THE USE OF TOCILIZUMAB FOR THE TREATMENT OF REFRACTORY HEPATITIS INDUCED BY CHECKPOINT INHIBITOR IMMUNOTHERAPY

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Introduction

The introduction of immune checkpoint inhibitors (ICI) is prominently used across diverse cancer types and offers patients improved disease control and survival. (1) However, increased T-cell response against self-tissue can cause immune-related adverse events (irAE) including hepatitis. (2)

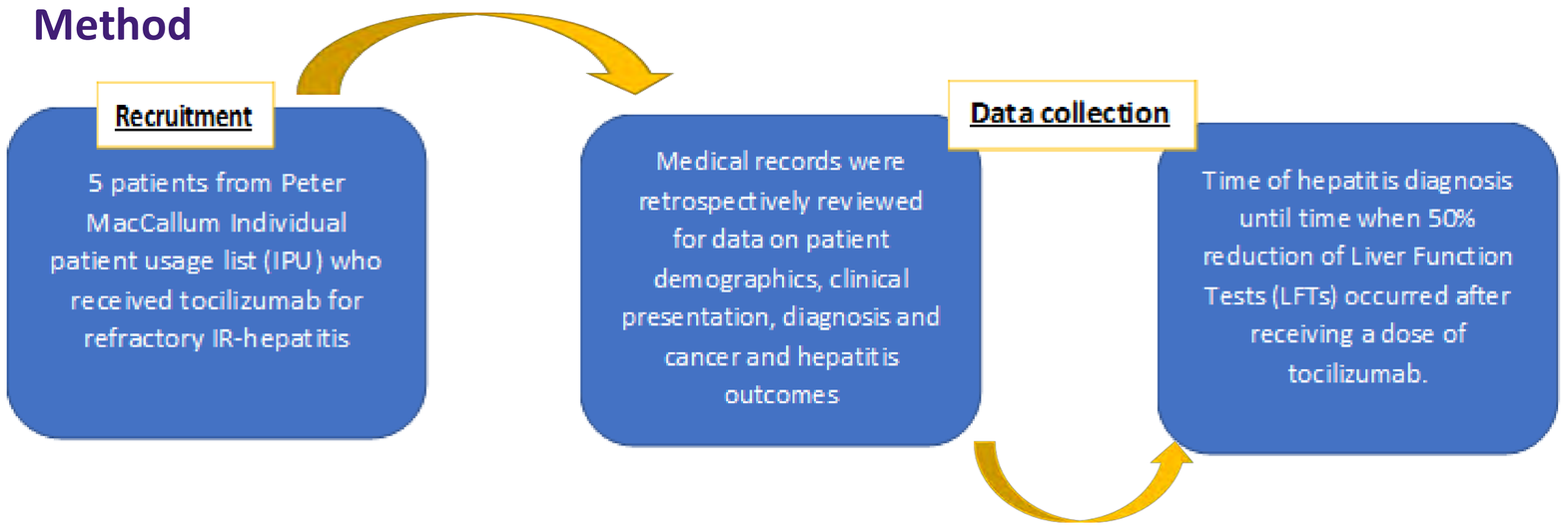
Hepatitis is often asymptomatic and usually manifests as elevations of alanine transaminase (ALT) (normal range <55 U/L) and/or aspartate transaminase (AST) (normal range <55 U/L) and limited after the discontinuation of treatment. (3) The current first line treatment for such immune related adverse event is mainly immunosuppressive therapy such as glucocorticoids as well as the discontinuation of ICI depending on the severity. (4) While the use of glucocorticoids is known to suppress the priming of the immune response, the long-term use can lead to severe systemic toxicity. (5)

Tocilizumab, an anti-cytokine agent, has shown significant anti-inflammatory properties. (4) Observational data suggest the use of tocilizumab to have potential benefits in patients experiencing severe cases of irAEs. (1) However, the possibility of continuing ICI treatment despite the development of irAEs and the subsequent initiation of tocilizumab has never been evaluated. (1) This review will help guide clinician practice and improve cancer care for patient.

Objective

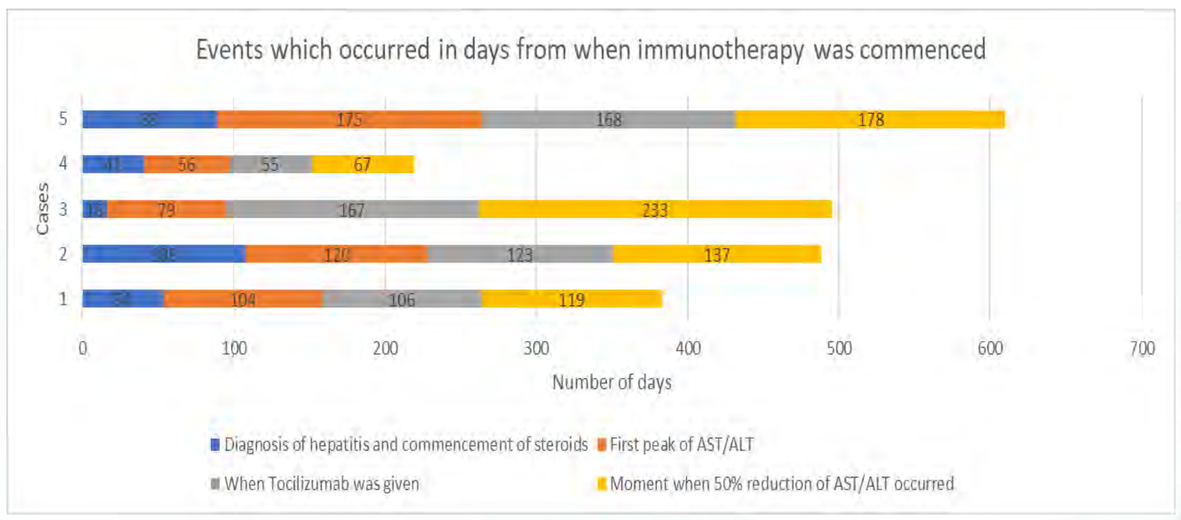
Tocilizumab has been used in limited cases of severe or refractory immune-related hepatitis (IR-hepatitis) induced by ICI immunotherapy. This case series described five patients who received tocilizumab as third-line treatment for refractory immune-related hepatitis.

