Journal of Clinical and Translational Hepatology **2024** vol. 12(11) | 949–954
DOI: 10.14218/JCTH.2024.00287

Illuminating and Instructive Clinical Case

A Case of Severe Cholestatic Hepatitis Induced by a Novel Dual Agonist of Glucagon-like Peptide-1 and Glucose-dependent Insulinotropic Polypeptide Receptors

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Received: August 16, 2024 | **Revised:** October 15, 2024 | **Accepted:** October 16, 2024 | **Published online:** October 30, 2024

Abstract

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists are increasingly used in the management of type 2 diabetes mellitus and obesity due to their ability to stimulate insulin secretion, delay gastric emptying, and suppress appetite. The combination of GLP-1 and GIP agonists improves glycemic control and promotes weight loss. However, the introduction of these novel therapies has raised safety concerns, including the risk of cholestatic hepatitis. We report a case of a patient with obesity who was prescribed a GLP-1/GIP dual-receptor agonist as part of his treatment regimen. Importantly, both before the initiation of this therapy and during the course of treatment, the patient was not taking any other medications. Shortly after receiving four doses of the therapy, the patient developed symptoms of severe cholestatic hepatitis, including jaundice and elevated liver enzyme levels. During hospitalization, no alternative causes for the condition were identified, and a liver biopsy confirmed the diagnosis of drug-induced cholestatic hepatitis. This is the first recorded case of cholestatic hepatitis induced by a GLP-1/GIP dual agonist, and it aimed to raise global awareness of this potential side effect.

Citation of this article: Jiang J, Shi M, Wu S, Cao M. A Case of Severe Cholestatic Hepatitis Induced by a Novel Dual Agonist of Glucagon-like Peptide-1 and Glucose-dependent Insulinotropic Polypeptide Receptors. J Clin Transl Hepatol 2024; 12(11):949–954. doi: 10.14218/JCTH.2024.00287.

Introduction

In recent years, the global obesity epidemic has driven the pursuit of effective weight management strategies. Among these, the emergence of glucagon-like peptide-1 (GLP-1) receptor agonists, combined with glucose-dependent insulinotropic polypeptide (GIP) receptor antagonists—collectively known as GLP-1/GIP dual agonists—has garnered significant attention as a promising therapeutic option for obesity and related comorbidities.[1] These novel drugs, with their dual mechanism of action targeting appetite regulation and energy expenditure, have become the "stars" of the weight loss arena. However, this narrative of success is not without complications, as evidenced by a recent case of severe cholestatic hepatitis associated with this class of medications.[2]

A proprietary dual agonist of GLP-1 and GIP receptors, developed by Borui pharmaceuticals (BGM0504), potently activates downstream pathways, leading to biological effects such as glycemic control, weight reduction, and potential therapeutic benefits for non-alcoholic steatohepatitis.[3] This demonstrates its therapeutic promise in treating metabolic disorders and represents an advancement over existing agents, such as semaglutide and liraglutide. However, clinical trials have revealed that this new dual-agonist drug can induce severe cholestatic hepatitis.[4] A 52-year-old male patient began exhibiting symptoms three weeks after receiving the fourth dose of BGM0504. The patient was not taking any other medications at the time the BGM0504 was initiated. During hospitalization, no causes other than the medication were identified, and a liver biopsy confirmed the diagnosis of drug-induced cholestatic hepatitis. The following is a detailed description of this case.

Case presentation

Patient information

A 52-year-old male presented with the sudden onset of jaundice in his conjunctiva and skin upon admission on June 12, 2024. Liver function tests revealed significantly elevated bilirubin levels. The patient, of Han Chinese ethnicity from mainland China, had no previous history of similar illnesses. Notably, there was no familial predisposition to jaundice in the patient's medical history. Physical Examination: The patient was obese, with a body mass index (BMI) of 28.7, and exhibited moderate to severe jaundice of the skin, mucous membranes, and sclera, with no signs of ascites or flapping tremors. The patient's family had no history of cholestatic hepatitis.

