Tumor Necrosis Factor Inhibitors Provide Longterm Clinical Benefits in Pediatric and Young Adult Patients with Blau Syndrome

To the Editor:

Blau syndrome is an autoinflammatory disease caused by mutations in the *NOD2* gene[1]. The initial symptoms of Blau syndrome usually include polyarthritis and rash followed by uveitis. In addition, various clinical manifestations beyond the classic clinical triad have been reported in patients with Blau syndrome[2,3,4].

Although controlling ocular and articular involvements are critical to improve prognosis, no specific therapy for Blau syndrome has yet been established. The use of thalidomide, immunosuppressives [methotrexate (MTX) or azathioprine], and biologic therapy [tumor necrosis factor-α (TNF-α) or interleukin (IL)-1β inhibitor] has been reported in corticosteroid-refractory cases[1,4,5,6]; however, the small number of patients with Blau syndrome in these studies and case reports makes drawing a definite conclusion difficult.

To address these issues, we report a series of 6 patients (3 men and 3 women) with Blau syndrome who received biologic therapy between 2005 and 2013 at the Kagoshima University Hospital, Kagoshima, Japan. Clinical findings and laboratory data were collected from their medical records. No patient had achieved clinical remission with prior treatments, including nonsteroidal antiinflammatory drugs, MTX, and systemic corticosteroids. In all cases, the patients or their legal guardians provided written informed consent before administration of biologic therapy. The publication of the patients' data was approved by the Institutional Review Board at Kagoshima University Hospital (No. 26-129).

Patients' baseline characteristics are shown in Table 1. Median age at the start of biologic therapy was 14.0 years (5.3–20.8). Median age at disease onset and median disease duration were 1.7 years (0.5–4.5) and 13.4 years (0.8–18.1), respectively. Four of 6 patients received oral corticosteroids (1–15 mg/day) in combination with MTX. Articular manifestations were observed in all 6 patients, and the most commonly affected joints were the wrist, followed by the proximal interphalangeal and metacarpophalangeal joints. Three patients had active uveitis and 2 of them also had panuveitis, whereas 2 younger patients (cases 4 and 5) were uveitis-free at baseline. Lower extremity erythema nodosum was observed in 3 of 6 patients.

Clinical course and outcome are summarized in Table 2. Four patients showed a favorable response to TNF-α inhibitors: infliximab (IFX; cases 1 and 2), adalimumab (ADA; case 3), or etanercept (ETN; case 4) used as the first biologic agent. In contrast, 1 patient (case 5) discontinued ETN followed by tocilizumab (TCZ) owing to a lack of clinical efficacy. Another patient (case 6) developed anti-TCZ immunoglobulin E (IgE) antibodies and discontinued TCZ. Both cases 5 and 6 achieved clinical remission after switching to IFX. Changes in inflammatory biomarkers such as erythrocyte sedimentation rate, C-reactive protein, and matrix metalloproteinase 3 between baseline and the last visit are shown in Appendix 1.

In our case series, all patients had achieved clinical remission by the last visit. Overall, TNF-α inhibitors showed a favorable effect, except for ETN in 1 patient.

TNF-α inhibition with IFX or ADA has shown successful results in a few patients with Blau syndrome[7,8], which is in agreement with our findings. In contrast, IFX, ADA, or ETN were inefficacious in several patients[1]; further, ETN-induced myelopathy has been reported in a pediatric patient with Blau syndrome[9]. Use of the IL-6 receptor inhibitor TCZ has not been reported in patients with Blau syndrome. In our study, TCZ was administered to 2 patients, but was discontinued because of recurrent arthritis or development of anti-TCZ IgE antibodies. This might have resulted from the absence of co-therapy with MTX, which is used in combination with other biologic drugs; nevertheless, its efficacy remains unclear. Taken together, biologic therapy might be a promising approach, but is not always effective

Table 1. Characteristics of patients at initiation of treatment with biologic agents.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, yrs	20.8	15.4	17.9	6.0	5.3	12.5
Sex	M	M	M	F	F	F
Age at disease onset, yrs	2.7	0.5	0.6	3.4	4.5	0.6
Disease duration, yrs	18.1	14.9	17.3	2.6	0.8	11.9
NOD2 mutations	R334Q	R334Q	R334Q	R587C	R334Q	R587C and R471C
Medication						
MTX, mg/week*	7.5	7.5	10	8	8	7.5
PSL, mg/day*	15	9	1	Not used	Not used	7.5
Clinical features						
Arthritis						
No. per site	2	2	12	33	15	40
Affected joint(s)	W	W	W, MCP, PIP	H, K, A, MTP, E, W, MCP, PIP	K, A, MTP, E, W, MCP, PIP	H, K, A, MTP, E, W, MCP, PIP
Uveitis						
Age at onset, yrs	5	2	4	—	—	2
Main findings	Bi. IC, Rt. Cat.	Bi. IC, VO, RV, PE	Inactive			Bi. IC, VO, RV, PE
Rash	EN	EN	None	None	None	EN
Lesion and area affected	Lower leg	Lower leg				Lower leg
Laboratory findings						
ESR, mm/h	11	4	4	54	45	37
CRP, g/dl	3.9	9.9	5.2	25.6	16.4	17.6
MMP-3, ng/ml	278	123	129	654	322	297

* MTX or PSL was given orally; cases 4 and 5 had never received systemic corticosteroids previously. MTX: methotrexate; PSL: prednisolone; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MMP-3: matrix metalloproteinase 3; W: wrist; MCP: metacarpophalangeal; PIP: proximal interphalangeal; H: hip; K: knee; A: ankle; MTP: metatarsophalangeal; E: elbow; Bi.: bilateral; IC: iridocyclitis; Rt.: right; Cat.: cataract; VO: vitreous opacity; RV: retinal vasculitis; PE: papilledema; EN: erythema nodosum.

