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Comparative analysis of adverse event reporting signals between Satralizumab and Inebilizumab in neuromyelitis optica spectrum disorder: A pharmacovigilance study using the FDA Adverse Event Reporting System

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SUMMARY: Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disorder predominantly driven by anti-aquaporin-4 immunoglobulin G (AQP4-IgG), which mediates astrocyte injury, neuroinflammation, and demyelination. Satralizumab and Inebilizumab represent two promising therapeutic options with distinct mechanisms of action and clinical profiles. This study conducted a retrospective pharmacovigilance analysis of data from the U.S. FDA Adverse Event Reporting System (FAERS) from January 2020 to June 2025 to assess and compare adverse event (AE) reporting signals associated with Satralizumab and Inebilizumab. The analysis revealed a higher number of reported adverse events for Satralizumab compared to Inebilizumab (1,114 cases *vs.* 349 cases). A higher reporting proportion of AEs was observed in female patients for both drugs, with no statistically significant difference between them (exploratory $p = 0.760$). The reported AEs for both agents were primarily categorized under System Organ Classes (SOCs) such as infections and infestations and nervous system disorders. Urinary tract infection and pneumonia were among the most frequently reported preferred terms (PTs) for Satralizumab, whereas headache and COVID-19 were prominent for Inebilizumab. Reports classified as serious were more frequent for Satralizumab than for Inebilizumab (exploratory $p < 0.01$), noting that "seriousness" in FAERS may encompass outcomes related to underlying disease activity. This signal detection study highlights distinct adverse event reporting profiles for these biologics and offers insights that may inform clinical monitoring and personalized treatment strategies in NMOSD. Further studies with rigorous prospective designs are recommended to validate these findings and elucidate the mechanisms underlying the observed adverse events.

Keywords: NMOSD, Satralizumab, Inebilizumab, adverse events, FAERS

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease characterized by optic neuritis and transverse myelitis, typically causing devastating outcomes such as blindness and paralysis (*1*). Infiltration of anti-aquaporin 4 (AQP4) antibodies into the central nervous system (CNS) contributes critically to the pathogenesis of NMOSD by inducing astrocyte injury (*2*). Epidemiological studies indicate an estimated prevalence in Europe of approximately 1 per 100,000 individuals. In contrast, East Asian populations exhibit a higher prevalence, reported at around 3.5 per 100,000, suggesting that genetic or ancestral background may influence susceptibility to NMOSD (*3*). The primary goal of NMOSD treatment is to mitigate the risk of irreversible neurological damage through relapse prevention and attenuation of acute attack severity (*4*). Among the emerging therapeutic agents, Satralizumab and Inebilizumab have become notable additions to the pharmacological management of NMOSD (*5*). Satralizumab exerts its therapeutic effect by reducing inflammation and inhibiting interleukin-6 (IL-6) mediated activation of autoimmune T and B cells, thereby preventing the differentiation of B cells into AQP4-IgG-secreting plasmablasts. In June 2020, Satralizumab received its first global approval in Canada for the treatment of NMOSD as a monotherapy or as combination therapy with immunosuppressant in adults and children aged ≥ 12 years who are AQP4-IgG seropositive. Subsequent approvals were granted in Japan, Switzerland, and the

United States (*6*). Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody that targets the B-cell surface antigen CD19. It is indicated for the treatment of a range of autoimmune diseases associated with CD19-expressing B cells (*7*). Inebilizumab received its first global approval on 11 June 2020 in the USA for the treatment of adult patients with NMOSD who are seropositive for IgG autoantibodies against AQP4 (*8*).

Satralizumab and Inebilizumab were respectively approved in China for the treatment of adult patients with AQP4-IgG positive NMOSD in May 2021 and March 2022. The accumulation of real-world evidence for Satralizumab and Inebilizumab has led to their designation as first-line therapies in the Chinese Guidelines for the Diagnosis and Treatment of NMOSD. Separately, the Chinese Evidence-Based Guidelines for the Diagnosis and Treatment of Demyelinating Optic Neuritis, incorporating cost-effectiveness analyses, propose Satralizumab or Inebilizumab (Level of evidence 2B) as options for patients whose disease is refractory to prior immunosuppressant therapy (*e.g.*, azathioprine, mycophenolate mofetil, or rituximab) (*9-11*).

However, the introduction of these novel therapeutic agents underscores the need for a comprehensive understanding of their safety profiles. Although Satralizumab and Inebilizumab have demonstrated significant clinical efficacy, the spectrum of associated AEs raises pertinent clinical concerns that necessitate careful evaluation (*12,13*). For Satralizumab, reports have surfaced indicating potential risks such as nasopharyngitis, upper respiratory tract infection, and headache (*14*). AEs associated with Inebilizumab treatment have been reported to include urinary tract infections, arthralgia, and infusion-related reactions. Notably, a case of severe respiratory failure was documented in a patient with NMOSD following inebilizumab administration, which was subsequently diagnosed as Pneumocystis jirovecii pneumonia (*15*). The occurrence of such adverse reactions may compromise patient compliance and present clinical challenges in balancing therapeutic efficacy with safety considerations.

