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Guillain-Barré syndrome and checkpoint inhibitor therapy: insights from pharmacovigilance data

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ABSTRACT

Background There are increasing reports of cases of Guillain-Barré syndrome (GBS), as an adverse event of an immune checkpoint inhibitor (ICI) but postmarket data on the incidence of this remains scarce. This study sought to conduct a comprehensive review of GBS events arising as a secondary outcome of ICI treatments in real-world patients, using the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods Data covering the period from the third quarter of 2003 to the second quarter of 2023 were extracted from the FAERS database. GBS cases (associated with the usage of avelumab, atezolizumab, ipilimumab, nivolumab and pembrolizumab) were subjected to disproportionality analysis to detect potential signals.

Results A total of 2208 reports of GBS were identified within the FAERS database, with 242 of these cases (10.9%) being associated with ICIs. All five drugs exhibited a disproportionality in the reporting of adverse events, with the highest observed for avelumab (reporting OR, ROR: 29.8), followed by atezolizumab (ROR: 17.0), ipilimumab (ROR: 16.0), pembrolizumab (ROR: 11.9) and nivolumab (ROR: 8.2).

Conclusion These checkpoint inhibitors are associated with a statistically significant disproportionate number of reports of GBS as an adverse event, with avelumab being the ICI with the highest association. The present pharmacovigilance study serves as a valuable tool, offering a more comprehensive and nuanced perspective on GBS associated with ICIs. This study contributes to a deeper comprehension of this rare adverse drug effect.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Guillain-Barré syndrome (GBS), an autoimmune nerve disorder and the most common cause of acute flaccid paralysis worldwide, has been linked to immune checkpoint inhibitors (ICIs) used in cancer treatment, although its occurrence is rare. ICIs, such as avelumab, atezolizumab, ipilimumab, nivolumab and pembrolizumab, can induce immune-related adverse events, including GBS.

WHAT THIS STUDY ADDS

⇒ This study adds valuable insights into the association between ICIs and GBS by conducting a comprehensive analysis of real-world data from the Food and Drug Administration Adverse Event Reporting System. It contributes to existing knowledge by demonstrating a disproportionality of adverse event reports for GBS linked to various ICIs, evaluating avelumab, atezolizumab, ipilimumab, nivolumab and pembrolizumab. This information is crucial in expanding our understanding of the safety profile of ICIs, particularly in the context of rare adverse events such as GBS, and can guide healthcare professionals and regulators in making informed decisions regarding the use of these immunotherapies in cancer treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may raise awareness among healthcare professionals, leading to improved monitoring and early detection of GBS in ICI-treated patients. Policymakers and regulators could use these findings to update safety guidelines and enhance risk communication. Patient education efforts could also benefit from this study, empowering individuals to make informed treatment decisions and report symptoms promptly, ultimately improving cancer care and patient outcomes.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have emerged as a revolutionary approach in cancer therapy, offering new hope to patients by harnessing the power of the immune system to combat malignancies. This new class of antitumour drugs is used to treat multiple tumour types, including melanoma, oesophageal, urothelial and non-small-cell lung cancer. These monoclonal antibodies activate the T cells to target tumour cells, by blocking checkpoint proteins from binding with their partner proteins expressed in tumourous surface. Immune checkpoints are part of the normal immune system that work as a physiological barrier to avoid an excessive immune response. These surface proteins, when activated by tumourous cells, send a blocking signal, preventing the immune system from destroying the cancer.

ICIs prevent this protein binding, which allows T cells to kill cancer cells. There are multiple receptors that may be targeted by these drugs, such as programmed cell death receptor 1 (PD1), programmed cell death ligand 1 (PDL-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). However, amidst their promising success, these immunotherapeutic agents have brought to light a distinct and challenging facet of treatment—neurological adverse events. These events encompass a spectrum of neuromuscular complications that can occur as unintended consequences of checkpoint inhibitor therapy, ranging from mild and reversible symptoms to severe and potentially life-threatening conditions.[1–3]

Guillain-Barré syndrome (GBS) is a rare neurological disorder characterised by the immune system's misguided attack on the peripheral nerves, resulting in muscle weakness and paralysis and is the most common cause of flaccid paralysis worldwide.[4 5] The link between checkpoint inhibitors and the development of GBS has been described in case reports.[6–11] Conversely, there have been reports highlighting the safety of ICI administration in patients with a history of GBS.[12–14]

This data alerts us to the importance of understanding the incidence of this type of event with the ICI class. The aim of this study was to investigate and analyse data sourced from a significant pharmacovigilance database (FAER) the incidence of GBS as an adverse event in patients receiving ICI therapy.

