Should mycophenolate mofetil be first-line treatment in autoimmune hepatitis?

¿Debe ser micofenolato de mofetiloel tratamiento de primera línea en la hepatitis autoinmune?

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that can progress to fibrosis, cirrhosis, and liver failure if remission is not achieved. It affects persons of all ages, races, and ethnicities, albeit 70–95% of affected adults are female. AIH treatment goals include the resolution of symptoms and liver inflammation, prevention of the development of fibrosis or progression to it, and the maintenance of remission. The first-line treatment currently recommended by the international guidelines is remission induction with steroids, followed by maintenance with nonsteroidal immunosuppressants.[1] Several studies have evaluated biochemical response with different steroid doses. For example, a recent retrospective, multicenter study found there were no differences in reaching complete response after 6 months of treatment, comparing a dose of 30 mg/day of prednisolone with a dose of more than 30 mg/day. However, other studies have shown that using a higher dose of prednisolone at the start of treatment was related to a faster normalization of ALT and better long-term survival.[2]

On the other hand, for decades we have known that azathioprine (AZA) has been the standard maintenance treatment in AIH, but this recommendation is based on studies conducted more than 20 years ago, with limited methodological designs. We also know that with the current treatment regimen, only 50–60% of patients achieve complete biochemical response, conditioning limited histologic resolution and a greater risk of disease progression. In addition, between 15 and 25% of patients treated with AZA develop intolerance or lack of response, making it necessary to interrupt treatment and use second-line regimens.[3]

Mycophenolate mofetil (MMF) is a selective, reversible, noncompetitive inhibitor of the type II isoform of inosine-5'-monophosphate dehydrogenase, considered a selective immunosuppressant with few adverse effects. Retrospective studies have evaluated the safety and effectiveness of MMF as second-line treatment in AIH, in which the desired biochemical response was reached. MMF is currently considered an option in patients with standard treatment intolerance or refractoriness.[4] Given those findings, MMF use has recently been studied as first-line treatment. Relevantly, Zachou et al.[5] prospectively evaluated MMF as induction and maintenance treatment and reported a clinical and biochemical response of 88% and a partial response of 12%, superior to standard treatment. Only two patients with cirrhosis presented with severe adverse events (septicemia). In the CAMARO study, Snijders et al.[6] described a significant difference in favor of MMF for achieving biochemical remission at 24 weeks, compared with AZA (56.4% vs 29%, a percentage difference of 27.4%; 95% CI 4–46.7 $p = 0.022$), and the serious adverse event rate was lower with MMF vs AZA (0% vs 12.9% $p = 0.034$), as well. Likewise, in their study, Dalekos et al.[7] reported complete biochemical remission at 12 months, in favor of MMF vs AZA (86% vs 71.8%; $p < 0.05$), and at the end of the follow-up at 57 months, the results were similar (96% vs 87.2%; $p = 0.03$). Compared with MMF, AZA use had more serious adverse effects (18.8 vs 3.8%; $p = 0.0003$).

Despite the different promising results, those articles had limitations, the main one being the fact that the sustained biochemical response to long-term MMF use or discontinuation of the immunosuppressant were not evaluated. Another disadvantage was the lack of a report on the impact of histologic remission. Lastly, regarding methodology, some of the studies were not randomized and others were open label trials. Table 1 describes other related studies.

Unlike AZA, the main reasons for treatment abandonment with MMF are its high cost, and in reproductive-age women, the desire for pregnancy. Reports have shown that the administration of MMF during pregnancy was associated with a higher risk of miscarriage in the first trimester of 49% and congenital malformation in up to 27%. The most common birth defects were facial malformations (cleft lip and palate, micrognathia, hypertelorism), eye and ear defects (coloboma, microphthalmos, outer ear malformation), heart malformations (atrial and ventricular septal defects), esophageal atresia, and spina bifida.[8] Therefore, in reproductive-age women, MMF should be administered under strict contraceptive measures, which limits its use in that group of patients. Another important limitation of MMF, compared with standard treatment, is its elevated cost.

In conclusion, the recent published evidence has shown that MMF use results in better biochemical remission rates and fewer adverse effects, compared with AZA. Therefore, the need to update the current guidelines for the treatment of AIH, with MMF possibly being a first-line option in the treatment of the disease, should be considered.

Ethical considerations

The aim of this work was to express an opinion based on the results of previous studies, and so patient privacy was not jeopardized. Because no interventions were carried out, we consider that our study did not require submission to the institutional ethics committee.

Table 1 Studies on MMF use in AIH.

