplementemia was not detected. Her anti-nuclear antigen (ANA) titer was 1:320 (speckled type), but anti-double-stranded DNA antibodies and anti-Smith antibodies were negative. Cryoglobulins, antistreptolysin O (ASO) antibodies, anti-glomerular basement membrane antibodies, anti-proteinase (PR) 3 antibodies, and anti-myeloperoxidase (MPO) antibodies were not detected. A kidney biopsy showed focal segmental glomerulonephritis with fibrous crescents. Global sclerosis in 2/16 and fibrotic crescents in 4/16 glomeruli were present. Segmental mesangial cell proliferation and moderate interstitial fibrosis (20%) were observed. Immunofluorescent staining showed the deposition of IgA, complement component (C) 3, and C9 in the glomeruli (Fig. 1). According to these findings, the patient was diagnosed with IgA nephropathy with a histological (H)-grade II severity and an Oxford classification of mesangial hypercellularity (M) 1, endocapillary hypercellularity (E) 0, segmental glomerulosclerosis (S) 1, tubular atrophy/interstitial fibrosis (T) 0, C-grade III. Taking these findings together, an absolute renal risk (ARR) of dialysis or death score of 2 was determined for this patient, which accounted for her proteinuria of ≥1 g/g and a MEST score of ≥2, which was based on findings reported from a previous study (2). Systemic lupus erythematosus (SLE) was ruled out based on The American College of Rheumatology revised classification criteria for systemic lupus erythematosus (8).

Because steroid therapy was not suitable as global sclerosis was prominent in the kidney biopsy specimen, we began treatment with highly purified eicosapentaenoic acid (EPA) (1,800 mg/d) and aspirin (100 mg/d) in May 2009 that was later increased to 2,700 mg/d and 200 mg/d, respectively, without the need for steroids or immunosuppressants (Fig. 2A). Although an angiotensin receptor blocker (ARB) was initially administered, the patient showed hypotension. Therefore, the ARB was discontinued to prevent hypotension. After the initiation of therapy, the patient’s proteinuria and hematuria gradually improved, and no adverse events were noted. In April 2014, which was 5 years after therapy was initiated, the patient’s hematuria was minimal, her proteinuria had reduced to 0.21 g/g, and her renal function was stable (Cr, 1.15 mg/dL; eGFR, 39.0 mL/min/1.73 m²), indicating clinical remission.

**Case 2**

In April 2010, a 62-year-old Japanese man presented with significant hematuria (3+) and proteinuria (2+), and his medical history included hypertension and repetitive tonsillitis. He had been receiving anti-hypertensive therapy with an angiotensin-converting enzyme inhibitor since 2009, however, his renal function had deteriorated, and he had experienced progressive proteinuria. A tonsillectomy was performed in December 2010. In January 2011, the patient’s urinalysis indicated hematuria (20-29 RBCs/HPF), proteinuria (2+), and a pre-treatment urinary protein/Cr ratio of 0.81 g/g Cr. His eGFR was 31.9 mL/min/1.73 m². The blood tests revealed the elevated levels of serum Cr (1.78 mg/dL), LDL-C (108 mg/dL), CRP (0.21 mg/dL), and IgA (658 mg/dL); hypocomplementemia was not detected. ANA, anti-PR3 antibodies, anti-MPO antibodies, and anti-ASO antibodies were not detected. A kidney biopsy showed global sclerosis in 4/20 glomeruli, mild mesangial matrix expansion, segmental mesangial cell proliferation, mild interstitial fibrosis (10%), and fibroelastosis of the arcuate artery. There were no extracapillary lesions including crescents formation. Immunofluorescent staining showed the deposition of IgA, C3, and C9 in the glomeruli (Fig. 1). These observations led to a diagnosis of IgA nephropathy with an H-grade I severity and an Oxford classification of M1, E0, S1, T0, C-grade III. Taking these findings together, an ARR of dialysis or a death score of 2 was determined for this patient, which accounted for his hypertension and a MEST score of ≥2.

We treated this patient with a combination of EPA and aspirin, and we did not use steroids due to his impaired renal function (Fig. 2B). Therapy was initiated in January 2011, and his proteinuria and hematuria gradually resolved and the progression of his renal impairment was arrested. In March 2014, which was 39 months after therapy was initiated, the disease was in clinical remission, with the patient demonstrating an absence of hematuria, reduced proteinuria (0.08 g/g Cr), and improved renal function (Cr, 1.04 mg/dL; eGFR, 56.6 mL/min/1.73 m²).

**Case 3**

A 22-year-old Chinese woman was referred to our hospital due to hematuria and proteinuria, which had been detected during a health checkup in July 2010. The patient’s blood pressure was 120/60 mmHg. A urinalysis detected hematuria (20-29 dysmorphic RBCs/HPF), proteinuria (2+), and her urinary protein/Cr ratio was 2.64 g/g Cr. Her eGFR was 79.7 mL/min/1.73 m². The blood tests revealed her Cr (0.76 mg/dL), LDL-C (122 mg/dL), CRP (0.01 mg/dL), and IgA (293 mg/dL) levels; hypocomplementemia was not detected. Her ANA titer was 1: 40 (homogenous and nucleolar type), but anti-double-stranded DNA antibodies were negative, and anti-PR3 antibodies, anti-MPO antibodies, and anti-ASO antibodies were also negative. A kidney biopsy revealed fibrocellular crescents in 2/13 glomeruli and segmental mesangial matrix expansion and mesangial cell proliferation in 7/13 glomeruli. Immunofluorescent staining indicated the deposition of immunoglobulins (IgG, IgA, IgM), C3, C3d, and C9 in the glomerular mesangium (Fig. 1). SLE was ruled out based on The American College of Rheumatology revised classification criteria (8). According to these
findings, we diagnosed the patient with IgA nephropathy with diffuse mesangial proliferative glomerulonephritis, an H-grade II severity, and an Oxford classification of M1, E0, S1, T1, C-grade II. Taking these findings together, an ARR of dialysis or death score of 2 was determined for this patient, which accounted for her proteinuria (≥1 g/g Cr) and a MEST score of ≥2.