METHODS

Data sources

This observational investigation examines postmarketing pharmacovigilance information concerning checkpoint inhibitors, obtained from patients, healthcare providers and pharmaceutical company submissions. The research is centred on adverse events documented within the Food and Drug Administration Adverse Event Reporting System (FAERS) database, using the Medical Dictionary for Regulatory Activities hierarchy. Specifically, the scrutiny focuses on the reports labelled as 'GBS' Low-Level Term. Furthermore, IQVIA (IMS Health and Quintiles Via, Inc.) Analytics databases provided sales data spanning from 2018 to 2022, with queries executed in August 2023, encompassing the assessment period extending from 1 January 2018 to 31 December 2022.

Data analysis

The analysis centred around ICIs, specifically avelumab (anti-PD-L1), atezolizumab (anti-PD-L1), ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1) and pembrolizumab (anti-PD-1), which belong to distinct classes of ICIs extensively employed in a wide range of cancer therapies.

To conduct a thorough assessment of safety profiles, a two-pronged evaluation approach was employed. This approach involved the examination of absolute numbers of adverse reports and their relative frequencies obtained from post-market surveillance (FAERS) data spanning from 1 January 2018 to 31 December 2022. Simultaneously, a disproportionality analysis was performed, using the reporting OR (ROR) with a 95% CI, to investigate reporting frequencies of GBS in relation to immune ICIs.

To explore the potential associations between medication sales, utilisation and reported adverse events, we conducted a comprehensive 5-year analysis of the frequencies or adverse events. This analysis aimed to uncover possible correlations between medication sales, usage patterns and reported adverse events, thus providing valuable insights into safety profiles and the real-world impact of these medications. Given the diversity of indications and patient groups, we addressed challenges related to data standardisation by quantifying adverse events per 10 000 units sold in North America, allowing for meaningful comparisons despite variations in incidence rates.

Disproportionality analysis and ROR

Disproportionality analysis is a method employed in pharmacovigilance to assess and quantify potential associations between a specific medical intervention, typically a drug or vaccine, and adverse events or side effects. It involves the examination of data from spontaneous reporting systems or electronic health records to identify whether a particular adverse event occurs more frequently than would be expected by chance alone.[15] Disproportionality analysis helps in detecting signals of potential safety concerns associated with a medical intervention.

ROR is a statistical measure frequently used in disproportionality analysis. It is calculated by comparing the odds of a specific adverse event being reported for a particular medical intervention (eg, a drug) relative to all other drugs in the database. A high ROR suggests a potential association between the medical intervention and the adverse event, indicating the need for further investigation. The ROR is a valuable tool in pharmacovigilance for prioritising and identifying potential safety signals that may require regulatory action or additional research to assess causality and risk mitigation strategies.

RESULTS

In the analysis conducted, a total of 11 439 756 adverse events reports were found, within which 2208 cases of GBS were identified. Remarkably, the examination of the 5 specific drugs (checkpoint inhibitors) under scrutiny revealed 242 reported instances of GBS, constituting 10.9% of the overall GBS cases reported.

Table 1 provides a breakdown of the number of GBS events associated with each of the ICIs, while figure 1 shows the sales volume in North America for each drug from 2018 to 2022.

Figure 2 illustrates the absolute count of GBS cases reported, devoid of any adjustment for sales volume. Among the drugs examined, pembrolizumab exhibited the highest incidence of reported cases linked to its usage, surpassing nivolumab, ipilimumab and atezolizumab in this regard. Notably, avelumab garnered the highest total

Table 1 Reported GBS related to peripheral neuropathy for each checkpoint inhibitor

Medication	Reported GBS (n)	Units sold (2018–2022)
Avelumab	8	466 870
Ipilimumab	59	647 872
Atezolizumab	42	930 048
Nivolumab	61	5 859 631
Pembrolizumab	72	10 154 878

GBS, Guillain-Barré syndrome.

count of absolute cases reported among the drugs under consideration.