Addressing this critical gap, the present study utilizes the extensive repository of the FDA Adverse Event Reporting System (FAERS) database to conduct a comprehensive analysis of adverse events associated with Satralizumab and Inebilizumab. The FAERS is a publicly accessible database maintained by the FDA. All data within FAERS are freely available and can be downloaded directly from the official FDA website without any registration or application process. To protect patient privacy, all case data undergo de-identification, removing personal identifiers such as names and contact information. As such, the dataset primarily comprises demographic information (*e.g.*, age, gender), drug exposure details, and adverse event reports, with no content that could directly reveal a patient's identity. Consequently, the use of this database typically does not require additional ethical approval. With its broad coverage and real-time reporting of adverse drug events (ADEs), FAERS plays a crucial role in identifying and evaluating potential safety signals (*16*). This study aims to systematically assess ADE signals related to Satralizumab and Inebilizumab following their market approval, using data extracted from the FAERS database. The findings are expected to enhance the clinical management of NMOSD by supporting informed treatment decisions based on a balanced evaluation of therapeutic benefits and associated risks.

2. Materials and Methods

2.1. Study design and data acquisition

This retrospective pharmacovigilance analysis covered the period from Q1 2020 to Q4 2024, a timeframe selected to accommodate the market availability of the two drugs. The corresponding ASCII data packages were downloaded from the FAERS database and imported into SAS 9.4 software. The FAERS data were obtained on a quarterly basis and comprised seven files: demographic and administrative information (DEMO), drug information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start and end dates for reported drugs (THER), indications for use (INDI). The FAERS data were retrieved from the FAERS quarterly data extract files, which can be accessed at *https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html*. The analysis focused on identifying and comparing AE signals associated with Satralizumab and Inebilizumab, taking into account their distinct pharmacodynamic profiles.

2.2. Data mining

The target drugs were defined as "satralizumab", "enspryng", "inebilizumab", "upliznatm". We used CASEID to remove duplicate reports and verified the FDA_DT date to ensure the uniqueness of each patient's record. In the database, each report is assigned a single Primary Suspect (PS) drug. To identify the target drug user population, only cases in which a target drug was designated as the PS were considered. Thus, if a patient's PS drug in the analyzed dataset matched one of the target drugs, the patient was included in the target drug cohort; all other patients were assigned to the non-target drug cohort. Each report underwent thorough review to confirm relevance; essential information collected included demographic characteristics (such as age and gender), descriptions of AEs, event outcomes, and the type of reporter (healthcare professional or consumer). Data extraction and management were performed using R 4.3.2 and OpenVigil, which facilitated efficient

processing of large datasets and improved accuracy in the identification of duplicate records.

2.3. Adverse event codification

AEs were coded in accordance with the terminology established by the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0. The hierarchical framework of MedDRA supports the systematic categorization of AE information, thereby promoting consistency in reporting across diverse pharmacovigilance studies. AEs were classified based on the principal System Organ Classes (SOCs) and Preferred Terms (PTs) as specified in MedDRA, enabling a granular analysis of the AE profiles for both therapeutic agents.

2.4. Statistical methodology

In this study, four disproportionality analysis methods were employed for signal detection: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinker (MGPS). The integration of these methods aims to leverage their respective advantages to broaden the scope of signal detection, enable multi-perspective validation, and enhance the comprehensiveness and reliability of identified safety signals (*17*). By combining multiple algorithms, cross-validation can be performed to mitigate false positives, while the adjustment of thresholds and variance parameters facilitates the identification of potential rare adverse reactions. The ROR was applied to evaluate the disproportionality in reporting between a target drug-event pair and all other events. A higher ROR value suggests a potential safety signal (*18*). The PRR measures the proportion of reports for a specific drug-event combination relative to all other drugs reported with the same event. A PRR significantly greater than 1 is indicative of a signal (*19*). The BCPNN method computes the Information Component (IC) within a Bayesian framework, where a positive IC value reflects a statistically relevant association (*20*). MGPS, as an empirical Bayesian data mining approach, calculates the Empirical Bayes Geometric Mean (EBGM) to quantify association strength, with higher EBGM values pointing to stronger signals (*21*). A signal was considered significant when it met all the following criteria: *i*) ROR $\geq$ 3 with the lower limit of the 95% confidence interval (95% CI) > 1; *ii*) PRR $\geq$ 2 with the lower limit of the 95% CI > 1; *iii*) IC025 > 0; and *iv*) EBGM05 > 2. Detailed algorithms and formulas are provided in the Appendix (Supplementary Tables S1-S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=284*). Furthermore, we used χ^2 tests to compare demographic characteristics between the two drug groups. A p-value < 0.05 was considered statistically significant for these comparisons. Given that FAERS data are derived from a spontaneous reporting system without a defined population denominator, these statistical tests are considered descriptive. While p values are reported, they are intended for exploratory comparison and should not be interpreted as indicating population-level significance.

3. Results

3.1. Descriptive analysis

The extensive dataset compiled by FAERS is depicted in Figure 1, showcasing a total of 23,168,942 AE reports collected from the first quarter of 2020 to the second quarter of 2025. After cleaning the data, FAERS collected a total of 19,252,329 AE reports, of which 1,114 were related to Satralizumab and 349 were related to Inebilizumab. Both Satralizumab and Inebilizumab were launched in 2020; however, the number of adverse reaction reports associated with Inebilizumab was substantially lower than that of Satralizumab.