The patient was of childbearing age and showed normotension; therefore we did not prescribed anti-hypertensive agents such as ARBs and angiotensin-converting enzyme inhibitors. Since the patient rejected steroid therapy, we initiated treatment with EPA (1,800 mg/d) and aspirin (100 mg/d) in September 2010, and increased the EPA dose to 2,700 mg/d (Fig. 2C). After the initiation of therapy, her protein-
Figure 2. The clinical courses of the three cases with IgA nephropathy. The renal function (indicated by serum creatinine [Cr] levels), urinary protein (UP), and red blood cells (RBC) (number/high-power field [HPF]) in cases 1 (A), 2 (B), and 3 (C) after the initiation of treatment with aspirin and eicosapentaenoic acid (EPA).

Discussion

Since Hamazaki et al. (9) first reported the efficacy of EPA in the treatment of IgA nephropathy, several clinical trials have been conducted using fish oils. However, the effects of omega-3 polyunsaturated fatty acids, which contain EPA and docosahexaenoic acid, on IgA nephropathy remain

uria and hematuria gradually resolved, and her renal function stabilized. In March 2014, she maintained clinical improvements with mild hematuria and proteinuria (0.37 g/g Cr), and her renal function was stable (Cr, 0.69 mg/dL; eGFR, 84.5 mL/min/1.73 m²).
Table. Hematologic and Nephrologic Parameters before and after Treatment with Aspirin and Eicosapentaenoic Acid.

<table>
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<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Treatment period (months)</td>
<td>60</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Serum Cr (mg/dL)</td>
<td>1.09</td>
<td>1.15</td>
<td>1.78</td>
</tr>
<tr>
<td>eGFR (mL/min.1.73 m²)</td>
<td>41.7</td>
<td>39.0</td>
<td>31.9</td>
</tr>
<tr>
<td>Urine protein (g/g Cr)</td>
<td>2.55</td>
<td>0.21</td>
<td>0.81</td>
</tr>
<tr>
<td>Serum IgA (mg/dL)</td>
<td>264</td>
<td>253</td>
<td>658</td>
</tr>
<tr>
<td>Serum AA (μg/mL)</td>
<td>156.6</td>
<td>134.4</td>
<td>293</td>
</tr>
<tr>
<td>Serum EPA (pg/mL)</td>
<td>75.3</td>
<td>224.3</td>
<td>232.9</td>
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Cr: creatinine, eGFR: estimated glomerular filtration rate, AA: arachidonic acid, EPA: eicosapentaenoic acid, n.d.: not detected. Urine protein excretion expressed as the urine protein-creatinine ratio (g/g Cr).

controversial (10-12). In relation to the patients whose cases are herein reported, an ARR score of 2 at diagnosis indicates an estimated cumulative incidence of death or dialysis at 10 years and 20 years of 7% and 18%, respectively (2). In all the present cases, the clinical remission of IgA nephropathy was achieved following the initiation of a therapeutic strategy that combined aspirin with highly purified (>98%) EPA (Table). Aspirin’s inhibition of prostaglandin formation is well established, however, recent sequential studies by Serhan et al. (13) have revealed that aspirin initiates the biosynthesis of endogenous proresolving and anti-inflammatory lipid mediators. EPA is a substrate of aspirin-acetylated cyclooxygenase (COX)-2, which generates aspirin-triggered resolvins that have proresolving and anti-inflammatory potential (14). Aspirin switches COX-2 activity to produce 18R-hydroxyeicosapentaenoic acid from EPA (13), which is cardioprotective (14), and promotes RvE1 formation in vivo in experimental animals (13) and human beings (15). Therefore, the specific aspirin-mediated enhancement of EPA-derived anti-inflammatory lipid mediator production may be the mechanism that underlies the remarkable amelioration achieved with this combination therapy. In fact, we have recently reported several successful cases of anti-neutrophil cytoplasmic antibody-related vasculitis in which the combination of aspirin and EPA supported inducing and maintaining remission (16, 17). We have not yet determined the optimal doses of EPA and aspirin for the treatment of IgA nephropathy. We simply start at the doses of 1,800 mg/day and 100 mg/day for EPA and aspirin, respectively, and increase the doses of these agents to 2,700 mg/day and 200 mg/day, respectively, to accelerate the improvement of proteinuria. In case 1 and case 2, increasing the dose of EPA from 1,800 mg/day to 2,700 mg/day and aspirin from 100 mg/day to 200 mg/day accelerated the decrease in proteinuria without any adverse events. In case 3, the proteinuria improved by 100 mg/day of aspirin without increasing the dose. Therefore, we did not change the dose of aspirin from 100 mg/day to 200 mg/day. According to these experiences, the optimal doses of EPA and aspirin must be determined in future studies.

Whether the combination therapy can be terminated is an exciting and critical question, which we must study in the future. However, this study demonstrates the potential of EPA/aspirin combination therapy to combat IgA nephropathy.

In conclusion, we successfully treated 3 patients with progressive IgA nephropathy using a combination of low-dose aspirin and highly purified EPA as a substitute for steroid therapy. This therapeutic strategy is based on recently identified pharmacological interactions between aspirin and EPA. However, future clinical trials are required to determine the full potential of this combination therapy.

The authors state that they have no Conflict of Interest (COI).

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References