Figure 3 illustrates a straightforward division of the incidence of GBS per unit of drug sales in North America. According to this metric, ipilimumab exhibited the highest GBS incidence rate at 0.009%, followed by atezolizumab at 0.004%, avelumab at 0.001%, nivolumab at 0.001%, and finally, pembrolizumab at 0.0007%.

A disproportionality analysis was conducted to compare the five drugs against the entire database, following standard methodology. This preliminary assessment unveiled statistically significant disproportionalities in adverse event reporting across all drugs (p<0.001). The drug that showed the highest disproportionality, evaluated by the ROR, was avelumab (ROR 29.8, 95% CI 14.8 to 59.8, p<0.001), followed by atezolizumab (ROR 17.0, 95% CI 12.5 to 23.1, p<0.001), ipilimumab (ROR 16.0, 95% CI 12.4 to 20.8, p<0.001), pembrolizumab (ROR 11.9, 95% CI 9.4 to 15.1, p<0.001), and lastly, nivolumab (ROR 8.2, 95% CI 6.3 to 10.6, p<0.001) (see table 2 and figure 4).

In figure 5, the proportions of GBS relative to other reported adverse events associated with the same drug are depicted. Notably, all drugs exhibited a small proportion, consistently below 1%, reflecting the disproportionality analysis results in their sequence.

DISCUSSION

This study centred on GBS occurrences linked to ICIs within the FAERS database. Although GBS cases in the database were relatively infrequent, comprising merely 0.01% of all reported cases, the five selected drugs under investigation accounted for a substantial 10.9% of all GBS instances documented in the database. This underscores the imperative need to carefully assess the GBS risk associated with these specific drugs.

Initially, pembrolizumab may appear to be the drug most closely associated with GBS, with 72 reported cases. However, it is essential to factor in the sales volume. Given that pembrolizumab boasts a broader range of indications (and consequently, higher sales volume), it is reasonable to anticipate a higher number of cases in comparison to, for instance, avelumab, which exhibited the lowest sales volume and eight reported cases.

To standardise the data, particularly considering the substantial sales volume disparities, an events-to-sales ratio can be used. According to this metric, ipilimumab, with sales volume slightly surpassing that of avelumab, exhibited the highest GBS incidence, nearing 1 event for every 10 000 units sold. In contrast, pembrolizumab,