Keywords: GLP-1 receptor; GIP receptor; Cholestatic hepatitis; Obesity.
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Table 1. Timeline and drugs used in the last six months

Time	2024.1–2024.3	2024.4.26	2024.5.3	2024.5.10	2024.5.20	2024.6.7–2024.6.11
Suspicious drug	None	The first injection of BGM0504 (2.5 mg)	Second injection of BGM0504 (2.5 mg)	Third injection of BGM0504 (5 mg)	Fourth injection of BGM0504 (5 mg)	Symptoms appeared
Other medications	None	None	None	None	None	1 Compound glycyrrhizin; 2 Ursodeoxycholic acid; 3 Reduced glutathione

Clinical findings and timeline

During hospitalization, a review of his medical history revealed a prior diagnosis of obesity and no history of alcohol consumption. Notably, three weeks prior to the onset of illness, the patient had completed his fourth injection of a weight-loss medication (BGM0504), administered biweekly at doses of 2.5 mg, 2.5 mg, 5 mg, and 5 mg, respectively (Table 1). This medication is a dual agonist targeting both GLP-1 and GIP receptors, similar to the novel drug tirzepatide. The patient did not take any other medications during the three months before starting BGM0504, during the period of receiving the four injections, or in the three weeks following the fourth injection, until the onset of his illness (Table 1). Prior to developing symptoms, he experienced influenza-like symptoms, including headaches and muscle aches.

Admission labs

ALT 327 U/L, AST 129 U/L, total bilirubin 123.8 μmol/L, TG 2.70 mmol/L, TC 5.04 mmol/L, HDL-C 0.79 mmol/L, LDL-C 2.23 mmol/L, INR 0.88, and a MELD score of 15.09. WBC: 3.82×10^9/L; HGB: 141 g/L; PLT: 159×10^9/L; hsCRP: 2.53 mg/L (negative). APOE-CT genotype: E3; ALDH2 genotype: Glu504Glu. Comprehensive screening tests for hepatitis A, B, C, D, and E viruses, Epstein-Barr virus, cytomegalovirus, influenza virus, and common respiratory viruses were all negative. Immunoglobulin levels and autoantibody profiles showed no abnormalities. Subsequent tests showed improved ferritin levels at 187.36 ng/mL (normal range: 4.63–204.00 ng/mL) and transferrin saturation at 41.9% (normal range: 15–45%).

Ceruloplasmin, Coombs' test, and G6PD levels were negative. Upon admission, the patient's predominant symptoms were jaundice, fatigue, and weakness, without fever or abdominal pain. Abdominal ultrasonography and MRI did not reveal any signs of biliary obstruction or gallstones (Figs.1 and 2). Liver biopsy revealed punctate hepatocyte necrosis accompanied by inflammatory cell infiltration, cholestatic pigment granules, capillary bile duct dilation, and bile plug formation, predominantly in zones 3 and 2 of the hepatic acinus (Fig. 3). Viral, autoimmune, and genetic characteristics of the liver were unremarkable.

Diagnostic assessment and therapeutic intervention

Based on an RUCAM score of nine, a clinical diagnosis of drug-induced liver injury was established. In the fifth week after BGM0504 administration, jaundice peaked, with bilirubin levels exceeding 311 μmol/L. Consequently, four sessions of artificial liver bilirubin adsorption therapy were initiated in conjunction with hormonal treatment. Methylprednisolone sodium succinate (GYZZ No. 20160039) was administered intravenously at 40 mg qd IV for five days (from July 3, 2024, to July 8, 2024). Concurrent medications included liver-protecting agents: 1) Compound Glycyrrhizin (60 mg, qd, ivdrip); 2) Ursodeoxycholic Acid (250 mg, tid, po); 3) Reduced Glutathione (1.8 g, qd, ivdrip). Following these aggressive interventions, the patient's condition began to stabilize in the fifth week after BGM0504 administration, and bilirubin levels began to decline from the sixth week onward (Tables 1 and 2).

Discussion

According to the World Health Organization and recent meta-analyses incorporating data from multiple international sources,[1] the global obesity rate is anticipated to surpass 20% of the adult population, with some regions experiencing even higher rates due to factors such as sedentary lifestyles, unhealthy diets, and decreased physical activity. By regulating insulin secretion, inhibiting glucagon, delaying gastric emptying, and reducing food intake, GLP-1 receptor agonists

