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SCIENTIFIC LETTER

Mycophenolate mofetil as a treatment of severe steroid-resistant immune-related hepatitis

Utilidad del Micofenolato Mofetilo como tratamiento de las hepatitis inmunomediadas secundarias a inmunoterapia resistentes a corticoides

Immune checkpoint inhibitors (ICPIs) are a novel class of oncological therapy that improves survival in patients with advanced-stage tumors.[1] ICPIs inhibit the T-lymphocyte receptors that downregulate T-cell immunity. ICPIs activate immune population that reacts against tumors but also against non-tumor host cells[1] and they can cause immune-related adverse events including hepatotoxicity.[2,3] Usually, the interruption of the treatment is sufficient to solve a mild case of hepatotoxicity, but in severe cases it is necessary to start treatment with corticosteroids.[3,4] Only a few cases are steroid-resistant and need to be treated with another immunosuppressant as mycophenolate mofetil (MMF).[2,4] We present a case of severe steroid-resistant immune-related hepatitis treatment with MMF and review previous cases described.

A 70-year-old woman with a stage-IV melanoma started with itching, jaundice and choluria twelve days after the first doses of nivolumab. Liver analysis found ALT of 141 U/l, AST of 123 U/l, gamma glutamyl transferase (GGT) of 103 U/l, alkaline phosphatase (AP) of 231 U/l and Total Bilirubin of 0.4 mg/dl. Ultrasound and abdominal tomography were normal. Antinuclear antibodies, anti-liver-kidney microsomal antibody and anti-smooth muscle actine antibodies were negative and hepatitis A, B and C virus serologies were also negative.

After diagnosis of grade-1 CTCAE (Common Terminology Criteria of Adverse Events) immune-related hepatitis, nivolumab was interrupted. Following a control analysis an increase of ALT, AST, TB with normal clotting was found (grade 3 CTCAE), so methylprednisolone (MP) at dose of 1 mg/kg was started. Due to a persistent increase of ALT, AST and TB during the following 48 h the dose of MP was increased to 2 mg/kg without improvement within the following 5 days, so we decided to start MMF at a dose of 2 g/day. After that, a progressive improvement of liver function tests was observed (Supplementary Image 1). During the next two months the patient presented a Coxiella Burnetti respiratory infection and a left hip fracture.

We searched using PubMed the cases of immune checkpoint inhibitors hepatitis or hepatotoxicity. We included every study wherein patients received treatment with MMF: 16 studies were found. We excluded four articles because they showed no description of the characteristics of the patients. A total of 12 studies were included in the analysis. We found a total of 30 previous cases of patients treated with MMF (Table 1). If we include our patient in the analysis, 60.0% were female with a mean age of 58.7 years. The more frequent tumor was melanoma in 20 of cases and 16 patients received combined ICPI therapy. The mean time between ICPIs and hepatotoxicity was 80 days. All patients received corticosteroids. MMF was used in doses of 1 or 2 g per day, in five cases associated with other treatments (Plasma exchange, Ursodeoxycholic acid, Antithymocyte globulin or Infliximab). Only four patients did not present an improvement of liver analysis. Ten patients presented complications due to immunosuppression therapy, four of them due to steroid use (hyperglycemia, fractures, steroid-induced psychosis).

ICPIs are commonly used in oncological therapy and between 3% and 10% of cases can cause hepatotoxicity.[2] Usually, interruption of the treatment and treatment with corticoisteroids are enough to heal the hepatotoxicity.[5] However, some cases are steroid-resistant and another immunosuppressant is needed. We found that MMF was effective in the majority of the cases. ICPIs-induced hepatotoxicity in these cases was developed after 8–12 weeks from the start of the treatment.[2,3] A strict follow-up of these patients is recommended for an early diagnosis and treatment of hepatotoxicity. MMF is a reversible inhibitor of inosine monophosphate dehydrogenase and it is used in second-line therapy for autoimmune hepatitis. In the cases that we analyzed, we observed that MMF can be safely used on second line in patients with steroid-resistant immune-related hepatitis with a normalization of the liver analysis in the majority of the cases. Some patients presented complications related to the immunosuppression and steroid treatment. As a consequence, it is important to decrease the dose of immunosuppressant treatment as soon as possible.