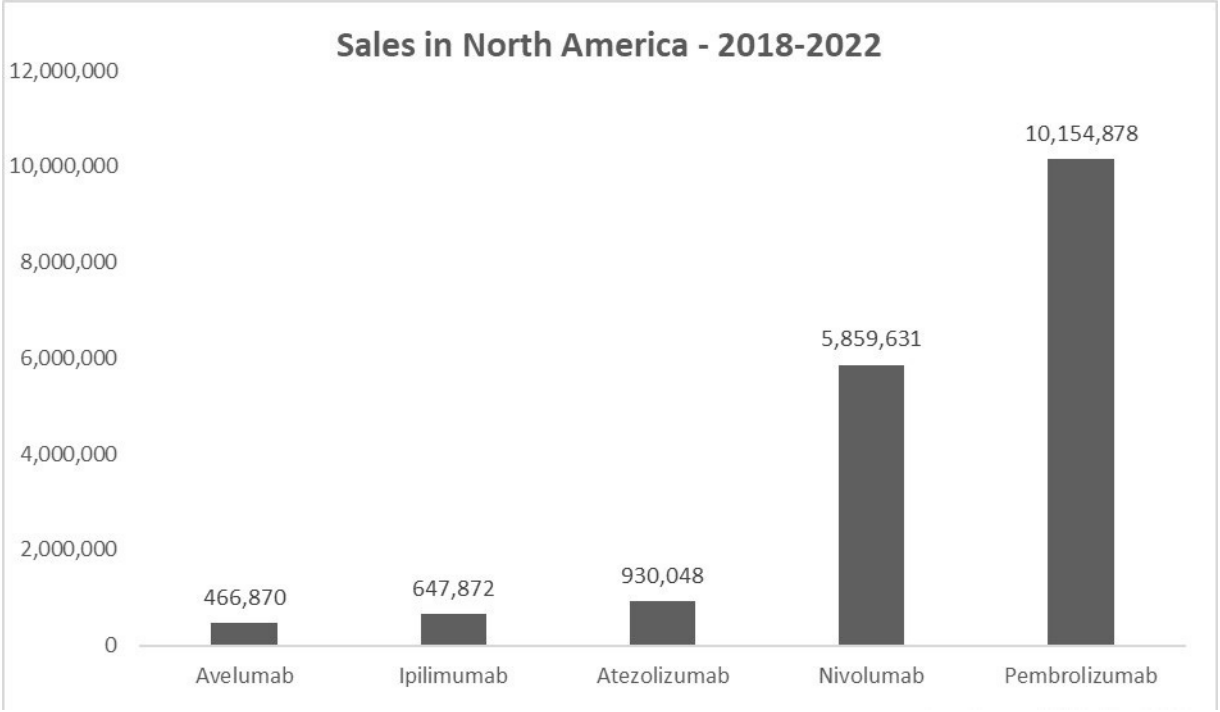

Figure 1 Total sales in North America between 2018 and 2022. Data Source: IQVIA (IMS Health and Quintiles Via, Inc.), May 2023.

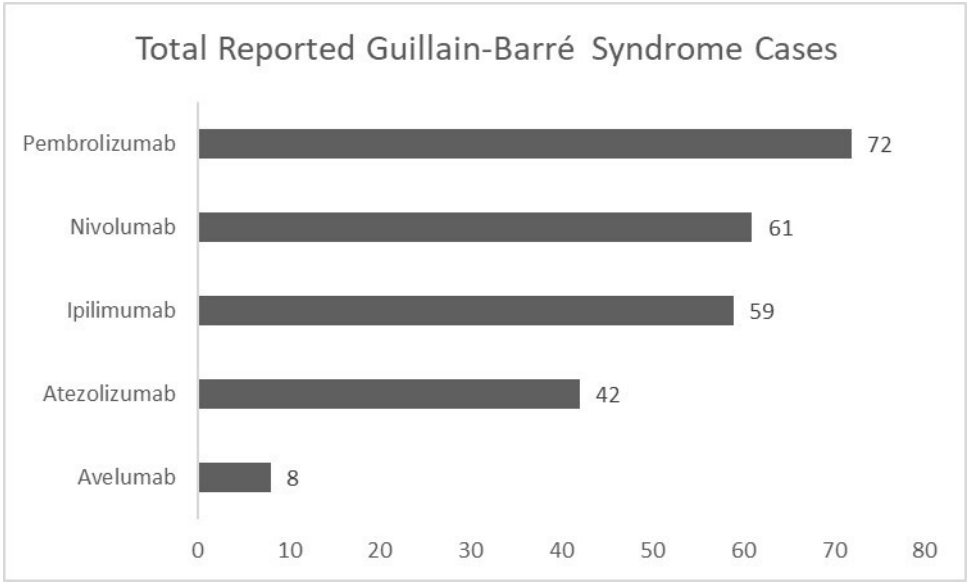

Figure 2 Absolute number of reported cases of Guillain-Barré syndrome by drug.

despite having the highest absolute number of reported events, presented the lowest rate, approximately seven cases for every million units sold.

In pursuit of a comprehensive analysis, our team opted for disproportionality analysis, a cornerstone approach in pharmacovigilance. This methodology transcends basic event-to-sales ratios, instead embracing a nuanced and statistically robust assessment, offering a deeper understanding of the data and potential associations within.

Disproportionality analysis assesses whether a specific adverse event is reported more frequently for a particular medical intervention compared with all other interventions in a comprehensive dataset. This evaluation is crucial as it considers the inherent variability in reporting rates, healthcare practices and population characteristics. By employing statistical methods such as the ROR or Bayesian data mining algorithms, disproportionality analysis can detect signals that might otherwise be obscured by confounding factors.

