Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Health status of patients with autoimmune hepatitis is not affected by the SARS-CoV-2 outbreak in Flanders, Belgium

To the Editor:

In December 2019 an outbreak of a novel coronavirus (SARS-CoV-2) started in Wuhan, China, and has since become a global threat to human health.[1] Abnormal levels of alanine aminotransferase and aspartate aminotransferase (AST) have been reported during disease progression in 14–53% of patients infected with this virus.[1] Autoimmune hepatitis (AIH) is a rare autoimmune liver disease that is still poorly understood.[2] The cornerstone of treatment is the use of immunosuppressive drugs including azathioprine and corticosteroids. In patients with advanced liver disease, liver transplantation is sometimes necessary.

In the current COVID-19 pandemic, these patients require special attention as most of them have underlying liver damage. Furthermore, the effect of immunosuppression on the severity of COVID-19 disease is unclear. Several reports suggest that even in highly endemic areas patients with AIH are not showing increased risk of adverse outcomes.[3] In the early phase of the pandemic, management protocols were proposed for these patients based on the preliminary experience in Northern Italy and China.[4]

In Belgium, the epidemic started in early March 2020 leading to a generalized lockdown on 15 March 2020. The peak of the pandemic was reached on 9 April 2020. At that moment, the COVID-19 notification rate was 161 per 100,000 inhabitants.[5]

We carried out a phone-based survey in our patients treated for AIH between 1 May and 30 June 2020. The questionnaire asked for the presence of COVID-19-related symptoms (fever, anosmia, respiratory symptoms), testing for COVID-19 and adherence to national guidelines for the prevention of COVID-19 contamination (social distancing, use of face mask *etc.*). The goal of this survey was to assess the number of patients with AIH developing COVID-19 and the impact of AIH on disease course and outcome. A second goal was to evaluate the effect of quarantine measures on the number of infections with SARS-CoV-2 in patients with AIH.

At the moment of the survey, 160 patients with biopsy-proven AIH were followed in our center. After exclusion of patients with PBC and PSC overlap syndromes, 110 patients were eligible for inclusion. Of these, 85 patients could be reached by phone and were included in the survey. Clinical characteristics and study results are summarized in Table 1.

In this cohort, 7 patients developed symptoms compatible with a COVID-19 infection. The infection was confirmed by a positive nasal-pharyngeal swab for SARS-CoV-2 nucleic acid using a real-time reverse-transcriptase PCR assay in only one of these patients. This 51-year-old woman had undergone a liver transplant in 2017 for decompensated AIH-related cirrhosis. Her husband developed a COVID-19 infection the week before. Her immunosuppressive regimen consisted of cyclosporine and mycophenolate mofetil (MMF). She was admitted to the hospital due to respiratory insufficiency and required supplemental oxygen. However, there was no need for invasive ventilation and the patient did not develop other organ failures. Only supportive treatment was provided and the patient recovered well. MMF was stopped upon admission. There was no decline in liver function. At the last visit the patient shows a full recovery.

Table 1. Clinical characteristics, COVID-19 infection and outcome in patients with autoimmune hepatitis.

Number of patients	110
Survey Response rate	85 (77.3%)
Female	64
Male	21
Age (Mean)	53
Immunosuppressive regimen	
Azathioprin	41 (48.23%)
6-Mercaptorpurin	2 (1.8%)
MMF	4 (3.6%)
Clyclosporin	2 (1.8%)
Tacrolimus	1 (0.9%)
Methylprednisolone	13 (11.8%)
Budesonide	16 (14.5%)
Azathioprine + Budesonide	3 (2.7%)
Azathioprine + Methylprednisolon	3 (2.7%)
Symptoms compatible with COVID-19	
Fever (>38°C)	6 (7.1%)
Cough	7 (8.2%)
Anosmia	3 (3.5%)
Malaise	0 (0%)
COVID-19 test performed	7 (8.2%)
COVID-19 test positive	1 (1.2%)
Outcome	
Hospitalisation	3 (3.5%)
Decompensation liver disease	0 (0%)
Survived	85 (100%)

At the start of the pandemic, all patients with AIH attached to our hospital were sent a letter advising them to adhere to protective measures (social distancing, ….) and to continue immunosuppressive treatment. Only 1 patient considered stopping this treatment, but all patients continued treatment after all.

