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【 ORIGINAL ARTICLE 】

Urosepsis Risk in Neuromyelitis Optica Spectrum Disorder Patients Administered Satralizumab

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Abstract:

Objectives The interleukin-6 (IL-6) inhibitor satralizumab is an established treatment for neuromyelitis optica spectrum disorder (NMOSD). Although IL-6 inhibitors are generally well-tolerated, serious infections, including sepsis, can occur. In this study, we compared the sepsis characteristics in NMOSD patients administered satralizumab (NMOSD-satralizumab) to those in rheumatoid arthritis patients administered tocilizumab (RA-tocilizumab), another IL-6 inhibitor.

Methods We examined adverse event reports from the Japanese Pharmaceuticals and Medical Devices Agency regarding NMOSD-satralizumab from August 2020 to March 2022 and RA-tocilizumab from April 2008 to November 2019 (term 1) and to March 2022 (term 2).

Results We identified 6 sepsis cases in NMOSD-satralizumab, of which 5 (83%) developed from urinary tract infections (UTIs). Although data were unavailable for two patients, three cases had urologic complications in addition to recognized risk factors for serious infections, such as an older age, corticosteroid use, obesity, diabetes mellitus and motor disability. Urosepsis was relatively infrequent in RA-tocilizumab (term 1: 24.2%, term 2: 20.1%).

Discussion Safe satralizumab use requires risk factor assessment to minimize the incidence of severe infections. Management of UTIs is also recommended.

Key words: neuromyelitis optica spectrum disorder, satralizumab, sepsis, urinary tract infections

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Introduction

The interleukin-6 (IL-6) inhibitor satralizumab has been proven to be highly effective in preventing relapse in neuromyelitis optica spectrum disorder (NMOSD) (1). Although IL-6 inhibitors, such as satralizumab and tocilizumab, have well-established safety and tolerability profiles for various autoimmune inflammatory diseases, infection is the most frequent complication, and there can be serious adverse events. Sepsis is well documented in rheumatoid arthritis (RA) patients administered tocilizumab (RA-tocilizumab), developing most frequently from respiratory infections. However, how frequently and under what conditions sepsis occurs in NMOSD patients administered satralizumab (NMOSD-satralizumab) is unknown, as the drug was only first marketed in August 2020.

In this study, we compared sepsis characteristics in an NMOSD-satralizumab cohort to an RA-tocilizumab cohort.

Methods

Data source

We analyzed NMOSD-satralizumab sepsis cases between August 2020 and March 2022 using data from the Japanese Adverse Drug Event Report (JADER) database available on the Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.pmda.go.jp/). The RA-tocilizumab data were extracted from the JADER database from April 2008

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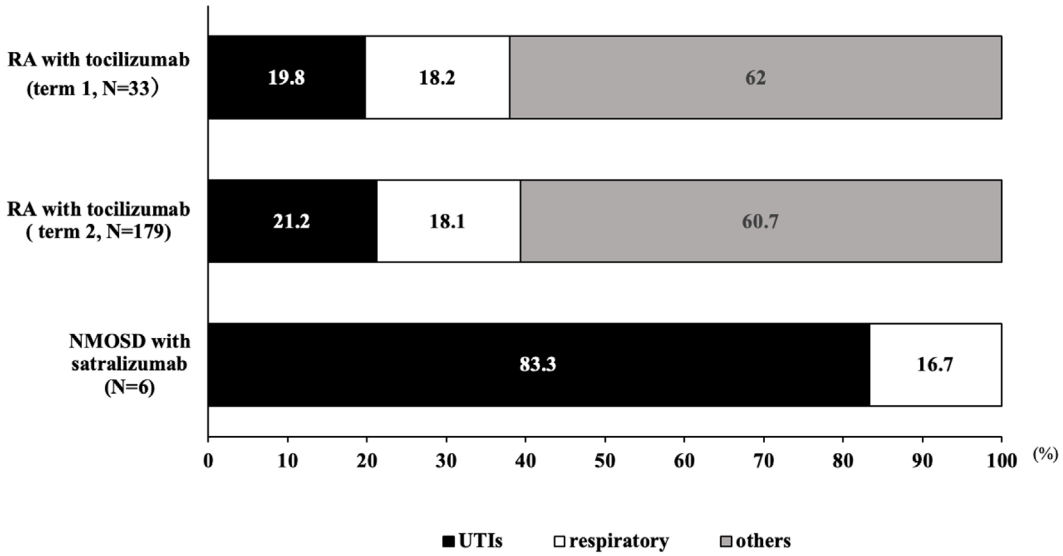