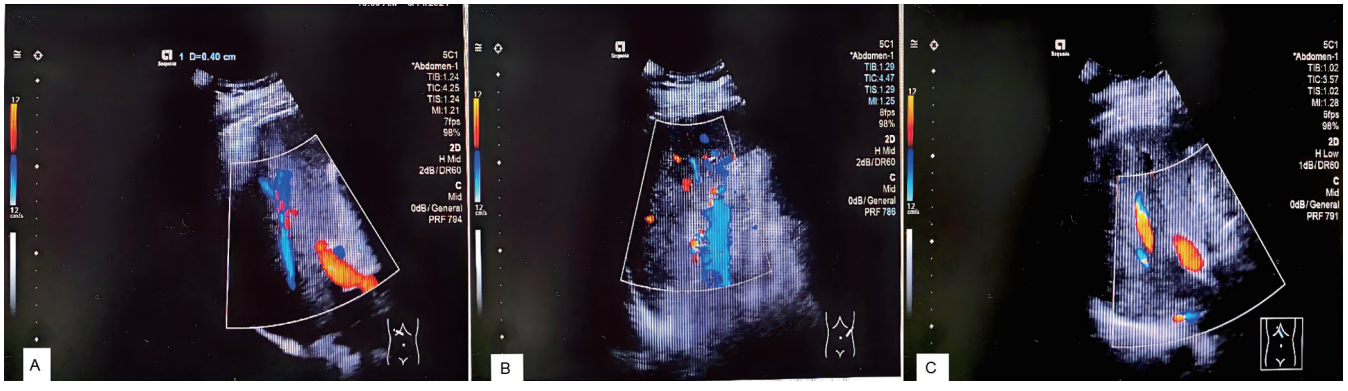

Fig. 1. Abdominal ultrasound findings (2024-6-14). (A) No abnormalities were found in the portal vein, and blood flow into the liver was unobstructed. (B) The spleen size is basically normal. (C) The liver parenchyma shows dense echogenicity. The gallbladder is small in volume.