Table 1 presents a detailed demographic analysis of AE reports associated with Satralizumab and Inebilizumab in the treatment of NMOSD. The data indicate a slight predominance of AE reports among females. Specifically, males accounted for 12.39% and 7.45% of AE reports for Satralizumab and Inebilizumab, respectively, reflecting a subtle gender disparity in AE reporting patterns; however, no statistically significant difference was observed in gender distribution between the two treatment groups (exploratory $p = 0.760$). With the exception of gender, significant differences were observed between the two drugs in terms of age, report year, reporter, reporter country, indications, serious reports, and adverse event occurrence time ($p < 0.01$). The details are presented in Table 1.

The AEs associated with Satralizumab and Inebilizumab both peaked in 2024, with 360 and 120 cases reported, respectively. Physicians constituted the primary source of reports. The majority of these reports originated from the United States, followed by Japan and other countries, including China.

The specific indications for Satralizumab and Inebilizumab, primarily in NMOSD and myasthenia gravis, are supported by the data presented in Table 1, which show that these conditions collectively account for more than 60% of all AE reports. The substantial proportion of reports with unspecified indications points to potential gaps in documentation or possible off-label use, introducing additional complexity into drug safety monitoring.

Furthermore, the proportion of reports classified as serious was higher for Satralizumab than for Inebilizumab. It is important to note that the "serious" designation in FAERS is based on outcomes such as hospitalization and may reflect disease relapse. We evaluated reported outcomes to assess the prognosis

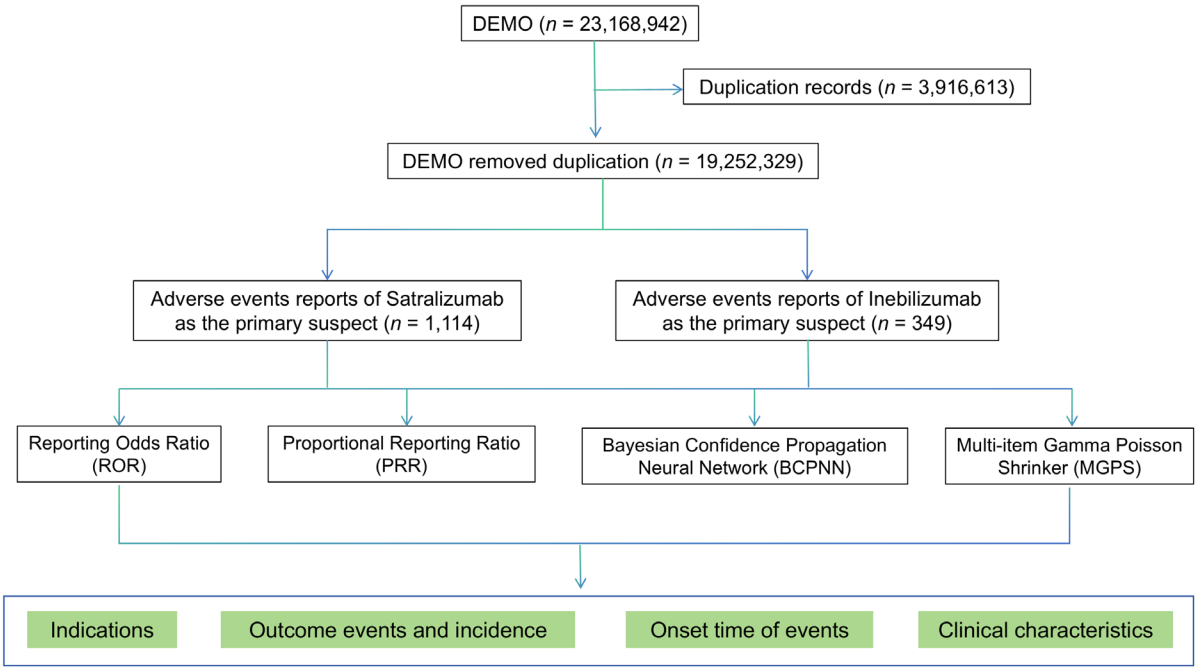

Figure 1. Flowchart of the research. The study comprises data collection and cleaning, disproportionality analysis methods to calculate signal strength, and presentation of results.

of patients experiencing AEs following treatment with either agent. Among all documented AEs, congenital anomalies were the least frequently reported (0.18% for Inebilizumab and 0.29% for Satralizumab), whereas initial or prolonged hospitalization represented the most common outcome (37.25% and 27.79%, respectively). Time-to-onset (TTO) analysis indicated that both Satralizumab and Inebilizumab exhibited a higher proportion of adverse reactions occurring within 30 days after treatment initiation

3.2. Disproportionality analysis

A comprehensive disproportionality analysis of AE reports associated with Satralizumab and Inebilizumab was conducted using data extracted from the FDA's FAERS database, providing significant insights into the safety profiles of these therapeutic agents. Based on a robust statistical framework, Satralizumab reported 874 PTs, while Inebilizumab reported 373 PTs, with 221 PTs shared between them. This analysis identified 64 and 28 strong disproportionality signals for Satralizumab and Inebilizumab, respectively, using four distinct algorithms (ROR, PRR, BCPNN, and MGPS).As shown in Supplementary Table S3 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=284*), these signals, indicative of a statistically significant disproportionality between the observed and expected number of AE reports, highlight potential areas of concern and necessitate a deeper examination of the drugs' safety profiles.

