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Immune checkpoint inhibitor rechallenge after immune-related adverse events: a retrospective study from VigiBase update in 2024 looking for emergent safety signals

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ABSTRACT

Objectives Limited information is available on the safety of a rechallenge with an immune checkpoint inhibitor (ICI) after occurrence of an immune-related adverse event (irAE). We aim to identify potential emergent safety signals.

Design This is an update of our observational pharmacovigilance cohort study.

Setting We exanimated individual case safety reports from the WHO database VigiBase.

Participants We included all individual case safety reports with ICI and rechallenged ICI.

Interventions We identified that incident irAE cases using the Medical Dictionary for Regulatory Activities V.26.1 related with at least one ICI administration were systematically collected until 1 March 2024.

Primary and secondary outcome measures The primary outcome was the recurrence rate (expressed as a percentage with its 95% CI) of the initial irAE postrechallenge with the same ICI.

Results We identified 1016 irAEs cases from ICI rechallenges. Of these, 323 irAEs recurrences occurred (31.8%, 95% CI 28.1 to 34.0). The most common postrechallenge irAEs were nephritis (recurrence rate: 50%, 95% CI 25 to 75), skin irAEs (44%, 95% CI 31 to 58) and colitis (39%, 95% CI 33 to 44).

Conclusions In this updated, largest cohort study on rechallenge (NCT04696250), we observed a 31.8% recurrence rate of the same irAE postrechallenge with the same ICI, building on our previous findings.

Trial registration number NCT04696250.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Largest cohort of immune-related adverse event.
⇒ International.
⇒ Emergent safety signals.
⇒ Retrospective.
⇒ No Common Terminology Criteria for Adverse Events grade differentiation.

INTRODUCTION

The advent of immune checkpoint inhibitors (ICIs) has profoundly transformed oncological therapeutics over recent years.[1] Sustained therapeutic responses have been documented, such as in metastatic melanoma, where overall survival (OS) at 6.5 years reaches 42% and 49% for nivolumab and the combination of nivolumab and ipilimumab, respectively.[2] These substantial clinical benefits at the metastatic stage have led to the broadening implementation of ICIs across the therapeutic spectrum, including in the adjuvant[3] and neoadjuvant settings.[4] Now endorsed for the management of all solid cancers, ICIs have indeed been conceded as the contemporary standard of care. This efficacy is paradoxically mediated by the same mechanism that prompts immune-related adverse events (irAEs), stemming from systemic immune activation.[5 6] Up to 80% of patients may encounter any-grade irAEs, with Common Terminology Criteria for Adverse Events grades 3–5 irAEs affecting 8%.[7] Although the majority of irAEs abate on cessation of ICI therapy and corticosteroid administration, their influence on oncological outcomes remains a subject of ongoing debate.[8] For severe or corticoresistant irAEs, the introduction of immunomodulatory agents is recommended, adhering to established guidelines.[9] The term 'rechallenge' is frequently used to describe the resumption of an ICI following a hiatus required for the irAE resolution.[10] With ICIs being introduced earlier in the disease trajectory and concomitant with OS extension, patients frequently face the prospect of multiple exposures to ICIs during their lifetime. Therefore, understanding the safety of rechallenge is critical, in the context of limited alternative treatments. Our study is an expansive cohort

of our initial recruitment[11] in which we documented a recurrence rate of 28.8% for the original irAE on rechallenge, noting particularly high recurrence rates for irAEs such as colitis and pneumonitis. Herein, we extend our prior inquiry and provide an updated analysis on irAE recurrence post-rechallenge.

MATERIALS AND METHODS

Data were sourced from VigiBase, the WHO pharmacovigilance database managed by the Uppsala Monitoring Centre (Sweden).