Figure. **Proportion of preceding or coexisting infection in sepsis patients with neuromyelitis optica spectrum disorder (NMOSD) treated with satralizumab and those with rheumatic arthritis (RA) treated with tocilizumab (term 1 and term 2). A total of six sepsis cases in neuromyelitis optica spectrum disorder (NMOSD) patients administered satralizumab (NMOSD-satralizumab) and 33 (term 1) and 179 (term 2) sepsis cases in rheumatoid arthritis (RA) patients administered tocilizumab (RA-tocilizumab) were identified. Five of the 6 NMOSD-satralizumab sepsis cases (83.3%) developed from urinary tract infections. In contrast, only 8/33=24.2% (term 1) and 36/179=20.1% (term 2) of sepsis cases in RA-tocilizumab were urosepsis.**

to November 2009 (term 1) and from April 2008 to March 2022 (term 2) for comparison with the NMOSD-satralizumab sepsis cases.

Ethical considerations

Institutional review board approval and patient consent to disclose were not required for this observational study, as it used anonymized patient data recorded in the open-access JADER database from the PMDA website, in accordance with current ethical guidelines for medical and health research involving human subjects in Japan.

Results

Six NMOSD-satralizumab sepsis cases were identified. Clinical information was not consistently available for all patients. There was no comorbidity information for two patients, and the height and body weight of one patient were unavailable. Five of the 6 NMOSD-satralizumab sepsis cases (83.3%) developed from urinary tract infections (UTIs) (Figure). All 6 patients were women over 50 years old, and the 5 patients for whom information was available had concomitant use of corticosteroids (CS). Obesity [body mass index (BMI) ≥25] or emaciation (BMI <18.5) was observed in 4 patients (75% of all patients for whom information was available). Diabetes mellitus (DM) or abnormal glucose tolerance was found in 75% of patients, as was the occurrence of urological complications, such as nephrolithiasis and neurogenic bladder. All urosepsis cases in the NMOSD-satralizumab cohort had ≥1 of the above complications, other than being >50 years old (Table)

The frequencies of the type of causal infections leading to sepsis were distinct between the NMOSD-satralizumab and RA-tocilizumab cohorts. Urosepsis was identified in only 24.2% (term 1) and 20.1% (term 2) of the RA-tocilizumab sepsis cohort (Figure). The risk factors (RFs) of sepsis among the RA-tocilizumab cohorts agreed with those of previous reports, including advanced age, concomitant use of CS, DM, and abnormal body weight (2, 3)2, 3). Nine out of the 36 RA-tocilizumab urosepsis cases (31% of all patients for whom information was available) had urologic complications. Approximately 92% of the urosepsis cases in the RA-tocilizumab cohort had ≥1 RF (Figure). Notably, urosepsis was reported as occurring 75 days after the initiation of the treatment in the NMOSD-satralizumab cohort and only 10 days in the RA-tocilizumab cohort.

Discussion

Our data demonstrated that sepsis could be life-threatening to NMOSD patients administered satralizumab and to RA patients administered tocilizumab, sometimes rapidly occurring after the initiation of treatment. Patients in both groups had similar RFs for recognized serious infections. All sepsis patients in the NMOSD-satralizumab cohort were >50 years old, which was consistent with observations that sepsis rates are increased in adults in their 40s and usually become problematic after 65 years old (4). All patients for whom information was available used CS or immunosuppressants, and they also had either an abnormal body

Table. Risk Factors of Urosepsis Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) Treated with Satralizumab, and Rheumatic Arthritis (RA) Treated with Tocilizumab.