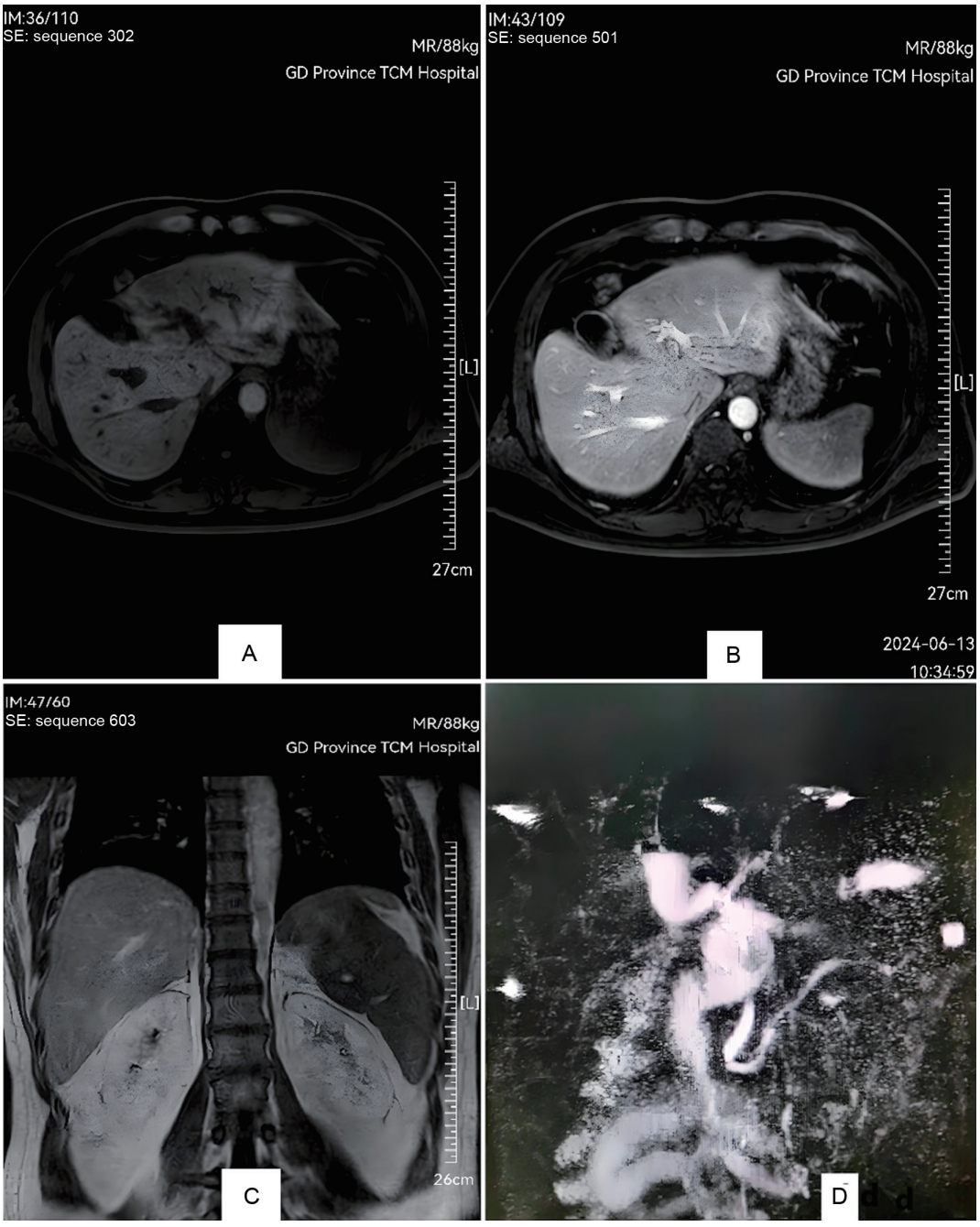

Fig. 2. Abdominal MRI + MRCP examination (2024-6-13). (A) The liver was normal in size and shape. (B) The MR-enhanced scan showed no enhancement and no focal signal abnormalities. (C) The spleen size was normal, with no abnormal signal. There was no thickening of the gallbladder wall, and no abnormal signal shadow was observed in the cavity. (D) MRCP showed normal intrahepatic duct movement, no significant dilatation, good development of the common bile duct and left and right hepatic ducts, and normal duct diameter.

have shown efficacy in managing type 2 diabetes and obesity with favorable safety profiles.[5] Examples of GLP-1 receptor agonist injections include liraglutide (Saxenda®), semaglutide (Ozempic® for diabetes, Wegovy® for obesity), and dulaglutide (Trulicity®, primarily for diabetes but with potential off-label use for obesity). Another class of anti-obesity injections includes those targeting the melanocortin-4 receptor, such as setmelanotide, which is primarily indicated for rare genetic forms of obesity associated with melanocortin-4 receptor deficiency.[6] In this study, BGM0504 was similar to tirzepatide, a dual agonist that concurrently activates the GLP-1 receptor and another metabolism-related target, the glucose-dependent insulinotropic polypeptide receptor. This dual activation ultimately leads to a 22.5% reduction in body weight. Additionally, activation of the GIP receptor can alleviate gastrointestinal adverse reactions induced by GLP-1 receptor activation.