Author	Year	Type of study	Population	Aim	Definition	Results	Safety
Zachou et al.[5]	2011	Prospective	Treatment-naive AIH patients. n = 59 MMF + PDN Cirrhosis = 14	Complete biochemical response at 3 months	Normalization of IgG and transaminases	Complete response in 88%	Serious adverse events in 3.4%, 95% CI 0.5—7.3%
Zachou et al.[9]	2016	Prospective, observational, open	Treatment-naive AIH patients. n = 109 MMF + PDN vs 22 AZA + PDN Cirrhosis = 26	Biochemical response	Normalization of IgG and transaminases	MMF vs AZA (72% vs 45% p = 0.03)	MMF well tolerated (2 patients discontinued the drug due to septicemia)
Nicoll et al.[4]	2019	Retrospective, cohort, observational	Nonresponders to treatment. PDN ± AZA (n = 42); treatment intolerance (n = 63) Cirrhosis = 38	Biochemical response at 2 years of treatment	ALT, AST, and IgG < ULN	Biochemical remission in 60%	NR
Dalekos et al.[10]	2021	Prospective	Treatment-naive AIH patients. n = 64 (32 MMF + PDN / 32 AZA + PDN) Cirrhosis = 6	Complete biochemical response at 12 months	Normalization of IgG and transaminases	MMF vs AZA (93.8 vs 78%)	Intolerance to AZA 28.1%
Dalekos et al.[7]	2022	Prospective	Treatment-naive AIH patients. n = 292 (19 PDN alone/ 183 MMF + PDN / 64 AZA + PDN)	Complete biochemical response at 6 and 12 months	Normal levels of IgG and transaminases	Complete biochemical remission at 12 months (86 vs 71.8%; p < 0.05) in favor of MMF	Serious complications AZA vs MMF (18.8 vs 3.8% p = 0.0003)
Snijders et al.[6]	2024	Randomized, prospective, multicenter	Treatment-naive AIH patients. n = 70 (39 MMF + PDN / 31 AZA + PDN)	Biochemical remission at 24 weeks	Normalization of IgG and transaminases	56% vs 29% in favor of MMF (difference of 27% p = 0.022)	Serious adverse events AZA vs MMF (12.9 vs 0%; p = 0.034).

AIH: autoimmune hepatitis; AZA: azathioprine; MMF: mycophenolate mofetil; NR: Not reported; PDN: prednisone; ULN: upper limit of normal.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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Desmoid tumor: Clinical analysis and literature review

Tumor desmoide: análisis clínico y revisión de literatura

A 27-year-old woman with a family history of breast cancer (mother) initially presented with an abdominal tumor (Fig. 1) that increased in volume. She was programmed for surgical examination and a 15 × 20 cm abdominal tumor that invaded the deep planes, aponeurosis, and muscle was found. Due to the extensive tissue invasion, an incisional biopsy was performed and sent to the oncologic surgery service. Invasion of the abdominal wall involving all layers up to the parietal peritoneum was reported. The tumor was resected with macroscopic tumor-free margins. The definitive histopathologic study confirmed desmoid tumor (Fig. 2).

Desmoid-type fibromatosis is an aggressive benign tumor of mesenchymal origin that has an incidence of 2–4 cases per million inhabitants and accounts for 0.03% of all tumors and 3% of soft tissue tumors. This type of tumor is related to trauma and previous surgery, to radiotherapy, and to increased estrogen levels, as occur in pregnancy. It affects soft tissues, is divided into superficial and deep, and consists of a single entity known as the desmoid tumor. The biologic behavior of desmoid tumors varies and is an intermediate stage between a benign fibroblastic tumor and fibrous sarcoma.[1]

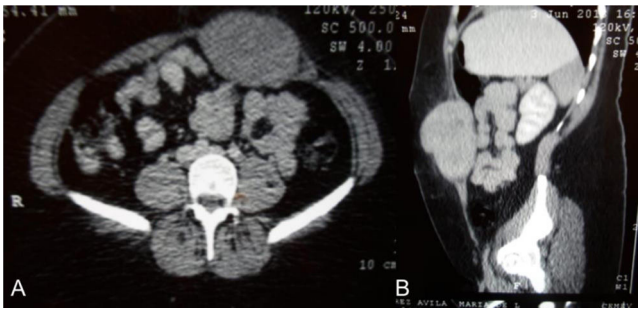

Figure 1 Axial view (A) of the tomography scan of the chest and abdomen and sagittal view (B) showing the tumor that is dependent on the abdominal wall layers up to the parietal peritoneum, without local invasion to adjacent organs.

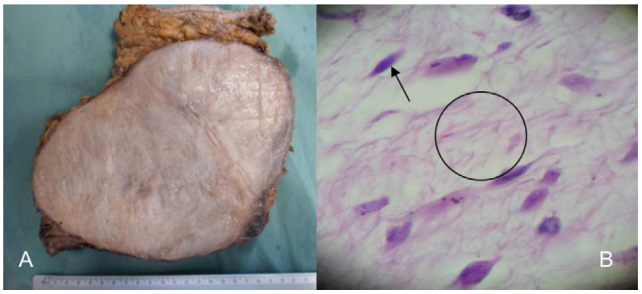

Figure 2 (A) Macroscopic section of the surgical specimen, showing a solid, well-delimited, light gray tumor. (B) Microscopic image of the surgical specimen, showing fusiform cells that correspond to fibroblasts, cells that make up the cellular component of the tumor (arrow), and surrounding fibrillar structures that correspond to collagen fibers of the stromal content of the tumor (circle).