The top 20 PTs associated with Satralizumab and Inebilizumab are presented in Table 2. Apart from NMOSD, AEs related to Satralizumab were predominantly infection-related, including urinary tract infection (*n* = 79, ROR = 10.16, 95% CI: 8.12–12.70), pneumonia (*n* = 58, ROR = 3.66, 95% CI: 2.8–4.75), COVID-19 (*n* = 46, ROR = 5.49, 95% CI: 4.1–7.34), and sepsis (*n* = 25, ROR = 4.78, 95% CI: 3.22–7.09). In contrast, AEs associated with Inebilizumab were more frequently related to pain, such as headache (*n* =28, ROR = 3.11, 95% CI: 2.14–4.53), pain (*n* = 21, ROR = 2.34, 95% CI: 1.52–3.61), arthralgia (*n* = 17, ROR = 2.87, 95% CI: 1.78–4.64), and back pain (*n* = 9, ROR = 2.63, 95% CI: 1.37–5.08).

A statistical analysis of adverse events was performed across two drugs based on SOC standards. The results indicate that Infections and infestations had the highest reporting proportion among overall adverse events (*n* = 681, 18.81%) (Table 3). This was followed by nervous system disorders (*n* = 582, 15.22%), general disorders and administration site conditions (*n* = 485, 12.69%), injury, poisoning and procedural complications (*n* = 343, 8.97%), and musculoskeletal and connective tissue disorders (*n* = 265, 6.93%).

3.3. Comparison of safety signals in serious group

In the analysis, 60 serious AEs associated with Satralizumab and 11 with Inebilizumab met the criteria across four statistical methods, the top 20 serious AEs are shown in Figure 2. Unique serious AEs specific to Satralizumab included pyelonephritis, compression fracture and lymphocyte count decreased. In contrast,

Table 1. Data of reports associated with Satralizumab and Inebilizumab From Q1 of 2004 to Q2 of 2025

Characteristic	Satralizumab (*n* = 1,114) Reports, *n* (%)	Inebilizumab (*n* = 349) Reports, *n* (%)	χ^2/Z	*p*
Gender			0.093	0.760
Female	886 (79.53)	179 (51.29)		
Male	138 (12.39)	26 (7.45)		
Not Specified	90 (8.08)	144 (41.26)		
Age			16.097	0.01
< 18	17 (1.53)	1 (0.29)		
18–44	171 (15.35)	52 (14.90)		
45–64	344 (30.88)	81 (23.21)		
≥ 65	269 (24.15)	34 (9.74)		
Not Specified	313 (28.10)	181 (51.86)		
Report year			124.641	0.00
2020	4 (0.36)	19 (5.44)		
2021	77 (6.91)	71 (20.34)		
2022	163 (14.63)	21 (6.02)		
2023	278 (24.96)	45 (12.89)		
2024	360 (32.32)	120 (34.38)		
2025	232 (20.83)	73 (20.92)		
Reporter			68.481	0.00
Consumer	383 (34.38)	111 (31.81)		
Pharmacist	99 (8.89)	90 (25.79)		
Physician	625 (56.10)	148 (42.41)		
Not Specified	7 (0.63)	0 (0)		
Reporter country			158.052	0.00
United States	431 (38.69)	269 (77.08)		
Japan	468 (42.01)	51 (14.61)		
China	58 (5.21)	5 (1.43)		
Other	157 (14.09)	24 (6.88)		
Indications (TOP 3)			113.029	0.00
Neuromyelitis optica spectrum disorder	988 (88.69)	235 (67.34)		
Product used for unknown indication	78 (7.00)	98 (28.08)		
Myasthenia gravis	9 (0.81)	2 (0.57)		
Other	39 (3.50)	14 (4.01)		
Serious Report			462.577	0.00
Serious	820 (73.61)	180 (51.58)		
Non-Serious	294 (26.39)	169 (48.42)		
Outcome			5.502	0.358
Life-Threatening	26 (2.33)	7 (2.01)		
Hospitalization - Initial or Prolonged	415 (37.25)	97 (27.79)		
Disability	23 (2.06)	4 (1.15)		
Death	55 (4.94)	23 (6.59)		
Congenital Anomaly	2 (0.18)	1 (0.29)		
Other	424 (38.06)	111 (31.81)		
Adverse event occurrence time - medication date (days)			20.960	0.04
0–30 d	140 (12.57)	64 (18.34)		
31–60 d	38 (3.41)	8 (2.29)		
61–90 d	34 (3.05)	5 (1.43)		
91–120 d	29 (2.60)	5 (1.43)		
121–150 d	28 (2.51)	2 (0.57)		
151–180 d	16 (1.44)	2 (0.57)		
181–360 d	57 (5.12)	19 (5.44)		
> 360 d	87 (7.81)	18 (5.16)		
Missing	685 (61.49)	226 (64.76)		

Inebilizumab was associated with distinct serious AEs such as blood immunoglobulin G decreased, COVID-19 pneumonia and acute respiratory distress syndrome.