Incident irAE cases related with at least one ICI administration were systematically collected, until 1 March 2024. We identified irAEs using Preferred Terms from the Medical Dictionary for Regulatory Activities V.26.1. ICI therapies included anti-PD-1 antibodies (cemiplimab, dostarlimab, nivolumab, pembrolizumab, retifanlimab), anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab), anti-CTLA-4 antibodies (ipilimumab, tremelimumab), and anti-LAG3 therapy (relatlimab). ICI regimen types were classified as anti-PD(L)−1 monotherapy, anti-CTLA-4 monotherapy, combined anti-PD(L)−1/anti-CTLA-4 therapy and combined anti-PD(L)−1/anti-LAG3 therapy. For the initial irAE event, a comprehensive collection of administrative, demographic, drug- and irAE-specific data were pursued, encompassing parameters such as patient age, sex, drug indication, rechallenge, irAE type and severity, and irAE-associated mortality. Each irAE was designated as 'serious' or 'non-serious' in accordance with WHO criteria, and cases were discerned as either initial or updated with progressive follow-up details.

The primary outcome was the reported irAE recurrence rate postrechallenge with the same ICI agent, ascertained among informative rechallenge cases. Exploratory secondary outcomes were factors presumptively associated with irAE recurrence postrechallenge, which encompassed ICI regimens.

Statistical analyses were consistent with our princeps article.[11] Reported recurrence rates were denoted as percentages, dividing the number of irAE recurrence cases by the number of informative rechallenge cases. The 95% CIs for binomial proportions were estimated applying the Agresti-Coull approach. Qualitative variables were reported as frequencies and percentages, while quantitative variables were reported as medians with IQRs. Comparisons between rechallenge and non-rechallenge cohorts were conducted using the χ^2 test or Fisher's exact test for qualitative data, alongside the unpaired Kruskal-Wallis test for quantitative data. Univariate logistic regression was employed to compute reporting ORs with 95% CIs. Statistical significance was ascertained through the Wald test, where a p value less than 0.05 was deemed significant. Statistical computations were performed using the R software for Windows, V.4.3.2 (R Project for Statistical Computing).

The ethics committee at Caen University Hospital deemed formal review and consent procedures unnecessary due to the utilisation of anonymised data within this study.

RESULTS

The study encompassed 48 380 cases of irAEs associated with ICI administrations, which approximates a two-fold

Adverse drug reaction	No. of cases	Recurrence rate (95%CI), %
Diabetes	30	7 (1-22)
Adrenal	76	16 (9-26)
Hypophysitis	42	17 (8-31)
Neurological	39	21 (11-36)
Thyroiditis	119	22 (15-30)
Mucositis	20	25 (11-47)
Uveitis	16	25 (10-50)
Hematological	15	27 (10-52)
Pancreatitis	25	28 (14-48)
Pneumonitis	187	29 (23-36)
Myositis	17	29 (13-53)
Hepatitis	85	32 (23-42)
Myocarditis	15	33 (15-58)
Arthritis	74	35 (25-47)
Colitis	288	39 (33-44)
Skin	50	44 (31-58)
Nephritis	12	50 (25-75)

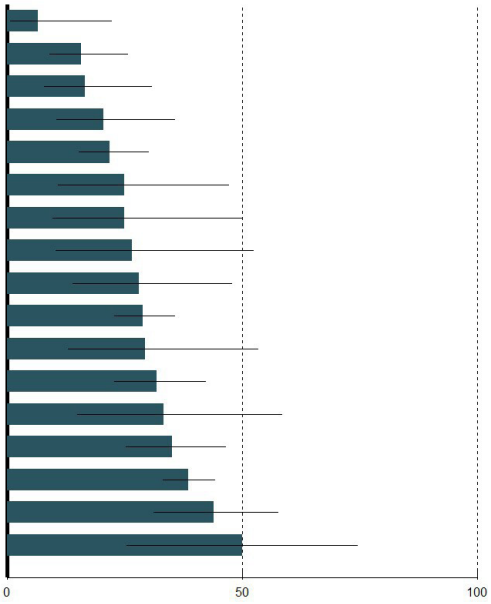

Figure 1 Recurrence rate of immune-related adverse events (irAEs) categorised by the initial affected site updated in March 2024.

increase compared with our inaugural study. A subset of 18 753 cases underwent an ICI rechallenge post-irAE, and 1016 cases had available data on irAE recurrence. Of these, 323 subjects were notified with a recurrence, equating to a 31.8% recurrence rate (95% CI 28.1 to 34.0). Within informative cases, 117 (36.0%) were female, and the modal age group was 65–74 years (n=116, 44.1%). Factors associated with the recurrence of the initial irAE are detailed in supplementary material.