In conclusion, MMF is an effective and safe therapeutic alternative for the treatment of steroid-resistant immune-related hepatitis.

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Table 1 Characteristics of patients treated with MMF.

Study	Age (years)	Sex	Tumor	Previous treatment with ICPIs	Treatment	Time I/H (days)/cycles (number)	Corticosteroid	Additional treatments	Normalization of liver analysis	Complications
Present Study	70	F	Melanoma	No	Nivolumab	12/1	MP	No	Yes	Coxiella Burnetti respiratory infection Left hip fracture
Ahmed et al., 2015 BMJ Case Report	50	F	Melanoma	No	Ipilimumab	ND	MP 2 mg/kg	No	Yes	Asymptomatic sinus bradycardia Lymphopenia
Tanaka et al., 2017 Jpn J Clin Oncol	59	M	Melanoma	Nivolumab	Ipilimumab	36/2	MP pulse 1000 mg/d x3 then P 1 mg/kg	No	Yes	No
McGuire et al., 2018 Cancer Immunol Immunother.	57	F	Melanoma	No	Anti-PD-1	189/9	MP 2 mg/kg	No	Yes	No
Hsu et al., 2020 Oncologist	67	M	Hepatocellular carcinoma	No	Nivolumab	183/ND	P 1 mg/kg	No	Yes	Steroid-induced Hyperglycemia
Doherty et al., 2017 ESMO Open	49	F	B-rapidly acceleratd fibrosarcoma	No	Pembrolizumab	8/1	P 1 mg/kg	Ursodeoxycholic acid	Yes	Neutropaenia DM Fracture T11
Doherty et al., 2017 ESMO Open	76	M	Epitheliod mesothelioma	No	Pembrolizumab	1/1	P 1 mg/kg		No	Lymphopaenia
Chmiel et al., 2011 J Clin Oncol	60	M	Melanoma	No	Ipilimumab	31/2	MP pulse 500 mg/d x 9 d	Antithymocyte globulin	Yes	Steroid-induce psychosis
Lomax et al., 2018 J Skin Cancer	58	M	Melanoma	Ipilimumab	Pembrolizumab	30/1	MP 0.5 mg/kg x3 d	No	Yes	Pneumocystis jiroveci pneumonia
Lomax et al., 2018 J Skin Cancer	67	M	Melanoma	Ipilimumab	Pembrolizumab	ND/2	MP 1 mg/kg then P	No	Yes	No
De Martin et al., 2018 J Hepatol	63	F	Melanoma	Pembrolizumab	Ipilimumab	49/ND	2.5 mg/kg	No	Yes	No

Table 1 (*Continued*)

Study	Age (years)	Sex	Tumor	Previous treatment with ICPIs	Treatment	Time I/H (days)/cycles (number)	Corticosteroid	Additional treatments	Normalization of liver analysis	Complications
Cheung et al., 2019 Frontline Gastroenterol	76	F	Melanoma	Ipilimumab	Pembrolizumab	ND	P	No	Yes	No
Cheung et al., 2019 Frontline Gastroenterol	42	M	Melanoma	Pembrolizumab	Ipilimumab	ND	DX then P	No	Yes	No
Cheung et al., 2019 Frontline Gastroenterol	49	F	Melanoma	No	Ipilimumab+ Nivolumab	ND	MP then P	Infliximab	Yes	No
Cheung et al., 2019 Frontline Gastroenterol	45	F	Melanoma	No	Ipilimumab+ Nivolumab	ND	P	No	Yes	No
Cheung et al., 2019 Frontline Gastroenterol	51	M	Melanoma	No	Ipilimumab+ Nivolumab	ND	MP then P	No	Yes	No
Cheung et al., 2019 Frontline Gastroenterol	21	F	Melanoma	No	Ipilimumab+ Nivolumab	ND	MP then P	No	Yes	No
Cheung et al., 2019 Frontline Gastroenterol	71	F	Melanoma	Nivolumab	Ipilimumab	ND	P	No	Yes	No
Corrigan et al., 2019 JHEP Rep.	53	F	Melanoma	No	Ipilimumab+ Nivolumab	39/3	MP 200 mg/day	No	No	Severe neutropenia
Riveiro-Barciel et al. 2020 Liver Int.	58	M	Renal Carcinoma	No	Anti-PD-1	28/1	CS 1 mg/kg	No	Yes	Pneumonia
Riveiro-Barciel et al., 2020 Liver Int.	58	M	Esophageal Adenocarcinoma	No	Anti-PD-1	336/4	CS 1 mg/kg	No	Yes	No