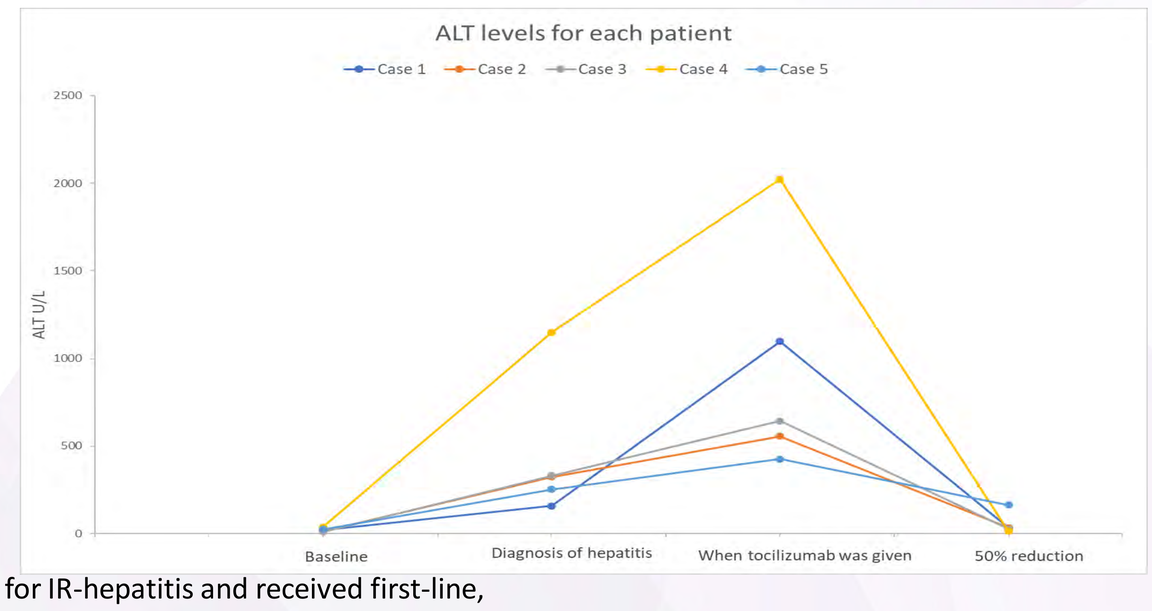
Method



- Retrospective analysis of EMR records
- Data collection occurred over a two-week period from 19/07/2023 to 02/08/2023.

Results





Five patients between the ages of 46-70 received a single-dose of tocilizumab 8mg/kg intravenous for IR-hepatitis and received first-line, high-dose glucocorticoids and either tacrolimus or mycophenolate. All patients were on ICI treatment for advanced melanoma, cervical adenocarcinoma, or prostate cancer. IR-hepatitis occurred after cycles 1-4 of ICI and was characterised by elevated aspartate aminotransferase (AST; mean 342U/L) and alanine aminotransferase (ALT; mean 444U/L).

Discussion

This case series in the largest retrospective analysis of ICI-treated patients with cancer who developed IR-hepatitis and were treated with tocilizumab. In this study, we observed a 50% reduction in AST and ALT from peak within two weeks in three patients following tocilizumab and one patient after two months. The fifth patient died due to cancer progression before IR-hepatitis resolved. Overall, four patients had resolution of IR-hepatitis. No patients experienced tocilizumab-related toxicity.

The retrospective nature of this case series means that there may be missing information that could not be captured. This was a single-centre study and therefore did not capture variations in practice for the use of tocilizumab for hepatitis.

We were limited by the small sample size of this study due to the novel use of tocilizumab, this in turn potentially impacted the generalisability of the study findings and made it difficult to determine whether the outcome was a true indication of the findings. Furthermore, the lack of previous research being conducted on this topic posed a limitation to the research project, this was the first case series on the use of tocilizumab for IR-hepatitis, which may hinder the creditability and scope of this research.

Conclusion

Tocilizumab is a therapeutic option for the management of steroid-refractory IR-hepatitis secondary to ICI. Ongoing data collection to form larger case series will support understanding of the relative efficacy and safety of tocilizumab for this patient population and cancer treatment outcomes.

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