In contrast, the simple division of event counts by sales, while straightforward, lacks the sophistication of disproportionality analysis. It may yield biased results due to

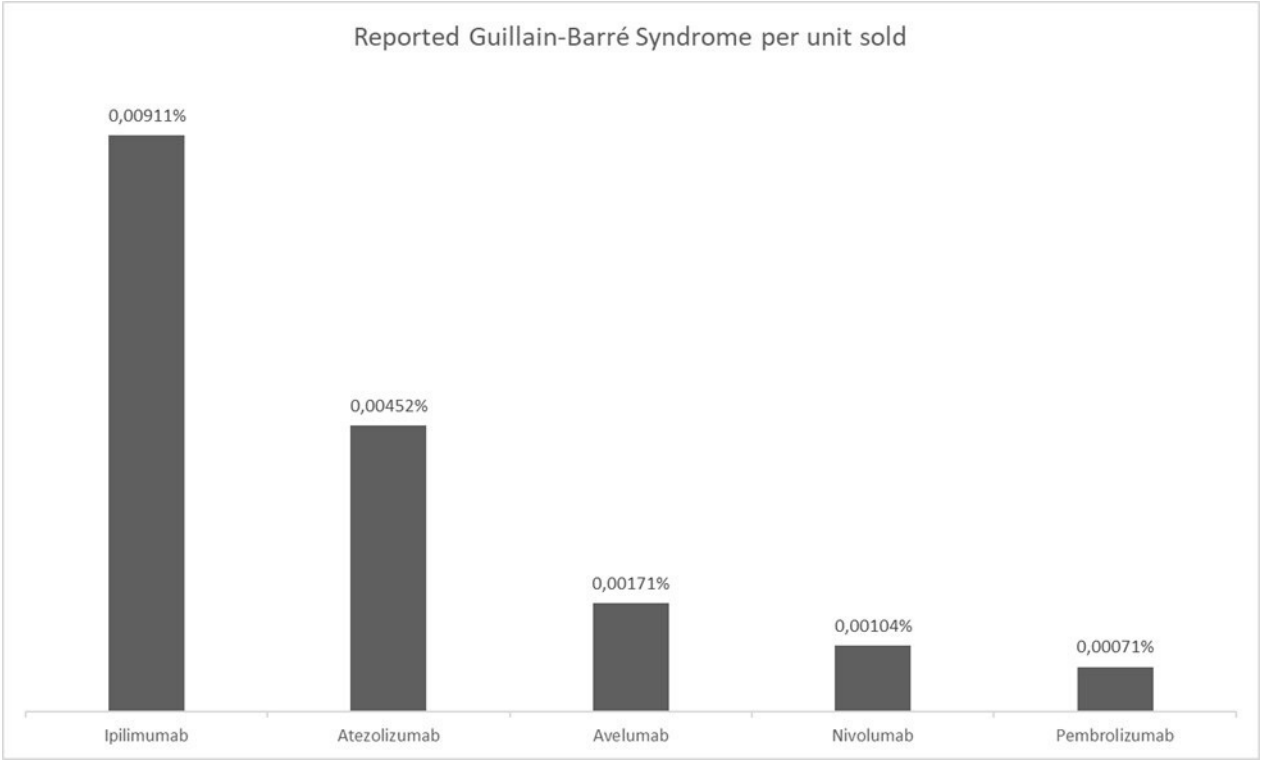

Figure 3 Guillain-Barré syndrome rate by unit sold in North America (2018–2022).

Table 2 Disproportionality analysis by drug

Drug	ROR	95% CI (p<0.001)	% GBS over other events
Avelumab	29.854	14.8 to 58.9	0.57
Atezolizumab	17.075	12.5 to 23.1	0.32
Ipilimumab	16.084	12.4 to 20.8	0.30
Pembrolizumab	11.977	9.4 to 15.1	0.22
Nivolumab	8.218	6.3 to 10.6	0.15

.GBS, Guillain-Barré syndrome; ROR, reporting OR.

varying sales volumes, reporting practices and underreporting of adverse events. Thus, disproportionality analysis is considered a more rigorous and data-driven approach for identifying potential safety concerns associated with medical interventions, enabling more accurate risk assessment and regulatory decision-making.

The disproportionality analysis indicated RORs exceeding two for all drugs. While Harpaz *et al*[16] set the threshold at 2, other authors suggest a threshold of 1.0. Regardless of the chosen threshold, it is evident that most drugs exhibit a statistically significant disproportional frequency of reported GBS.