GLP-1/GIP dual agonists represent a major breakthrough

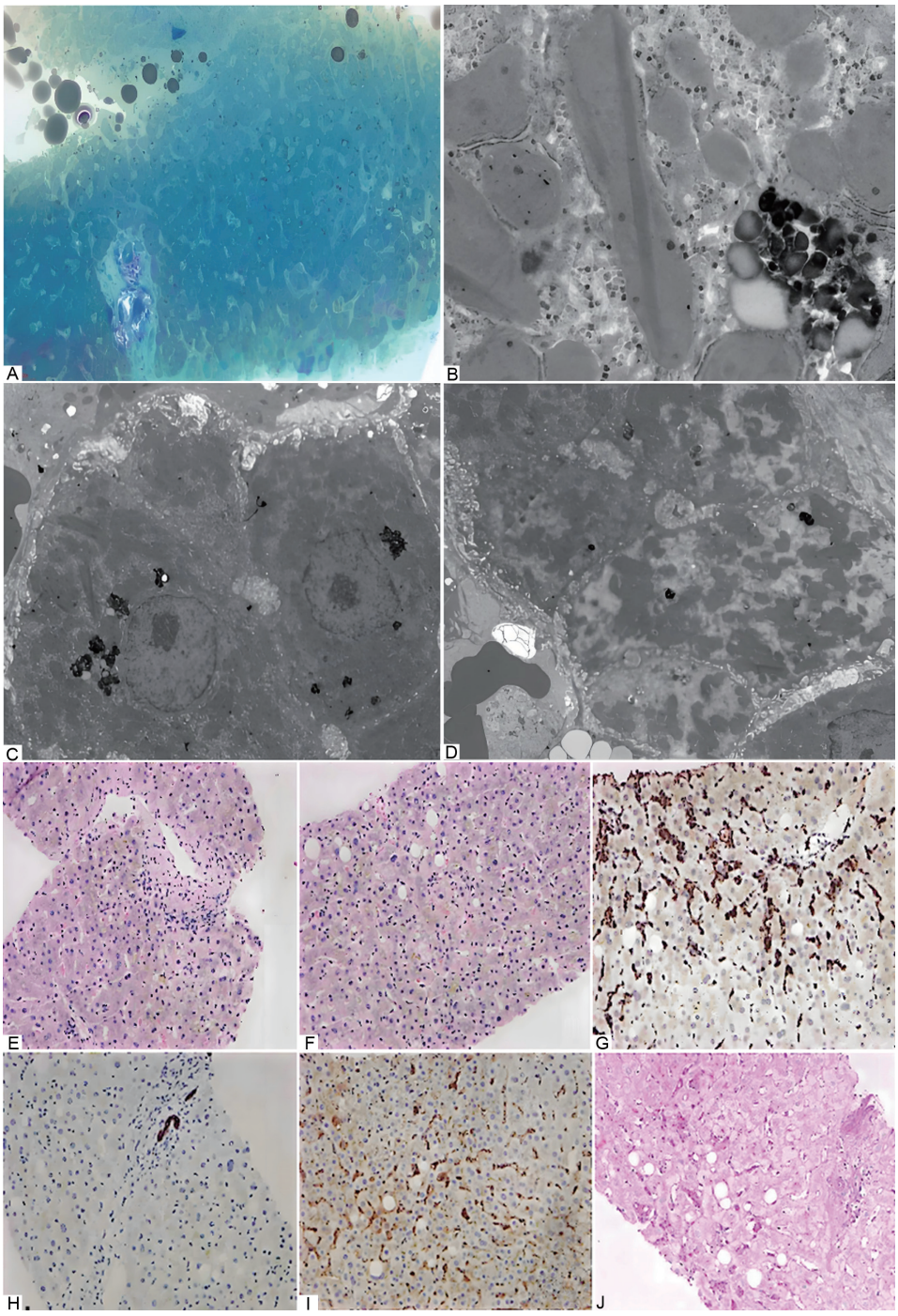

Fig. 3. Percutaneous liver biopsy - electron microscopy, immunohistochemistry, and special staining (2024-6-28). (A) Toluidine blue staining showed that the lobular structure of the liver tissue was preserved, including one portal area and one central vein. There was no obvious swelling of the liver cells, slight expansion of the rough endoplasmic reticulum, and no expansion of the smooth endoplasmic reticulum. Mitochondria were swollen, irregular, or abnormally large, with crystal formation observed. (B) Under electron microscopy, no swelling of hepatic sinusoidal endothelial cells, lymphocytes, Kupffer cells, or stellate cells was noted. Fascicular collagen fiber deposition was observed between hepatocytes and the space of Disse. (C) Under electron microscopy, the space between hepatocytes was significantly widened, with various types of cholestatic pigment granules in hepatocytes. Dense collagen fiber deposition with lymphocyte infiltration was seen in the sink area. (D) Under electron microscopy, lipid droplets were found in some hepatocytes. Increased capillary bile ducts with high dilatation and cholestasis were observed. Coelomic microvilli were reduced or absent. (E) HE staining showed slight enlargement of some portal areas, with a few infiltrating lymphocytes, neutrophils, and plasma cells. There was mild local interface inflammation and small bile duct injury. (F) HE staining showed mild hepatocyte edema, hepatocyte steatosis (<5%), spot-like necrosis with inflammatory cell infiltration, cholestatic pigment granules, and capillary bile duct dilatation. Bile thrombi were predominantly present in acinar zones 2 and 3. (G) Immunohistochemistry indicated that CD68 showed regionally activated Kupffer cells. (H) Immunohistochemistry indicated CK7 and CK19 positivity in bile duct epithelium. (I) Immunohistochemistry indicated that α-SMA showed slightly activated hepatic stellate cells. MUM1 showed a few plasma cells (+); IgG (−), IgG4 (−). (J) D-PAS staining showed numerous intracellular waxy samples in Kupffer cells; prussian blue (−) and copper stain (−).