Comparative analysis of serious AE reports revealed that reports of NMOSD, urinary tract infection, and optic neuritis were more frequently associated with Satralizumab. It should be noted that terms such as "NMOSD" and "optic neuritis" may reflect underlying disease activity rather than drug-induced toxicity. Conversely, reports of pneumonia, COVID-19, herpes zoster, blindness, and COVID-19 pneumonia showed a stronger association with Inebilizumab. Refer to Table 4 for further details.

4. Discussion

Comparative efficacy analyses provide valuable evidence to support informed decision-making. For healthcare

Table 2. The top 20 ADE signals of Satralizumab and Inebilizumab

Satralizumab						Inebilizumab					
PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)	PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)
Neuromyelitis optica spectrum disorder	178	3132.92 (2,664.56–3,683.60)	2941.61 (455,078)	11.32 (7.15)	2558.43 (2,175.95)	Neuromyelitis optica spectrum disorder	42	2,093.24 (1,528.66–2,866.34)	1,996.57 (81,198.0)	10.92 (4.94)	1,935.21 (1,413.25)
Urinary tract infection	79	10.16 (8.12–12.70)	9.91 (634.23)	3.31 (2.83)	9.90 (7.92)	Headache	28	3.11 (2.14–4.53)	3.05 (38.86)	1.61 (0.96)	3.05 (2.09)
Pneumonia	58	3.66 (2.82–4.75)	3.61 (110.02)	1.85 (1.41)	3.61 (2.78)	COVID-19	26	10.07 (6.82–14.88)	9.81 (206.37)	3.29 (2.32)	9.81 (6.64)
COVID-19	46	5.49 (4.10–7.34)	5.42 (166.10)	2.44 (1.88)	5.42 (4.05)	Pneumonia	22	4.47 (2.93–6.83)	4.39 (57.89)	2.13 (1.32)	4.39 (2.87)
No adverse event	41	4.96 (3.64–6.75)	4.90 (127.76)	2.29 (1.72)	4.90 (3.60)	Pain	21	2.34 (1.52–3.61)	2.31 (15.73)	1.21 (0.50)	2.31 (1.50)
Hypoaesthesia	27	3.80 (2.60–5.55)	3.77 (55.19)	1.92 (1.23)	3.77 (2.58)	Arthralgia	17	2.87 (1.78–4.64)	2.83 (20.32)	1.50 (0.67)	2.83 (1.75)
Sepsis	25	4.78 (3.22–7.09)	4.75 (74.07)	2.25 (1.48)	4.75 (3.20)	Product storage error	14	9.97 (5.88–16.90)	9.83 (111.21)	3.30 (1.88)	9.83 (5.80)
Infection	21	3.18 (2.07–4.89)	3.1 7(31.17)	1.66 (0.91)	3.16 (2.06)	Hypoaesthesia*	13	5.90 (3.41–10.19)	5.83 (52.08)	2.54 (1.34)	5.82 (3.37)
Cellulitis	20	8.36 (5.39–12.99)	8.31 (128.72)	3.05 (1.99)	8.31 (5.35)	Urinary tract infection	12	4.87 (2.76–8.62)	4.82 (36.47)	2.27 (1.09)	4.82 (2.73)
Muscular weakness	19	3.56 (2.27–5.59)	3.54 (34.70)	1.82 (1.00)	3.54 (2.25)	Pyrexia	11	2.17 (1.20–3.94)	2.16 (6.88)	1.11 (0.14)	2.16 (1.19)
Septic shock	19	9.56 (6.09–15.01)	9.50 (144.62)	3.25 (2.09)	9.50 (6.05)	Back pain	9	2.63 (1.37–5.08)	2.62 (9.03)	1.39 (0.25)	2.62 (1.36)
Hepatic function abnormal*	18	10.58 (6.66–16.82)	10.52 (155.11)	3.39 (2.14)	10.52 (6.62)	Muscle spasms	8	2.95 (1.47–5.91)	2.93 (10.19)	1.55 (0.30)	2.93 (1.46)
Herpes zoster	17	6.29 (3.90–10.13)	6.25 (75.09)	2.64 (1.59)	6.25 (3.88)	Vision blurred*	8	4.05 (2.02–8.12)	4.02 (18.19)	2.01 (0.62)	4.02 (2.00)
Lymphocyte count decreased	16	19.14 (11.71–31.29)	19.04 (273.28)	4.25 (2.50)	19.02 (11.63)	Infusion related reaction	8	8.83 (4.40–17.71)	8.76 (55.04)	3.13 (1.27)	8.76 (4.37)
Syringe issue	15	18.05 (10.87–29.99)	17.96 (240.13)	4.17 (2.40)	17.95 (10.80)	COVID-19 pneumonia	8	45.93 (22.89–92.15)	45.53 (348.26)	5.51 (1.97)	45.50 (22.68)
Compression fracture*	14	22.20 (13.13–37.55)	22.10 (281.80)	4.46 (2.45)	22.08 (13.06)	Burning sensation*	7	6.82 (3.24–14.34)	6.77 (34.46)	2.76 (0.95)	6.77 (3.22)
Optic neuritis	14	32.09 (18.97–54.27)	31.94 (418.95)	4.99 (2.63)	31.89 (18.85)	Paraesthesia*	7	3.00 (1.43–6.32)	2.99 (9.27)	1.58 (0.23)	2.99 (1.42)
Pyelonephritis	14	34.89 (20.63–59.01)	34.73 (457.83)	5.12 (2.67)	34.67 (20.50)	Visual impairment*	7	3.78 (1.80–7.95)	3.76 (14.20)	1.91 (0.46)	3.76 (1.79)

