THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Tocilizumab as an Effective Steroid-Sparing Agent for the Treatment of Recurrent and Steroid-Dependent Immune Checkpoint Inhibitor-Mediated Hepatotoxicity: A Case Study and Insight into Pathophysiology

Hao Chi "Joseph" Zhang, M.D.[1], Ethan Miller, M.D.[1], Lan Wang, M.D.[1]
[1]University of Texas MD Anderson Cancer Center, Department of Gastroenterology, Hepatology & Nutrition, Houston, TX

Introduction

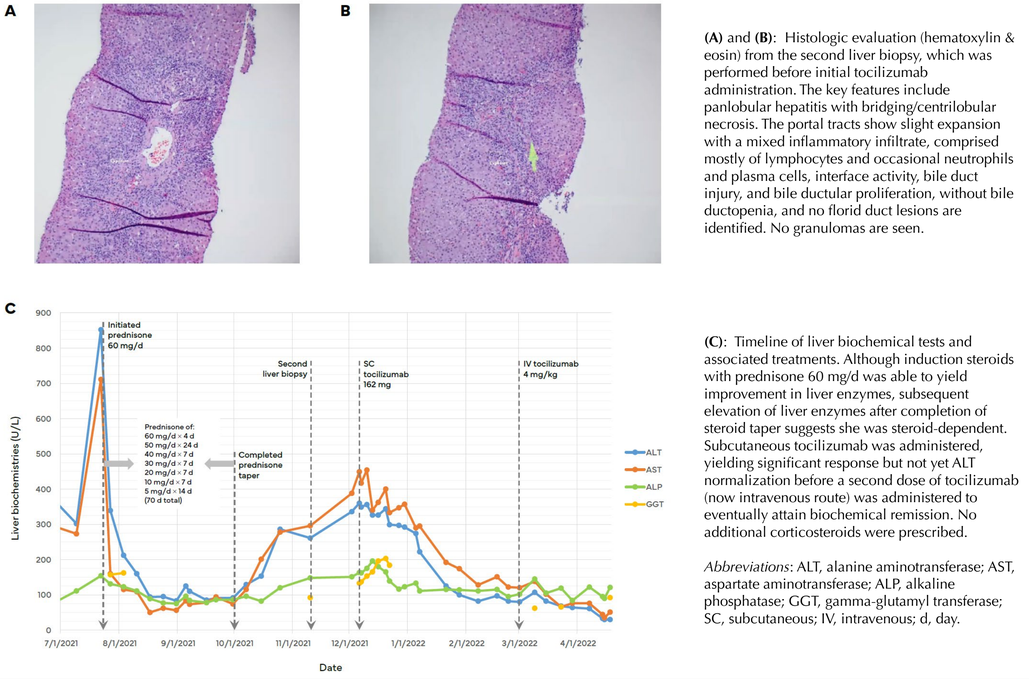
- Immunotherapy-mediated hepatotoxicity (IMH) is a well-recognized immune-mediated adverse event (irAE) in patients who undergo treatment with immune checkpoint inhibitors.
- An effective pathway for addressing steroid-resistant or steroid-dependent cases of IMH remains an area of ongoing investigation. Limited published experience has introduced tocilizumab, an IL-6 receptor antagonist, as a viable steroid-sparing agent to manage challenging cases of IMH.
- We describe a successful case of utilizing tocilizumab in both subcutaneous (SC) and intravenous (IV) forms, without concurrent steroids, to treat a case of recurrent and steroid-dependent IMH.

Case Presentation

- A 32-year-old woman with a history of Hodgkin lymphoma and no underlying liver disease was evaluated for elevated liver enzymes.
- Her lymphoma was managed with autologous stem cell transplant (SCT) (2011), allogenic SCT (2012), nivolumab (2016), and lenalidomide (2019). She started pembrolizumab in 3/2020; the dose was increased by 12/2020.
- Due to CTCAE grade 3 liver toxicity in 1/2021, pembrolizumab was held. A liver biopsy performed in 2/2021 confirmed IMH (instead of hepatic graft-vs-host disease). Initial treatment with prednisone (total of 66 days) yielded biochemical remission. By end of 4/2021, she was re-challenged with 1 dose of pembrolizumab but soon developed grade 4 liver enzyme elevations, so prednisone was reintroduced (induction dose 60 mg/d), but liver enzymes exhibited only partial improvement after 70 days of steroids. Liver enzymes increased again after stopping steroids.