Risk Factor	NMOSD treated with satralizumab (N=5)		RA treated with tocilizumab (N=36)	
	No. of all patients for whom information was available	No. of patients	No. of all patients for whom information was available	No. of patients
Age ≥ 50, n (%)	5	5 (100.0)	32	29 (90.6)
Concomitant use of CS/ IS, n (%)	5	4 (80.0)	29	15 (51.7)
Diabetes mellitus or Abnormal glucose tolerance, n (%)	4	2 (50.0)	29	11 (37.9)
Urologic complications, n (%)	4	3 (75.0)	29	9 (31.0)
Abnormal body weighta, n (%)	4	3 (75.0)	8	not determined[b]
Number of the above risk factors				
0 or unknown, n		0		3
1, n		1		10
2, n		1		18
3, n		0		4
4, n		1		1
5, n		2		0

[a]Abnormal body weight: BMI < 18.5 or ≥ 25

[b]Body weight data were available for only 8 out of 36 urosepsis cases in the RA-satralizumab cohort. Each estimated BMI ranged from normal to abnormal.

weight, glucose tolerance, or both.

Another highlight of this study was that sepsis predominantly developed from UTIs in the NMOSD-satralizumab cohort. It has been reported that motor deficits increase the risk of infections, and among patients with gait impairments, they are more susceptible to UTIs than other types of infections (5). Since PMDA did not supply data based on the Expanded Disability Status Scale (EDSS), we could not include EDSS data. However, via personal communication, we learned that at least three patients used wheelchairs. Although a neurogenic bladder was described in only one patient, its presence was probably underestimated due to an insufficient analysis, as previous reports focused on bladder dysfunction (6). The urosepsis observed here was therefore likely related to motor deficits and urinary complications due to myelitis and other issues.

The use of CS also increases infection risk (7). Furthermore, its long-term use increases other RFs such as obesity, abnormal glucose tolerance, and nephrolithiasis. Considering that the coexistence of RFs synergistically upregulates the risk of sepsis or urosepsis, the early administration of molecular-targeted drugs, such as satralizumab, is recommended to protect NMOSD patients from relapse and the adverse events associated with CS use, which can improve the quality of life.

The SAkuraSky and SAkuraStar studies, which were randomized, placebo-controlled, phase 3 clinical trials of satralizumab in patients with NMOSD, demonstrated the safety of satralizumab without marked adverse events (8). This is probably because the participants were relatively young. The mean age of the recruited patients in these studies was around 40 years old, and their EDSS scores were ≤ 6.5. This is consistent with our finding that satralizumab is safer for younger patients with less disability.

Of note, NMOSD itself often involves the above-mentioned RFs for infections, such as severe motor impairment and CS use. It has been also known that lower urinary tract symptoms and severe UTIs occur more frequently in NMOSD patients than in multiple sclerosis patients (9). In addition, it should be noted that IL-6 inhibitors, such as satralizumab, may mask signs of infection and inflammatory reactions. We therefore recommended performing regular urine tests and, when necessary, urine culture tests for NMOSD patients being administered satralizumab, especially for those with the above-mentioned RFs. These tests can detect urinary tract issues early, allowing for prompt management and preventing progression to urosepsis.

In summary, the prevalence of urosepsis increased after marketing satralizumab for NMOSD in Japan. Given that NMOSD itself often carries several RFs for infections, when using satralizumab, it is necessary to accurately assess the RFs and carefully observe signs of infection in order to prevent life-threatening sepsis. This analysis is preliminary, due to the small sample size and the inherent limitation of being a post-marketing survey. Thus, further analyses are needed. However, our report does provide urgent information on the safe use of satralizumab for NMOSD patients.

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

Acknowledgement

The views expressed in this study are those of the authors and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency of Japan.

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