*Note: *indicated the PT was not included in the specification.*

Table 2. The top 20 ADE signals of Satralizumab and Inebilizumab (continued)

	Satralizumab					Inebilizumab					
PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)	PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)
Blindness*	13	6.89 (4.00–11.89)	6.87 (65.18)	2.78 (1.50)	6.86 (3.98)	Circumstance or information capable of leading to medication error	7	14.56 (6.92–30.64)	14.46(87.73)	3.85 (1.41)	14.46 (6.87)
Cystitis	13	8.53 (4.95–14.72)	8.50 (86.03)	3.09 (1.69)	8.50 (4.93)	Intercepted product administration error	7	56.08 (26.65–118.01)	55.66 (375.44)	5.80 (1.80)	55.61 (26.43)

*Note: *indicated the PT was not included in the specification.*

providers, this evidence aids in developing patient care plans, while payers and fundholders utilize it to inform coverage and reimbursement policies. The most credible source of comparative evidence comes from head-to-head randomized controlled trials (RCTs). However, conducting such trials with adequate statistical power to compare all relevant treatments is often not feasible, particularly for rare diseases like AQP4-IgG-seropositive NMOSD, which is characterized by low prevalence and incidence. In this study, we performed a comprehensive analysis and comparison of ADE reports associated with two widely used biological agents, Satralizumab and Inebilizumab, using the FDA FAERS database. Our findings confirm previous reports (*22*) of a higher reporting proportion of ADEs for both Satralizumab and Inebilizumab in females (79.53% *vs.* 12.39% and 51.29% *vs.* 7.45%, respectively). This disparity may be attributed to the higher prevalence of NMOSD in females, as well as their potentially greater awareness or reporting of adverse reactions (*23*). Additionally, since the FAERS database is largely dominated by reports from the United States, the majority of ADEs originated from this country — particularly for Inebilizumab (Satralizumab: 38.69%; Inebilizumab: 77.08%) — suggesting a possible geographical bias. With the increasing incidence of NMOSD, ADE reports linked to Satralizumab and Inebilizumab have risen annually.

Based on our analyses, Satralizumab and Inebilizumab generated signals in urinary tract infection, pneumonia and COVID-19 similarly in the results of Top 20 PTs. Meanwhile, signals for terms such as NMOSD and hypoaesthesia were also detected. It is important to interpret these signals cautiously, as they may reflect the underlying relapsing nature of NMOSD rather than direct drug toxicity. The primary clinical manifestations of the disease, such as paresthesia and limb numbness, often reflect this refractory disease course (*24*). Furthermore, these AEs mentioned in labels may be linked to the drug's pharmacological mechanism. Satralizumab, a monoclonal antibody targeting the interleukin-6 receptor, works by inhibiting IL-6 signaling — a pathway central to the pathology of NMOSD. As IL-6 is a key pro-inflammatory cytokine, its inhibition can suppress classical signs of inflammation such as fever and an elevated C-reactive protein level. This effect poses a risk of concealing or delaying the diagnosis of infections, which are critical complications requiring vigilant monitoring following the initiation of biologic therapy. Particular attention should be paid to the potential exacerbation of urinary tract and respiratory infections (*25*). Consistent with its mechanism of action, Inebilizumab depletes B lymphocytes, leading to a reduction in lymphocyte counts. As is observed with other B-cell depleting therapies, this effect is associated with an increased risk of infection. Among the associated adverse events with an incidence greater than 10%, urinary tract infection was the most notable, occurring

Table 3. System organ classes (SOCs) for adverse events of Satralizumab and Inebilizumab