Table 1 (*Continued*)

Study	Age (years)	Sex	Tumor	Previous treatment with ICPIs	Treatment	Time I/H (days)/cycles (number)	Corticosteroid	Additional treatments	Normalization of liver analysis	Complications
Riveiro-Barciel et al., 2020 Liver Int.	44	F	NK/T-cell lymphoma	No	Anti-PD-1	168/2	CS 1 mg/kg	No	Yes	No
Riveiro-Barciel et al., 2020 Liver Int.	62	M	Non-small-cell lung Carcinoma	No	Anti-PD-1	140/5	Cs 1 mg/kg	No	Yes	No
Riveiro-Barciel et al., 2020 Liver Int.	38	F	Cervical Squamous cell Carcinoma	No	Anti-PD-1+Anti-CTLA	56/4	Cs 1 mg/kg	No	Yes	No
Riveiro-Barciel et al., 2020 Liver Int.	76	F	Melanoma	Nivolumab	Anti-CTLA	42/2	Cs 2 mg/kg	Plasma exchange	Yes	No
Riveiro-Barciel et al., 2020 Liver Int.	71	F	Urothelial Carcinoma	No	Anti-PD-L1	49/1	Cs 1 mg/kg	No	Yes	No
Riveiro-Barciel et al., 2020 Liver Int.	90	F	Sigma Adeno-carcinoma	No	Anti-PD-1	84/8	Cs 1 mg/kg	No	Yes	No
Riveiro-Barciel et al., 2020 Liver Int.	51	F	Melanoma	No	Anti-PD-1	56/3	Cs 2 mg/kg	No	Yes	No
Riveiro-Barciel et al., 2020 Liver Int.	69	M	Non-small-cell lung Carcinoma	No	Anti-CTLA-4	58/2	Cs 1 mg/kg	No	Yes	No
Ziogas et al., 2020 J Immunother Cancer	70	M	Melanoma	Nivolumab	Ipilimumab	ND/3	MP 2 mg/kg	Ursodeoxycholic acid	No	Thrombocytopenia
Spänkuch et al., 2017 Eur J Cancer	49	F	Melanoma	No	Nivolumab+Ipilimumab	ND/3	MP 2 mg/kg	No	No	No

Anti-CTLA-4: anticytotoxic T-lymphocyte antigen 4; Cs: corticosteroids; DM: diabetes mellitus; F: female; M: man; ICPIs: Immune checkpoint inhibitors; MMF: mycophenolate mofetil; MP: Methylprednisolone; ND: not described; P: Prednisone; Time I/H: Time between inmunotheraphy/hepatitis.

Ethics statement and consent

The study followed the criteria of the Helsinki Declaration and the patient has given the written informed consent for publication.

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Conflicts of interest

All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.gastrohep.2021.05.008.

References

1. Sambi M, Bagheri L, Szewczuk MR. Current challenges in cancer immunotherapy: multimodal approaches to improve efficacy and patient response rates. J Oncol. 2019;2019:4508794.
2. Cheung V, Gupta T, Payne M, et al. Immunotherapy-related hepatitis: real-world experience from a tertiary centre. Frontline Gastroenterol. 2019;10:364–71.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158–68.
4. Hsu C, Marshall JL, He AR. Workup and management of immune-mediated hepatobiliary pancreatic toxicities that develop during immune checkpoint inhibitor treatment. Oncologist. 2020;25:105–11.
5. Romanski NA, Holmstroem RB, Ellebaek E, Svane IM. Characterization of risk factors and efficacy of medical management of immune-related hepatotoxicity in real-world patients with metastatic melanoma treated with immune checkpoint inhibitors. Eur J Cancer. 2020;130:211–8.

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