

Relapse of Systemic Juvenile Idiopathic Arthritis after Influenza Vaccination in a Patient Receiving Tocilizumab

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We report the case of a patient with systemic juvenile idiopathic arthritis (s-JIA) receiving tocilizumab (TCZ) who experienced relapses of s-JIA after receiving influenza vaccination. Systemic symptoms of s-JIA might be masked during TCZ therapy. Careful observation with the monitoring of serum interleukin (IL)-18 and IL-6 levels may be useful.

CASE REPORT

A 3-year-old girl was initially diagnosed with systemic juvenile idiopathic arthritis (s-JIA) on the basis of the presence of spiky fever, a salmon-colored erythematous rash, polyarthritis, and leukocytosis (white blood cell count [WBC], 14,700/ μ l) as well as elevated serum levels of C-reactive protein (CRP; 5.38 mg/dl), matrix metalloprotease-3 (MMP-3; 626.4 ng/ml), and interleukin (IL)-18 (2,230 pg/ml). Her clinical symptoms improved rapidly after the administration of prednisolone (PSL; 1 mg/kg of body weight/day). After tapering the PSL dosage (0.6 mg/kg/day), the first relapse of s-JIA occurred, manifesting as high fever and polyarthralgia. The patient again responded to steroid therapy, but frequent relapses occurred when the PSL dosage was decreased. Treatment with tocilizumab (TCZ), a humanized anti-IL-6 receptor monoclonal antibody, was initiated, and long-term remission (7 months) was achieved along with a decrease in PSL dosage (0.4 mg/kg/day). Laboratory findings showed normal serum levels of MMP-3 (41.8 ng/ml), IL-18 (675 pg/ml), and IL-6 (<3 pg/ml). The girl subsequently received a 0.2-ml subcutaneous

injection of commercially available inactivated influenza vaccine on her left upper arm; the vaccine was approved for use in the 2010 to 2011 season in Japan (Kaketsuken, Kumamoto, Japan) (Fig. 1 and Table 1). Seven days later, she abruptly developed pain and limitation of the motion of her left arm, without accompanying fever or rash. Laboratory findings revealed leukocytosis (WBC, 10,880/ μ l) and elevated serum levels of MMP-3 (146.1 ng/ml), IL-6 (110 pg/ml), and IL-18 (4,800 IU/ml). However, her serum CRP level was normal (0.0 mg/dl). Computed tomography imaging of her left shoulder showed synovitis with effusion. After ad-

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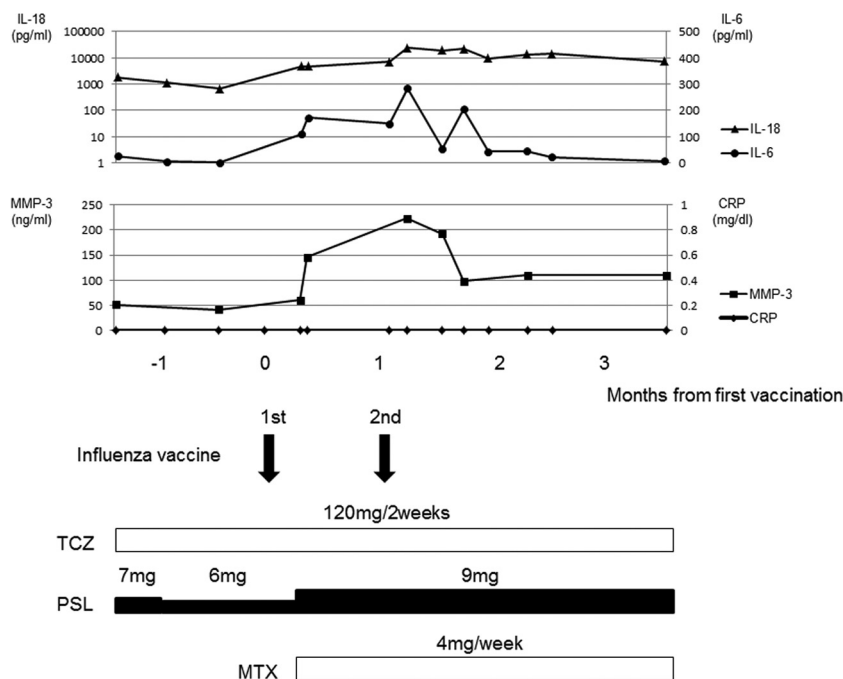


FIG 1 Patient's clinical course. IL-18, interleukin-18; IL-6, interleukin-6; MMP-3, matrix metalloprotease-3; CRP, C-reactive protein; TCZ, tocilizumab; PSL, prednisolone; MTX, methotrexate.