SOC	*n* (%)	Satralizumab *n* (%)	Inebilizumab *n* (%)
Infections and infestations	681 (17.81%)	558 (19.15%)	123 (13.53%)
Nervous system disorders	582 (15.22%)	432 (14.82%)	150 (16.50%)
General disorders and administration site conditions	485 (12.69%)	330 (11.32%)	155 (17.05%)
Injury, poisoning and procedural complications	343 (8.97%)	244 (8.37%)	99 (10.89%)
Musculoskeletal and connective tissue disorders	265 (6.93%)	191 (6.55%)	74 (8.14%)
Investigations	222 (5.81%)	189 (6.49%)	33 (3.63%)
Gastrointestinal disorders	194 (5.07%)	141 (4.84%)	53 (5.83%)
Eye disorders	135 (3.53%)	98 (3.36%)	37 (4.07%)
Respiratory, thoracic and mediastinal disorders	135 (3.53%)	97 (3.33%)	38 (4.18%)
Psychiatric disorders	100 (2.62%)	87 (2.99%)	13 (1.43%)
Skin and subcutaneous tissue disorders	108 (2.83%)	81 (2.78%)	27 (2.97%)
Hepatobiliary disorders	74 (1.94%)	69 (2.37%)	5 (0.55%)
Blood and lymphatic system disorders	78 (2.04%)	63 (2.16%)	15 (1.65%)
Product issues	56 (1.46%)	55 (1.89%)	1 (0.11%)
Metabolism and nutrition disorders	61 (1.60%)	52 (1.78%)	9 (0.99%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	57 (1.49%)	51 (1.75%)	6 (0.66%)
Renal and urinary disorders	56 (1.46%)	43 (1.48%)	13 (1.43%)
Vascular disorders	61 (1.60%)	42 (1.44%)	19 (2.09%)
Cardiac disorders	32 (0.84%)	28 (0.96%)	4 (0.44%)
Immune system disorders	29 (0.76%)	21 (0.72%)	8 (0.88%)
Social circumstances	12 (0.31%)	10 (0.34%)	2 (0.22%)
Surgical and medical procedures	14 (0.37%)	8 (0.27%)	6 (0.66%)
Reproductive system and breast disorders	13 (0.34%)	8 (0.27%)	5 (0.55%)
Endocrine disorders	11 (0.29%)	7 (0.24%)	4 (0.44%)
Ear and labyrinth disorders	8 (0.21%)	4 (0.14%)	4 (0.44%)
Pregnancy, puerperium and perinatal conditions	8 (0.21%)	4 (0.14%)	4 (0.44%)
Congenital, familial and genetic disorders	3 (0.08%)	1 (0.03%)	2 (0.22%)

in 20% of patients (*26,27*). These findings are consistent with our results.

Our analysis further revealed a distinct profile of treatment-emergent AEs between the two biologics. AEs associated with Satralizumab were predominantly infectious in nature, whereas those linked to Inebilizumab were more strongly correlated with pain-related disorders. This observation is consistent with published literature indicating that pain — including headache, back pain, extremity pain, and chest pain — is a recognized side effect of certain immunosuppressive agents such as Inebilizumab (*28*). In contrast, findings from Ikeguchi *et al*. suggest a potential therapeutic benefit of Satralizumab in pain management (*29*). This analgesic effect may be mechanistically explained by the blockade of IL-6, a pronociceptive cytokine critically involved in the pathogenesis of neuropathic pain. By inhibiting IL-6 signaling, Satralizumab not only reduces immunological activity but may also directly attenuate neuropathic pain (*30*). Consequently, for patients with a pre-existing risk or clinical presentation of neuropathic pain, Satralizumab may represent a more favorable therapeutic option compared to Inebilizumab.

There are slight differences in the SOC distribution between Satralizumab and Inebilizumab. Infections and infestations, nervous system disorders, general disorders and administration site conditions, injury, poisoning and procedural complications, and musculoskeletal and connective tissue disorders remain key concerns. This is similar to the results reported in previous literature (*31*).

The most frequently reported serious events associated with both Satralizumab and Inebilizumab were terms corresponding to the disease itself, such as "NMOSD" and "optic neuritis". This observation can be explained by the recurrent nature of NMOSD, in which disability accrual is primarily attributable to acute relapses (*32,33*). Literature reports indicate that Satralizumab was superior to Inebilizumab in reducing relapse rate (*34*). This finding contrasts with the trend observed in the present study, which indicated a higher reporting frequency of serious adverse event reports with Satralizumab compared to Inebilizumab. Furthermore, our signal detection analysis indicated that reports of COVID-19 and COVID-19 pneumonia showed a stronger association with Inebilizumab. It is unknown if Inebilizumab increases the susceptibility to SARS-CoV-2 or if it predisposes to a more severe infection. B-cell lymphopenia may impact T-cell activation which is involved in the early immune response against SARS-CoV-2 but more importantly may influence antibody-mediated long-term immunity against the virus potentially increasing reinfection risk. Furthermore, it is possible that Inebilizumab may impact the efficacy of viral protein vaccines including future SARS-CoV-2 vaccines when they become available (*35*). However, given the small case numbers and the nature of spontaneous reporting, this finding should be considered hypothesis-generating. Potential explanations include