Table 2. Clinical course and outcome with biologic therapy.

Patient	Biologic Agents/ Dosage/Route/Frequency/ Combination Use	Followup Period, Mos	Summary of Main Findings/No. Affected Joints/Daily PSL Use at Last Visit
1	IFX/300 mg (5 mg/kg)/IV/ every 6 weeks/MTX, PSL	70	An improvement in arthritis, erythema nodosum, and anterior uveitis; a reduction in daily PSL use/No. affected joints: 0/PSL: 10 mg/day
2	IFX/300 mg (5 mg/kg)/IV/ every 6 weeks/MTX, PSL	70	An improvement in arthritis, erythema nodosum, anterior, intermediate, and posterior uveitis; a reduction in daily PSL use/No. affected joints: 0/PSL: 6 mg/day
3	ADA 40 mg/SC/every 2 weeks/MTX, PSL	12	An improvement in arthritis; no recurrence in uveitis/No. affected joints: 0/ PSL: 0 mg/day
4	ETN/12.5 mg (0.4 mg/kg)/ SC/twice weekly/MTX	102	An improvement in arthritis; maintained uveitis-free/No. affected joints: 0/ PSL: not used
5-1	*ETN/5.5 mg (0.4 mg/kg)/ SC/twice weekly/MTX	5	Discontinuation due to an exacerbation of arthritis.
5-2	*TCZ/128 mg (8 mg/kg)/ IV/every 4 weeks/none	33	Discontinuation due to a recurrence of arthritis.
5-3	IFX/200 mg (5 mg/kg)/IV/ every 4 weeks/MTX	68	An improvement in arthritis; maintained uveitis-free/No. affected joints: 0/ PSL: not used
6-1	*TCZ/160 mg (8 mg/kg)/IV/ every 2 weeks/PSL	2	Discontinuation due to development of anti-TCZ IgE antibodies.
6-2	IFX/200 mg (10 mg/kg)/IV/ every 8 weeks/MTX, PSL	83	An improvement in erythema nodosum, anterior, intermediate, and posterior uveitis; increased dose of IFX (to 300 mg) and PSL (to 9 mg) due to an exacerbation of arthritis since 57 mos, thereafter, achieved clinical remission; a reduction in daily PSL use/ No. affected joints: 0/PSL: 5 mg/day

* Discontinued and switched to the second or third biologic agent. MTX was given orally once a week; cases 4 and 5 were treated without corticosteroids. IFX: infliximab; IV: intravenous; MTX: methotrexate; PSL: prednisolone; ADA: adalimumab; SC: subcutaneous injection; ETN: etanercept; TCZ: tocilizumab; IgE: immunoglobulin E.

in patients with Blau syndrome. Moreover, we should pay careful attention to the adverse effects of biologic agents.

An international multicenter study by Rosé, *et al*[4] including 18 children and 13 adults, with a median age of 16.5 years (range 1.9–58) showed that despite administration of systemic steroids and immunosuppressive and/or biologic drugs (ADA or IFX), about 60%–70% of the patients still had active arthritis and severe ocular involvement at baseline. Thus, Blau syndrome is resistant to currently available therapies in many cases.

Early intervention with biologic therapy may be a possible reason for the positive results we obtained because our study enrolled pediatric and young adult patients. Indeed, 2 younger patients (cases 4 and 5) who started biologic therapy at the ages of 6 years and 5 years, respectively, were maintained uveitis-free without the administration of systemic corticosteroids. Otsubo, *et al* reported the cases of a Japanese mother and her daughter with Blau syndrome who had contrasting outcomes; the daughter obtained clinical remission with TNF-α inhibitor while her mother missed the opportunity for biologic therapy because of far-advanced disease[10]. These results suggest that early intervention is essential to improve patients' quality of life and disease prognosis.

TNF-α inhibitor may be a promising approach in the management of Blau syndrome. However, our present study has limitations, including the retrospective design and the small sample size.

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APPENDIX 1. Changes in patients' laboratory variables. Laboratory variables at baseline and at last visit were compared. Overall, inflammatory biomarkers decreased in all patients. However, ESR and MMP-3 levels remained above normal range at the last visit (ESR for patients 4 to 6; MMP-3 for patients 1, 5, and 6). ESR: erythrocyte sedimentation rate; MMP-3: matrix metalloproteinase 3; CRP: C-reactive protein.