TABLE 1 Alterations of clinical symptoms and laboratory findings during the patient's clinical course^a

Parameter	Value or result				
	2 wk before first vaccine	At first vaccine	9 days after first vaccine	At second vaccine	7 days after second vaccine
Clinical symptoms					
Fever	–	–	–	–	–
Rash	–	–	–	–	–
Arthralgia	–	–	+	–	+
Laboratory data					
WBC (per μ l)	8,630	8,590	10,880	15,160	12,810
CRP (mg/dl)	0	0	0	0	0
AST (IU/liter)	28	25	27	34	40
MMP-3 (ng/ml)	41.8	ND	146.1	ND	223.3
IL-6 (pg/ml)	<3	ND	110	150	284
IL-18 (pg/ml)	675	ND	4,800	7,100	24,000
Treatments					
Tocilizumab	120 mg (8 mg/kg)/2 wk				
Prednisolone	6 mg (0.4 mg/kg/day)		9 mg (0.6 mg/kg/day)		
Methotrexate			4 mg/wk		

^a AST, aspartate aminotransferase; –, absent; +, present; ND, not done.

ministration of a methylprednisolone pulse, treatment with PSL (0.6 mg/kg/day) and methotrexate (4 mg/week) was initiated. The girl responded to the therapy, and her clinical symptoms improved rapidly. Four weeks after the first vaccination, she received another subcutaneous injection of inactivated influenza vaccine according to the schedule previously followed in Japan (patients aged 1 to <6 years of age were inoculated twice with a dose of 0.2 ml at intervals of 1 to 4 weeks). Seven days later, pain and swelling of her left ankle joint developed, but fever and rash were absent. Laboratory findings revealed leukocytosis (WBC, 12,810/ μ l) and elevated serum levels of MMP-3 (223.3 ng/ml), IL-6 (284 pg/ml), and IL-18 (24,000 IU/ml). However, the serum CRP level remained normal (0.0 mg/dl). Magnetic resonance imaging of her left ankle showed synovitis with effusion. After administration of a methylprednisolone pulse, her clinical symptoms improved rapidly. She has now been in long-term remission for 17 months under combination therapy with TCZ and PSL (0.25 mg/kg/day).

Infection is an important exacerbating factor in s-JIA. In particular, influenza is a major concern because the influenza virus is highly infectious and can cause severe complications. Influenza vaccination is encouraged in s-JIA patients to prevent primary influenza infection as well as secondary bacterial infections.

With regard to influenza vaccination in patients with juvenile autoimmune diseases (including JIA), a previous report showed that after vaccination, children with JIA are able to produce an antibody response similar to that seen in healthy children, even when they are taking steroids or disease-modifying drugs (4). Furthermore, reports have shown that there is no increase in disease activity after vaccination, and researchers concluded that patients with these diseases can therefore undergo influenza vaccination (1–3, 5).

TCZ is an effective cytokine inhibitor used for the treatment of s-JIA. Shinoki et al. investigated the safety and efficacy of the

influenza vaccine in 27 patients with s-JIA who were treated with TCZ and PSL (6). They found that the efficacies of vaccination did not differ significantly between the s-JIA patients and healthy controls. None of the s-JIA patients experienced severe adverse reactions or disease relapse after vaccination. Therefore, the researchers concluded that s-JIA patients treated with TCZ can be safely and effectively immunized with the influenza vaccine.

However, in our case, s-JIA relapses occurred after both injections of influenza vaccine. In some cases, s-JIA may not be completely controlled and could be exacerbated by a trigger such as influenza vaccination. Therefore, careful observation of patients with s-JIA is necessary after each dose of the influenza vaccine.

At the time of the relapses, our patient had no systemic symptoms, including fever, but she had definite features of arthritis. Furthermore, her serum CRP levels never increased. These findings are quite different from those seen during relapses in patients not receiving TCZ. Systemic symptoms of s-JIA can thus be masked by TCZ therapy. Furthermore, serum CRP levels never increase in patients receiving TCZ because of the complete blockade of IL-6 by the drug. Therefore, monitoring of serum levels of IL-18 and IL-6 may be useful for evaluating s-JIA activity during TCZ therapy. Further studies are needed to confirm that these markers are suitable for the monitoring of disease activity in s-JIA during TCZ therapy.

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We have no conflicts of interest to declare.

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