Table 2. Patient laboratory findings before and after medication

Test	Before injection	The first injection	Three weeks after the 4th injection	Four weeks after the 4th injection	Five weeks after the 4th injection	Six weeks after the 4th injection	Normal range
Body mass index (BMI)	33.02	32.53	28.7	28.7	28.6	28.4	18.5–24 kg/m^2
Fasting blood glucose (FBG)	5.10	7.61	6.22	5.45	4.88	3.94	3.9–6.1 mmol/L
White blood cells (WBC)	6.64	6.84	3.82	6.94	6.27	10.94	3.5–9.5*10^9/L
Hemoglobin (HGB)	156	145	141	136	134	128	130–175 g/L
Platelet (PLT)	162	127	159	208	150	173	125–350*10^9/L
Alanine aminotransferase (ALT)	24	53	327	93	33	44	9–50 U/L
Aspartate aminotransferase (AST)	16	37	129	28	32	40	15–40 U/L
Alkaline phosphatase (ALP)	80	84	379	278	150	117	45–125 U/L
γ-Glutamyl transferase (γ-GGT)	68	97	637	340	107	98	10–60 U/L
Total Bilirubin (TB)	9.9	6.8	123.8	180.7	311.9	248.7	0–23 umol/L
Conjugated bilirubin (CB)	3.8	3.4	102.5	157.0	261.5	209.8	0–8 umol/L
International normalized ratio (INR)	0.96	0.94	0.88	0.91	0.98	0.90	0.8–1.2

in this regard, harnessing the physiological roles of GLP-1 in enhancing insulin secretion, suppressing glucagon release, reducing appetite, and increasing energy expenditure, along with leveraging GIP antagonism to further modulate fat metabolism.[7] These properties have sparked a surge in popularity among healthcare professionals and individuals seeking to manage their weight. Initial studies[8,9] have reported a relatively favorable safety profile with fewer gastrointestinal side effects than traditional weight loss medications. Dual GLP-1/GIP agonists administered via injection offer a more convenient alternative to daily pill-taking, appealing to patients seeking a more streamlined treatment regimen.

However, this discussion focuses on the more commonly prescribed GLP-1 receptor agonists used in general obesity management. Although anti-obesity injections have demonstrated efficacy in promoting weight loss and improving metabolic parameters,[10] they are not without potential adverse effects. One notable concern is the potential for hepatic toxicity, given the liver's central role in drug metabolism and elimination. Recent studies have reported a range of hepatic adverse events associated with GLP-1 receptor agonists, although the overall incidence is low and typically mild to moderate.[11] A meta-analysis by Xie *et al*. reviewing the safety profiles of GLP-1 receptor agonists (including semaglutide) across multiple trials found that elevations in liver enzymes (aspartate aminotransferase and alanine aminotransferase) were among the most common adverse events, occurring in approximately 5–10% of patients.[12] However, these increases were generally transient, asymptomatic, and resolved with continued or discontinued treatment. More severe hepatic events, such as acute liver injury or hepatitis, are rare. For instance, a case report by Kern *et al*. described a patient who developed autoimmune hepatitis-like symptoms after initiating liraglutide therapy, highlighting the importance of close monitoring and prompt intervention when needed.[13] Overall, the benefit-risk profile of anti-obesity injections, particularly GLP-1 receptor agonists, remains favorable for many patients with obesity. Nonetheless, healthcare providers must carefully assess individual patient risk factors, monitor for adverse events, and adjust treatment plans as necessary to ensure safe and effective weight management.

In our meticulous review of the existing literature, we identified potential molecular mechanisms that may underlie the development of severe cholestatic hepatitis induced by GLP-1 and GIP dual-receptor agonists. We conducted a literature review and identified the following potential causative pathways: 1) Impaired bile acid transport: GLP-1 and GIP receptor agonists may interfere with the complex mechanisms involved in bile acid transport within the liver. Studies suggest that these drugs may alter the expression or function of transporters such as multidrug resistance protein 3/2, which is crucial for the secretion of phosphatidylcholine into bile—a necessary component for bile salt solubilization.[14–17] The inhibition of multidrug resistance protein 3 can lead to bile salt precipitation, resulting in intrahepatic cholestasis. 2) Alterations in hepatocyte function: Dual-receptor agonists may directly or indirectly affect hepatocyte function by disrupting bile formation and secretion. GLP-1 agonists have been shown to modulate intracellular signaling pathways that regulate cholesterol and bile acid metabolism.[18] The disruption of these pathways can impair bile acid synthesis and secretion, leading to bile stasis. 3) Inflammatory and immune responses: The onset of cholestatic hepatitis may also be mediated by inflammatory and immune responses. GLP-1/GIP agonists could trigger an immune response in the liver, leading to hepatocyte damage and bile duct obstruction. This is supported by increased levels of inflammatory markers and infiltrating immune cells in the liver tissue of affected patients.[19] 4) Genetic susceptibility: Individual genetic variations may contribute to severe adverse reactions to GLP-1 and GIP agonists. Polymorphisms in genes encoding bile acid transporters, or those involved in drug metabolism and elimination, may predispose certain individuals to bile stasis upon exposure to these drugs.[20]

