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Relapse After Cessation of Immunosuppressants in Seropositive Neuromyelitis Optica Spectrum Disorder With Long-Term Remission

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Dear Editor,

The disability experienced by patients with neuromyelitis optica spectrum disorder (NMOSD) depends on how incomplete their recovery is from the neurological deficits that occur during each relapse.[1] The use of immunosuppressant therapy (IST) has been strongly recommended for preventing relapses.[2] However, little is known about the maintenance duration or the effects of the cessation of IST in NMOSD. Here we present the clinical characteristics of NMOSD patients who had long-term remission but experienced relapses after the cessation of IST.

We retrospectively reviewed data from 69 patients with seropositive NMOSD who visited our neurology clinic at a tertiary hospital from 2009 to 2018. The diagnosis was determined according to the international consensus diagnostic criteria for NMOSD.[3] Patients were included if they had 1) prolonged periods of remission (≥3 years) with IST and then relapse after the cessation of IST, or 2) long-term remission (≥3 years) with no IST and relapse. We evaluated the clinical characteristics of the enrolled patients.

Fifty-nine of the 69 patients experienced at least 1 prolonged period of remission, and 32 patients were in remission at the last follow-up. Ten (19.2%) of the 52 patients who experienced clinical relapses after the cessation of IST or without IST (age at onset, 34.9±13.0 years, mean±SD) were finally identified: 3 of these patients refused to receive IST, 6 discontinued their treatment by themselves, and 1 discontinued IST due to pregnancy after consulting with a neurologist. The median duration of remission was 73.5 months (IQR, 57.8–91.8 months); it was 66.0 months (IQR, 55.0–73.5 months) in seven patients who discontinued IST and 103.0 months (IQR, 91.0–143.0 months) in three patients who refused IST. The median duration without IST of the seven patients who discontinued IST was 18.0 months (IQR 6.5–26.5 months). All patients were positive for anti-aquaporin-4 antibody (AQP4-Ab) at their diagnosis of NMOSD; four patients were still seropositive during the remission period, and three experienced seroconversion. However, at the time of relapse after prolonged remission, all patients were seropositive for AQP4-Ab. The details of the clinical relapses are presented in Table 1.

The long-term use of IST as a preventive treatment is recommended in all patients with NMOSD. However, there is no reliable evidence for whether or when to discontinue IST in patients with NMOSD who remain stable over a long period.[2] Kim et al.[4] reported recently that IST discontinuation may increase the risk of relapse in patients with seropositive NMOSD who are in a sustained remission period. In line with that report, our study found that even after long-term remission for ≥3 years, seven patients experienced relapse after the cessation of IST. This finding indicates that despite a stable period, there is a potential risk of relapse in patients with NMOSD who discontinue IST.

Most of our patients with long-term remission made their own decision to discontinue

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Table 1. Summary of patients with neuromyelitis optica spectrum disorder who had relapses after the cessation of immunosuppressant therapy

Patient no.	Sex	Age at onset (yrs)	Disease duration (yrs)	Annualized relapse rate*	IST during remission	Remission duration (months)			Reason for cessation of IST	AQP4-Ab status			Age at relapse (yrs)	Type of relapse†	Acute treatment during relapse	EDSS score		
						Total	With IST	Without IST		At diagnosis	During remission	At relapse				Before relapse	At nadir	After relapse
1	F	49	8.6	0.43	None	103	0	103	Refused treatment	+	N/A	+	58	LETM	IVMP, PLEX	7	8	7.5
2	F	18	12	0.83	MMF	96	92	4	Pregnancy	+	N/A	+	30	LETM	IVMP	1	5	1.5
3	F	30	15	1	None	79	0	79	Refused treatment	+	N/A	+	45	LETM	IVMP, PLEX	1	7	2
4	F	25	8	0.56	AZA, MMF	55	32	23	Self-cessation	+	+	+	33	LETM	IVMP	2	2.5	2.5
5	F	41	7	0.83	AZA	42	33	9	Self-cessation	+	+	+	48	uON	IVMP	3	3	3
6	F	48	5.9	2.18	MMF, AZA	75	43	32	Self-cessation	+	-	+	54	uON	IVMP	5	5	5
7	F	25	15	1.13	AZA	55	25	30	Self-cessation	+	-	+	40	STM	IVMP	2	3.5	3.5
8	F	22	14	0.34	AZA	66	48	18	Self-cessation	+	+	+	36	LETM	IVMP	1	2	1.5
9	M	35	15	0	None	183	0	183	Refused treatment	+	+	+	50	BS	IVMP	0	3.5	1
10	F	55	6.5	2	AZA	72	70	2	Self-cessation	+	-	+	62	LETM	IVMP	1	3.5	2

*Annualized relapse rate was calculated by dividing the number of relapses before long-term remission by the disease duration in years; †A relapse was defined as an acute episode of neurological symptoms lasting ≥24 hr that occurred ≥30 days after any previous attack.
AQP4-Ab, anti-aquaporin-4 antibody; AZA, azathioprine; BS, brainstem syndrome; EDSS, Expanded Disability Status Scale; F, female; IST, immunosuppressant therapy; IVMP, intravenous methylprednisolone pulse; LETM, longitudinally extensive transverse myelitis; M, male; MMF, mycophenolate mofetil; N/A, not assessed; PLEX, plasma exchange; STM, short transverse myelitis; uON, unilateral optic neuritis.

IST, which might have been due to concern about the adverse effects of long-term immunosuppression. However, profound neurological deficits may remain even after a single attack.[5] A recent study showed that patients with NMOSD can experience mixed courses of a period with sparse relapses or a 'clustered' period having frequent relapses.[6] Another case report indicated that two patients with seropositive NMOSD had a spontaneous remission period that lasted for longer than 1 decade.[7] These observations mean that individual patients could experience periods with different chronological characteristics of the disease, which makes it impossible to predict when relapse will occur. We have limited guidelines or evidence to advise these patients about whether to discontinue or to remain on treatment. Further studies to determine the risks and benefits of long-term IST in NMOSD are needed.

Biomarkers reflecting the disease activity of NMOSD may be useful when deciding about therapy discontinuation. Some authors have evaluated the use of serum glial fibrillary acidic protein (GFAP) as a biomarker of disease activity. The serum GFAP concentration has been found to increase after a recent relapse, but only a tendency of more future relapses in patients with a high level of GFAP was observed.[8] We evaluated the AQP4-Ab status, but the patients who experienced seroconversion during remission became seropositive at relapse, which indicated that the AQP4-Ab status could not predict future relapses; that is, the serostatus of AQP4-Ab also could not predict the response to IST in NMOSD.[9] However, AQP4-Ab testing was not performed regularly in our study, which makes the clinical significance of AQP4-Ab testing for relapse prediction unclear. Further longitudinal studies of biomarkers would be helpful to guide the strategy of long-term IST in NMOSD.

While the present case-series study revealed only the occurrence of relapses after discontinuation of therapy in patients with NMOSD, we did find a potential risk of relapse of NMOSD even during long-term remission. Therefore, physicians should apply caution when considering discontinuing IST in patients with NMOSD.

Ethics Statement

This study was approved by the local Institutional Review Board (#YUMC 2015-11-034-001, #SCHCA 2020-04-041-002). The requirement for informed consent was waived due to the retrospective design of this study.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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