All drugs presented high RORs, notably avelumab (ROR: 29.8), followed by atezolizumab (ROR: 17.0), ipilimumab (ROR: 16.0), pembrolizumab (ROR: 11.9) and nivolumab (ROR: 8.2). Collectively, this indicates a statistically significant increase in reported cases of GBS during checkpoint inhibitors therapy, underscoring the presence of a potential safety signal necessitating further investigation when GBS cases arise. Consequently, healthcare practitioners must incorporate discussions about GBS into therapeutic planning, remaining vigilant for related symptoms during the administration of these medications.

As with any retrospective study, this investigation has inherent limitations that require acknowledgement. Reliance on secondary data sources, such as the FAERS database, may introduce biases, data inconsistencies[17] or incomplete reporting.[18] To establish a more robust understanding of the safety profiles of checkpoint inhibitors, future prospective studies and real-world data analyses are warranted. Additionally, exploring potential factors contributing to the observed variation in neurological adverse events, including patient characteristics

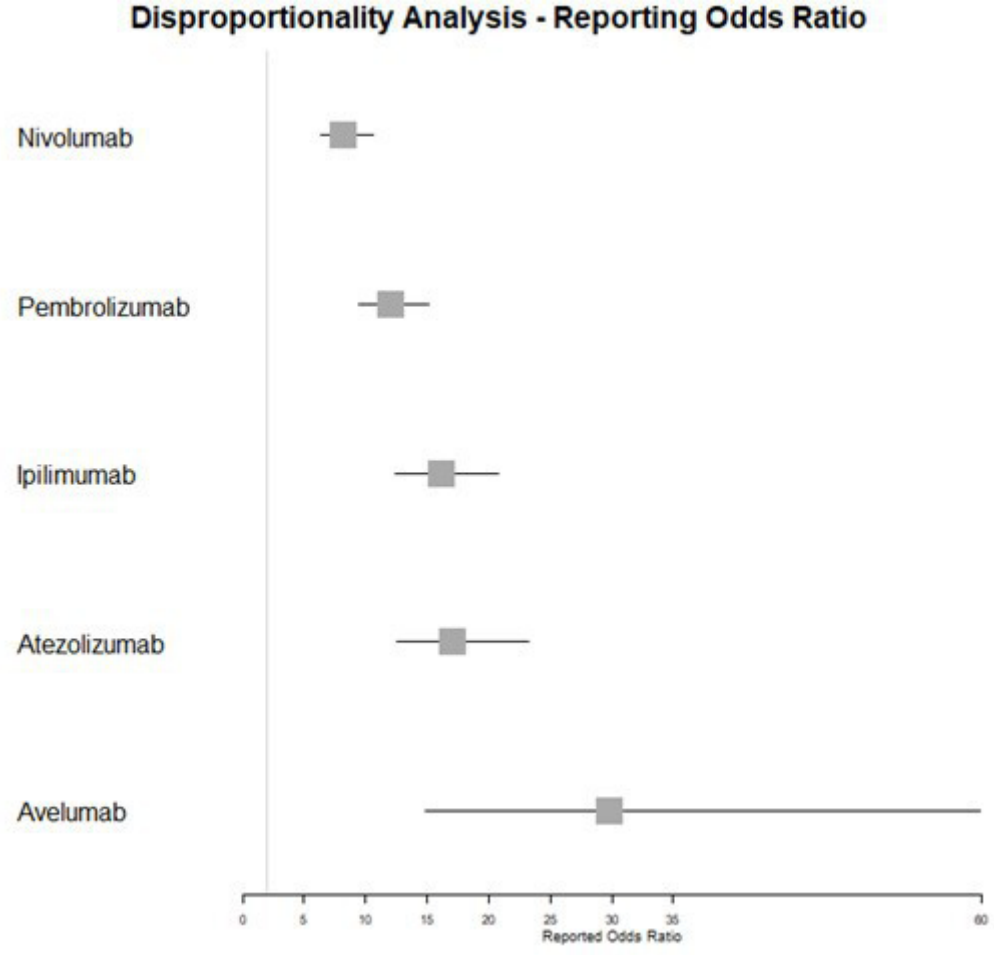

Figure 4 Disproportionality analysis by drug.