The unique response observed in this patient, compared with others taking GLP-1/GIP dual agonists, such as tirzepatide, may be attributed to several converging factors. First, the patient's pre-existing obesity, with a BMI of 28.7, may have predisposed him to a heightened metabolic and inflammatory state, amplifying the drug's effects on the liver. Obesity is associated with chronic low-grade inflammation and metabolic disorders, which can influence drug metabolism and sensitivity. Second, the patient's recent administration of BGM0504, a GLP-1/GIP dual agonist similar to tirzepatide but with potentially distinct pharmacokinetics and pharmacody-

namics, could have triggered an idiosyncratic reaction in the liver. Drug-induced liver injury is often idiosyncratic, occurring in a small subset of genetically or metabolically predisposed individuals. The rapid onset of jaundice and absence of viral, autoimmune, or genetic markers of liver disease support this hypothesis. Moreover, the patient's rapid dose escalation of BGM0504 from 2.5 mg to 5 mg during the third and fourth administrations may have contributed to the severity of the liver injury. Although this dose escalation aligns with clinical trial protocols for similar drugs, individual variations in drug tolerance and metabolism may have led to an exaggerated response in this patient. As body weight changes, the drug dose should be appropriately reduced, rather than increased. Finally, the patient's reported influenza-like symptoms preceding the onset of jaundice suggest an underlying inflammatory or immune-mediated process triggered or exacerbated by the drug. While the specific link between these symptoms and the subsequent liver injury remains unclear, they highlight the complexity of the body's response to pharmacological agents.

Conclusions

The increasing popularity of weight-loss injections, particularly GLP-1/GIP dual agonists, reflects the pressing need for effective obesity management strategies and significant advances in pharmaceutical innovation. However, the reported case of severe cholestatic hepatitis underscores the importance of maintaining a critical perspective toward emerging therapies and highlights the need for ongoing safety surveillance. As the field of obesity medicine continues to evolve, it is crucial to strike a delicate balance between harnessing the potential of novel drugs and ensuring the safety and well-being of patients relying on them.

Funding

None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Spearheading the diagnostic process and formulating the treatment plan, ensuring the accuracy and timeliness of the medical examinations and laboratory data (JJ); Assuming the crucial role of manuscript authorship, including the elaboration of the text and meticulous crafting of accompanying figures and tables (MC); Responsible for following up with the patient after his discharge from the hospital and supplementing the necessary clinical data (MS, SW). All authors have read and approved the final version and publication of the manuscript.

Ethical statement

This report followed CARE guidelines. Informed consent was obtained prior to publication.

Data sharing statement

Access to data was permitted with the authors' permission.