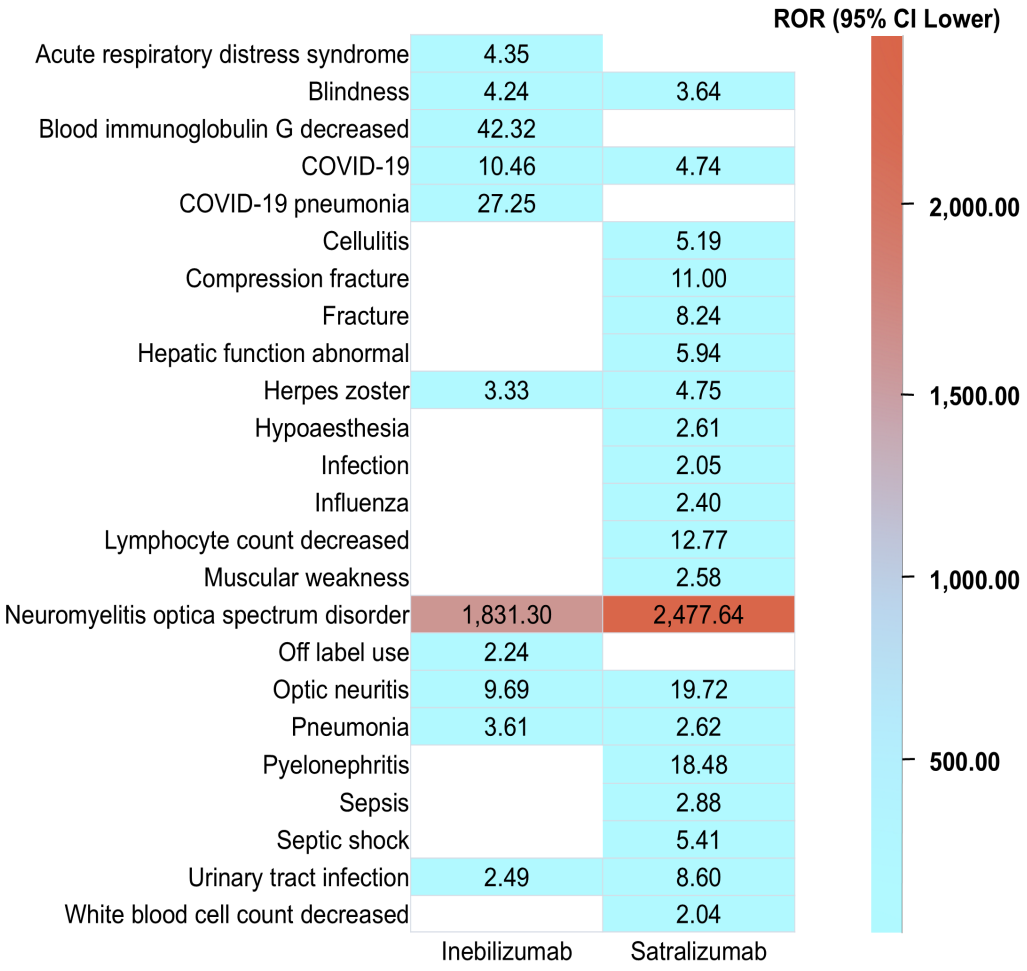

Figure 2. The top 20 serious AEs of Satralizumab and Inebilizumab.

Table 4. Comparison of ADE PTs in serious group between Satralizumab and Inebilizumab

ADE	Satralizumab		Inebilizumab		ROR (Satralizumab)/ ROR (Inebilizumab)
	Case Reports	ROR (95% CI)	Case Reports	ROR (95% CI)	
Neuromyelitis optica spectrum disorder	178	2918.23 (2477.64–3437.16)	41	2530.34 (1831.30–3496.20)	1.15
Urinary tract infection	72	10.88 (8.60–13.76)	8	5.01 (2.49–10.08)	2.17
Pneumonia	58	3.40 (2.62–4.41)	22	5.53 (3.61–8.48)	0.61
COVID-19	35	6.62 (4.74–9.25)	20	16.35 (10.46–25.55)	0.40
Herpes zoster	15	7.90 (4.75–13.12)	4	8.90 (3.33–23.79)	0.89
Optic neuritis	14	33.38 (19.72–56.48)	3	30.14 (9.69–93.77)	1.11
Blindness	13	6.27 (3.64–10.82)	5	10.22 (4.24–24.66)	0.61
COVID-19 pneumonia	4	6.40 (2.40–17.07)	8	54.79 (27.25–110.17)	0.12

reporting bias, temporal coincidence, and differential exposure during the pandemic, rather than a definitive causal relationship.

Given that both therapies were approved in 2020, differences in time since market introduction are unlikely to account for this discrepancy. Meanwhile, variations in trial designs, methodologies, treatment durations, and comparator groups limit the reliability of direct comparisons between these two agents (*36*). Therefore, further research is necessary to validate and extend these findings and to address remaining questions in this field.

Our analysis of the FAERS database provides valuable insights into the safety signals associated with Satralizumab and Inebilizumab. However, it is crucial to acknowledge the inherent limitations of spontaneous reporting systems. FAERS data are not derived from a defined population and are subject to significant reporting bias, under-reporting, and lack of

denominator data. Consequently, while we observed a trend toward lower SAE reports for Satralizumab, these findings are exploratory and should not be over-interpreted as conclusive evidence of a superior safety profile in the broader patient population. Second, due to the retrospective nature of the study, we can only identify associations between the drugs and adverse events rather than establish causal relationships. Third, FAERS data do not allow for the calculation of adverse event incidence rates or medication error frequencies in the monitored population; they are primarily useful for generating hypotheses rather than confirming them. Fourth, the effects of combination therapy, patient health status and disease progression cannot be excluded, although these are often inherent characteristics of patients.

5. Conclusion

Our comprehensive analysis underscores the critical role of pharmacovigilance in optimizing the management of NMOSD. As Satralizumab andInebilizumab remain pivotal therapeutic options for this condition, our findings provide valuable insights into their long-term safety profiles. This knowledge is essential for supporting evidence-based clinical decisions and ultimately improving patient outcomes. Future research, complemented by more robust pharmacovigilance methodologies, will be crucial to refine our understanding and advance the goal of safe and effective NMOSD therapy.

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