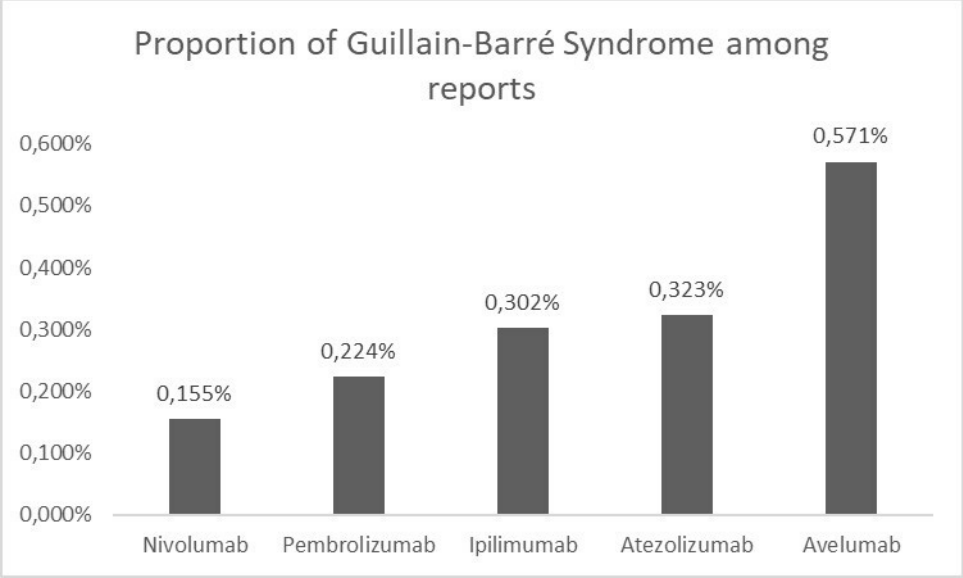

Figure 5 Proportion of Guillain-Barré syndrome among other reported adverse events.

and concomitant medications, may yield valuable insights for further refining therapeutic strategies.

In a similar study, Ruggiero *et al*[19] evaluated individual case safety reports from the European spontaneous reporting database, EudraVigilance, reviewing all forms of neuropathies. The author concluded that ipilimumab had an increased reporting probability of peripheral neuropathies when compared with anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 agents (atezolizumab, avelumab). It is noteworthy that ipilimumab was the only ICI authorised in the European market until 2015, when pembrolizumab was approved. The American market had, by 2015, 3 ICIs approved: ipilimumab (2011), nivolumab (2014) and pembrolizumab (2014). The availability of more ICIs may explain the different results found by the author, as well as the different approved indications of use.

This study found that the class with higher incidence of GBS was anti-PDL1 medications (avelumab, atezolizumab). This finding contradicts some published studies, such as the meta-analysis by Sonpavde *et al*[20] which reported higher total adverse events with anti-PD1 medications compared with anti-PDL1 medications. Our interpretation is that the source of data may explain the different results, while the metanalysis is based on published literature, our research is based on self-reported real-world data which provides practical insights but may carry bias and lack standardisation.

This study contributes to the growing body of evidence regarding the safety profiles of checkpoint inhibitors, particularly in the context of neurological adverse events such as GBS. The findings underscore the importance of vigilant pharmacovigilance practices and continuous evaluation of drug safety in clinical settings. A comprehensive understanding of adverse event reporting dynamics and management for this therapeutics is indispensable for guiding future regulatory decisions and optimising the landscape of precision medicine. Collaborative research efforts between clinicians, researchers and regulatory authorities will play a crucial role in advancing safer and more effective therapeutic interventions in the fields of oncology and immunotherapy.

CONCLUSION

The analysis of adverse event patterns linked to checkpoint inhibitors reveals a substantial association with GBS, with avelumab exhibiting the highest disproportionality of reports. While a rare adverse event, checkpoint inhibitors use is associated with more than 10% of reported GBS cases. This signals the necessity for heightened vigilance among healthcare practitioners when GBS cases arise during treatment with these medications. While the study offers valuable insights for oncology care, it acknowledges its limitations. Future prospective research and consideration of patient characteristics are essential. Maintaining vigilant pharmacovigilance practices remains crucial in oncology to optimise drug safety and enhance therapeutic strategies.

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