References

[1] World Health Organization. Obesity and Overweight: Report of WHO Scientific Group. Geneva: WHO; 2022.
[2] Rieger TR, Musante CJ. Benefits and challenges of a QSP approach through case study: Evaluation of a hypothetical GLP-1/GIP dual agonist therapy. Eur J Pharm Sci 2016;94:15–19. doi:10.1016/j.ejps.2016.05.006, PMID:27157042.
[3] Dinsmore T, Liu J, Miao J, Ünsal Ö, Sürmeli D, Beinborn M, *et al*. Potent and Protease Resistant Azapeptide Agonists of the GLP-1 and GIP Receptors. Angew Chem Int Ed Engl 2024. doi:10.1002/anie.202410237, PMID:39151024.
[4] Zaïmia N, Obeid J, Varrault A, Sabatier J, Broca C, Gilon P, *et al*. GLP-1 and GIP receptors signal through distinct β-arrestin 2-dependent pathways to regulate pancreatic β cell function. Cell Rep 2023;42(11):113326. doi:10.1016/j.celrep.2023.113326, PMID:37897727.
[5] Drucker DJ. Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity. Diabetes Care 2024;47(11):1873–1888. doi:10.2337/dci24-0003, PMID:38843460.
[6] Fansa S, Acosta A. The melanocortin-4 receptor pathway and the emergence of precision medicine in obesity management. Diabetes Obes Metab 2024;26(Suppl 2):46–63. doi:10.1111/dom.15555, PMID:38504134.
[7] Knerr PJ, Mowery SA, Douros JD, Premdjee B, Hjøllund KR, He Y, *et al*. Next generation GLP-1/GIP/glucagon triple agonists normalize body weight in obese mice. Mol Metab 2022;63:101533. doi:10.1016/j.molmet.2022.101533, PMID:3580977.
[8] Finan B, Douros JD. GLP-1/GIP/glucagon receptor triagonism gets its try in humans. Cell Metab 2022;34(1):3–4. doi:10.1016/j.cmet.2021.12.010, PMID:34986336.
[9] Bossart M, Wagner M, Elvert R, Evers A, Hübschle T, Kloeckener T, *et al*. Effects on weight loss and glycemic control with SAR441255, a potent unimolecular peptide GLP-1/GIP/GCG receptor triagonist. Cell Metab 2022;34(1):59–74.e10. doi:10.1016/j.cmet.2021.12.005, PMID:34932984.
[10] Rollnik JD, Meier PN, Manns MP, Göke M. Antral injections of botulinum a toxin for the treatment of obesity. Ann Intern Med 2003;138(4):359–360. doi:10.7326/0003-4819-138-4-200302180-00026, PMID:12585845.
[11] Hage C. GLP-1 receptor agonists in heart failure: how far to expand use? Lancet 2024;404(10456):909–911. doi:10.1016/S0140-6736(24)01763-X, PMID:39222643.
[12] Xie P, Abildlund MT, Bækdal TA, He X, Lyauk YK, Patted URH, *et al*. A phase 1, randomized, double-blind, placebo-controlled trial investigating the pharmacokinetics, pharmacodynamics, safety and tolerability of oral semaglutide in healthy Chinese subjects. Diabetes Obes Metab 2024;26(8):3068–3077. doi:10.1111/dom.15624, PMID:38808476.
[13] Kern E, VanWagner LB, Yang GY, Rinella ME. Liraglutide-induced autoimmune hepatitis. JAMA Intern Med 2014;174(6):984–947. doi:10.1001/jamainternmed.2014.674, PMID:24733687.
[14] Vaduganathan M. GLP-1 receptor agonists in heart failure. Lancet 2024;404(10454):727–729. doi:10.1016/S0140-6736(24)01598-8, PMID:39181582.
[15] Marso SP, Holst AG, Vilsbøll T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2017;376(9):891–892. doi:10.1056/NEJMc1615712, PMID:28249135.
[16] Chen YQ. NASH Drug Development: Seeing the Light at the End of the Tunnel? J Clin Transl Hepatol 2023;11(6):1397–1403. doi:10.14218/JCTH.2023.00058, PMID:37719961.
[17] Patoulias D, Michailidis T. SGLT-2 Inhibitor and GLP-1 Receptor Agonist Treatment for Patients with Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: Is Their Combination the Optimal Treatment Option? J Clin Transl Hepatol 2022;10(4):574–576. doi:10.14218/JCTH.2022.00278, PMID:36062276.
[18] Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, *et al*. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol 2018;6(8):605–617. doi:10.1016/S2213-8587(18)30104-9, PMID:29910024.
[19] Zhou Y, Chen M, Liu L, Chen Z. Difference in Gastrointestinal Risk Associated with Use of GLP-1 Receptor Agonists: A Real-World Pharmacovigilance Study. Diabetes Metab Syndr Obes 2022;15:155–163. doi:10.2147/DMSO.S348025, PMID:35046686.
[20] Liu L, Chen J, Wang L, Chen C, Chen L. Association between different GLP-1 receptor agonists and gastrointestinal adverse reactions: A real-world disproportionality study based on FDA adverse event reporting system database. Front Endocrinol (Lausanne) 2022;13:1043789. doi:10.3389/fendo.2022.1043789, PMID:36568085.