Final Diagnosis

Immune checkpoint inhibitor-mediated hepatotoxicity



(A) and **(B)**: Histologic evaluation (hematoxylin & eosin) from the second liver biopsy, which was performed before initial tocilizumab administration. The key features include panlobular hepatitis with bridging/centrilobular necrosis. The portal tracts show slight expansion with a mixed inflammatory infiltrate, comprised mostly of lymphocytes and occasional neutrophils and plasma cells, interface activity, bile duct injury, and bile ductular proliferation, without bile ductopenia, and no florid duct lesions are identified. No granulomas are seen.

(C): Timeline of liver biochemical tests and associated treatments. Although induction steroids with prednisone 60 mg/d was able to yield improvement in liver enzymes, subsequent elevation of liver enzymes after completion of steroid taper suggests she was steroid-dependent. Subcutaneous tocilizumab was administered, yielding significant response but not yet ALT normalization before a second dose of tocilizumab (now intravenous route) was administered to eventually attain biochemical remission. No additional corticosteroids were prescribed.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; SC, subcutaneous; IV, intravenous; d, day.

Management & Clinical Course

- Repeat liver biopsy reaffirmed IMH. To avoid prolonged exposure to systemic corticosteroids, SC tocilizumab 162 mg was given, leading to subsequent improvement in liver enzymes.
- She developed a brief episode of shingles that was successfully treated. IV tocilizumab 4 mg/kg was additionally given about 2 months later to bring her to biochemical remission that was achieved 1.5 months thereafter, without need for steroids.

Discussion

- IL-6 plays an important role in liver biology.
- Limited reports feature tocilizumab as a feasible and effective option to treat select cases of IMH, including cholangiohepatitis phenotypes and steroid-refractory cases.
- In this case, both SC and IV tocilizumab conferred efficacy in treating IMH without requiring the use of concurrent systemic steroids.
- Our example highlights an unmet clinical need to study steroid-sparing strategies in order avert a protracted course of steroids and to allow patients to engage sooner in additional treatment(s) for malignancy.
- Should a patient require more than 1 administration of tocilizumab, it may be reasonable to adopt current practices from treatment of rheumatoid arthritis, where IV tocilizumab may be given at 4-week intervals, and SC tocilizumab given at 2-week intervals. It is unknown whether IV tocilizumab 4 mg/kg vs. 8 mg/kg would be considered optimal during the first or subsequent dosing. Since achieving early biochemical remission is of importance for these patients, as they may be pending additional alternative malignancy treatment(s), initial dosing of IV tocilizumab of 8 mg/kg is favored. Alternatively, a standard dose of 162 mg of SC tocilizumab may be adopted as the first or second dose.

References

1. Fyada M, et al. Diagnosis and characteristics of immune checkpoint inhibitor-mediated cholangiopathy: a case series (Su327). 2021. Digestive Disease Week 2021. Virtual.
2. Moi L, et al. Personalized Cytokine-Directed Therapy With Tocilizumab for Refractory Immune Checkpoint Inhibitor-Related Cholangiohepatitis. *J Thorac Oncol* 2021;16(2):318-326. doi: 10.1016/j.jtho.2020.09.007. Epub 2020 Sep 19. PMID: 32956849.
3. Reddy CA, et al. Nivolumab-induced large-duct cholangiopathy treated with ursodeoxycholic acid and tocilizumab. *Immunotherapy* 2019;11(18):1527-1531. doi: 10.2217/imt-2019-0121. Epub 2019 Dec 2. PMID: 31789069.
4. Stroud CR, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract* 2019;25(3):551-557. doi: 10.1177/1078155217745144. Epub 2017 Dec 5. PMID: 29207939.
5. Zhang HC, et al. P1868 - Extrahepatic Biliary Sequelae in Immune Checkpoint Inhibitor-Mediated Cholangiohepatitis: Urgent Unmet Need for Early Effective Treatment. ACG 2021 Annual Scientific Meeting Abstracts. Las Vegas, Nevada: American College of Gastroenterology. AJG 2021;116:S1139. doi:10.14309/01.ajg.0000784424.97540.d9
6. Zhang HC, et al. P1869 - Clinical Presentation, Treatment Strategies, and Chronic Sequelae of Immune Checkpoint Inhibitor-Mediated Cholangiopathy: A Case Study. ACG 2021 Annual Scientific Meeting Abstracts. Las Vegas, Nevada: American College of Gastroenterology. AJG 2021;116:S1140. doi:10.14309/01.ajg.0000784428.93302.00