IrAE recurrence was significantly associated with ICI regimens, with a reporting OR of 0.70 (95% CI, 0.50 to 0.98) for anti-PD(L)1 monotherapy, 0.88 (95%CI, 0.36 to 2.15) for anti-CTLA-4 monotherapy, and 1.52 (95%CI, 1.07 to 2.17) for combination therapy.

The three highest recurrence rates were found for nephritis (50%, 95% CI 25 to 75), skin irAEs (44%, 95% CI 31 to 58) and colitis (39%, 95% CI 33 to 44) as shown in figure 1. Details are provided in supplementary material.

DISCUSSION

The safety profile of postrechallenge ICIs remains a relatively terra incognita within the field. Our study, which includes a cohort of 18 753 rechallenge cases—with 1016 yielding informative data—substantially enlarges on the evidence base previously established.[11] We observed 31.8% recurrence of the same irAEs postrechallenge, corroborating both current literature and our previous findings.[11]

Reflecting on retrospective analyses, such as one involving 40 rechallenged patients where 17 (42.5%) experienced a recurrence of the same irAE and 5 (12.5%) manifested a novel irAE,[12] our findings are aligned. Moreover, a meta-analysis surveying 789 cases documented incidences of all-grade and high-grade irAEs at 34.2% and 11.7%, respectively.[13] Gastrointestinal irAEs were associated with higher high-grade irAEs recurrence, while initial anti-PD(L)−1 correlated with lower recurrence. Despite an augmented incidence of all-grade irAEs postrechallenge (OR, 3.81; 95% CI 2.15 to 6.74; p<0.0001), the incidence of high-grade irAEs was not significantly different (p>0.05); hence, the tolerance profile persists as acceptable.

The present inquiry has additionally surfaced novel insights pertaining to nephritis and myocarditis, which were absent from our preceding study.[11] The recurrence rate of nephritis was 50%, which overshadows prior estimates documented in the literature.[14] Our analysis, comprising 12 cases of rechallenged nephritis, may suffer from insufficient statistical power. Additionally, we were unable to assess the potential influence of the temporal interval between the initial irAE and subsequent rechallenge, a factor that could affect nephritis recurrence risk, thereby constraining our ability to derive conclusive insights on risk modulation of nephritis recurrence. Myocarditis, a relatively infrequent but severe irAE,[15] portrayed a 33% recurrence rate postrechallenge in our cohort, underscoring the necessity for careful consideration when contemplating ICI rechallenge in the context of myocarditis.[15] Around one-third of colitis cases exhibited recurrence, although with low mortality rates, potentially allowing for rechallenge when treatment alternatives are absent. Although innovative, our study has certain limitations due to information not available in VigiBase, as data on treatments received to manage these initial and recurrent irAE, with impossibility to determine whether there had been a therapeutic escalation from corticosteroids to immunosuppressive agents from the initial to the recurrent irAE. Similarly, clinical outcomes as OS and PFS are not available in this database, to assess whether certain irAE are of predictive interest.

Provision of rechallenge necessitates cautious appraisal of the risk-benefit ratio by the clinician, with potential establishment of augmented surveillance protocols. In the absence of predictive models to forecast patient-specific irAE occurrences and recurrences, retrospective investigations furnish essential guidance for tailoring treatment strategies to individual patient profiles and their unique irAE histories.

CONCLUSION

The updated dataset of our cohort delineates a global irAE recurrence rate of 31.8% post-ICI rechallenge. This underscores the feasibility of rechallenge in a select patient population, with the stipulation that individualised patient monitoring is imperative, given the observed variability in irAE recurrence and severity.

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