In conclusion, in this AIH cohort, patients adhered to protective guidelines issued in the COVID-19 pandemic and showed a very limited infection ratio. This supports the idea that immunosuppressive treatment should not be stopped in patients with AIH, even during the COVID-19 pandemic,[4] but preventive measures remain crucial and life-saving.

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Conflict of interest

All authors declare no conflict of interest.

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Authors' contributions

Study design: XV, AG, HVV. Data collection: NS, HD. Data analysis: XV, NS. Drafting of mansucript: XV, HVV. Review of final manuscript: all.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.08.035.

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NAFLD: Time to apply quantitation in liver biopsies as endpoints in clinical trials

To the Editor:

We read with great interest the paper published by Davison *et al.*[1] In this study, the authors demonstrate that the low reproducibility of the non-alcoholic steatohepatitis (NASH) CRN scoring system affects the power of clinical trials in non-alcoholic fatty liver disease (NAFLD). Specifically, the lack of consistency has a significant impact on several fundamental aspects of the conduct of trials in NAFLD, for instance both inclusion criteria and histological endpoints. We agree with the conclusion of the investigators of this paper – along with other specialist groups[2] – on the need for different approaches, such as the use of quantitation, which provides more objective and reproducible results.[3] Following this, our group has recently developed a high-throughput, fully automated quantitation based on machine-learning. This methodology estimates the percentage of fat, inflammation, ballooning and fibrosis (collagen proportionate area, CPA) in routine histological images of liver biopsies from patients with NAFLD, with overall higher intra- and interobserver variability than conventional histological assessment.[3]

Several clinical trials have reported high screening failure rates due to low agreement between histopathologists. In the EMMINENCE study, the 3 expert pathologists agreed only on one-third of the screened patients meeting histological criteria.[1] From an industry perspective, the large number of ineffective biopsies adds significantly to the cost and duration of clinical trials, as well as impacting upon power calculations and consequently sample sizes. Furthermore, from a clinical standpoint, there is the potential for patients not suitable for treatment to be included in studies, with this affecting the interpretation of the drug effect on the disease. Regarding this, the quantitation of fat, inflammation, ballooning and collagen (or a combination of these) may allow for the standardisation of inclusion criteria and the optimised selection of study participants. In addition, our quantitation tool used principles of machine-learning, ensuring that it was high-throughput, a further key advantage for large clinical trials.

Assessing changes in disease activity over time represents an even greater challenge in NAFLD. In the EMMINENCE study, the magnitude of effect of the drug on histology was proportional to the degree of agreement between pathologists.[1] It should be noted that differences in semi-quantitative scores do not necessarily correspond to quantitative changes of histological features.[4] Specifically, we have previously demonstrated that quantitation is more sensitive than the CRN scoring system in showing changes in a subgroup of liver biopsies.[3] This finding has been particularly striking in the assessment of inflammation and ballooning, both essential features for diagnosing NASH, and for which quantitation provides more subjective results. As such – the ability of quantitation to define key histological features as continuous variables may delineate more subtle changes associated with a trial drug in NAFLD than is currently afforded by discrete scoring systems such as NASH CRN.

As fibrosis stage is the main outcome predictor in NAFLD, the regression of fibrosis is considered a crucial endpoint in clinical trials. However, the current staging system describes architectural features rather than the quantity of collagen present in a liver biopsy. Unsurprisingly, the actual collagen content has been shown to increase exponentially, not linearly with fibrosis stage.[3] As such, the regression of 1 fibrosis stage from stage 4 to stage 3

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