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High prevalence of acute onset autoimmune hepatitis in males: A real-life cohort from Northern Italy

Dear Editor,

We have read with great attention the paper from Muratori et al. [1] which evaluated the clinical and prognostic implications of acute onset autoimmune hepatitis (AIH) in a large multi-centric database including 479 patients (381 females and 98 males) with AIH from three Italian tertiary liver centers. Clinical presentation of AIH was defined as "acute" when transaminases reached as high as at least 10 times the upper normal limit (10× UNL) and/or serum bilirubin was greater than 5 mg/dl at the time of diagnosis. In absence of such a clinical profile at presentation AIH was judged chronic/asymptomatic. According to those criteria, the authors identified 204 patients with acute onset (43%). AIH diagnosis was based on liver histology in 298 patients (62%). The grading and staging of the disease were assessed by the Ishak score with cirrhosis diagnosis staged S5-6. In Muratori et al.'s study males and females had a similar rate of acute onset AIH (38% vs. 44%, NS). At diagnosis, patients with acute onset had significantly higher transaminases levels and serum bilirubin, while showing a significantly lower level of albumin and a more prolonged INR. By contrast, a lower rate of cirrhosis in acute onset AIH was found as compared to the group without acute onset. Despite the response to immunosuppressive therapy was similar in both groups of patients (66% vs. 57%, NS) the authors concluded that the acute presentation would have a better long-term prognosis.

As underlined by the authors in their study, AIH is an extremely heterogeneous disease with a large spectrum of clinical presentations in terms of gender, severity of disease and response to immunosuppressive therapy, probably related to a different genetic background [2,3]. Stimulated by this interesting paper evaluating the clinical implications of a symptomatic acute vs. a chronic/asymptomatic onset of AIH, we would like hereby to report on a "real-life" series of Italian male patients with AIH, consecutively enrolled in five liver centers in northern Italy between 2000 and 2016.

We have applied the same diagnostic criteria used by Muratori et al. [1] in order to classify our cohort of consecutive male patients. Non-response or incomplete response to immunosuppressive therapy was defined as abnormal liver function e/o IgG levels in spite of standard therapy at 48 weeks.

A total of 93 males (91 Caucasian) have been enrolled and followed up over a median number of 4.6 years (range 1–18.1 years). Eighty-eight patients (95%) had a liver biopsy available showing a diagnosis of AIH. The patients' median age at enrollment was 54 years (17–79), their median BMI at diagnosis was 24 kg/m^2 (range 19–42 kg/m^2). The IAHG score [4] was calculated for 80/93 patients (86%) and ranged from 10 to 19. Extra-hepatic autoimmune disease was observed in 22 patients (24%). Serum autoantibodies were positive in 80 patients (86%) as follows: ANA in 73 (78%), SMA in 27 (29%), LKM-1 in 1 (1%), AMA in 4 (4%). Forty-eight patients (53%) showed increased serum IgG levels at diagnosis. Twenty-two out of 88 patients (25%) had cirrhosis at baseline and 5 (4%) presented with ascites.

The acute onset was observed in 55 (59%) patients with 23 of them (42%) showing serum bilirubin values >5 mg/dl and 54 (98%) transaminase levels >10× UNL. The prevalence of cirrhosis at baseline was similar between the patients with acute onset (25%) and those without acute onset (21%).

At diagnosis, 89 patients were administered steroids (96%), and 4 started therapy with azathioprine alone; 43 received both drugs (46%). Complete response to therapy was achieved in 93% of patients at week 48. Only 9 patients (10%) completely withdrew from steroids and/or azathioprine.

In our population the progression to cirrhosis during follow-up was observed in only 3 patients (3%), of whom two with acute onset.

We have concluded that in our cohort of males with AIH, a higher rate of acute presentation was observed as compared with the data reported by Muratori et al. (59% vs. 38%, respectively). Moreover, an extremely favorable outcome of the disease in terms of both response to the immunosuppressive therapy and clinical progression rates was detected over time. Such preliminary data suggest a potential change in clinical and epidemiological profiles of this autoimmune disease and need validating by larger case control studies including both males and females.

Conflict of interest

None declared.

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Harmonising proton pump inhibitors treatment in the specialist setting following the SIGE recommendations

Dear Editor,

we read with great interest the position paper of the Italian Society of Gastroenterology (SIGE) on the appropriateness of prescription for proton pump inhibitor (PPI) drugs that was recently published in Digestive and Liver Disease, as we feel that the statements reported in the manuscript should actually represent a "Dos and don'ts" companion handbook in everyday clinical practice of both primary care physicians and specialists in gastroenterology [1].

As a fact, in Italy, the category of drugs used to treat gastrointestinal disorders ranks fourth in the list of categories responsible for drug-related health care costs, and within this category of drugs, PPIs embody the main item of expenditure, with a cost of 13.2 euros *per* inhabitant and 68 daily doses prescribed every 1000 inhabitants, in 2017 [2]. Thus, despite a decreasing trend in their prescription observed in the course of the last 5 years (2017–2013: −6.8%), PPIs still represent a relevant health-care associated cost, and this finding is even more crucial when considering that a significant proportion of these prescriptions – on the average approximately 40% – are not appropriate [1–5]. Indeed, the results of a survey performed ten years ago in Italy among primary care physicians, showed that even in patients where the use PPIs may be justified – such as gastro-protection in patients taking non-steroidal anti-inflammatory drugs – there was a misuse of PPIs that led to underutilization of gastro-protection in at least one out of four patients, while approximately 60% of patients received gastro-protection despite the absence of well-defined risk factors for gastrointestinal bleeding [6,7]. Lastly, beyond increased sanitary costs, chronic use of PPIs may also be associated with the onset of potentially harmful effects that may affect the respiratory and the gastrointestinal systems, and may determine bone and electrolytic disturbances, although there is still much debate on the actual cause-effect of these associations [3]. All in all, therefore, while PPIs are an effective, useful, and manageable class of drug that represents the cornerstone of treatment of acid-related disorders, they also show a "dark side" related to incongruous, prolonged, and unjustified prescriptions that may be associated with harms and increased health-care costs.

In the majority of the published reports on this issue, mainly from the United States, some of the main reasons for prolonged and inappropriate PPI treatment – besides the above-referenced over-prescription in non-steroidal anti-inflammatory drugs users – are the lack of drug withdrawal after hospital discharge, where initial prescription might have been motivated by acute illness, and the absence of adequate re-evaluation after initial prescription in patients who suffer from gastroesophageal reflux disease, where PPI intensity of prescription or actual necessity are often overlooked, and where other therapeutic means may be effective [1,5–9]. Therefore, following the statements enunciated in the SIGE position paper, and in order to critically assess the real necessity of chronic PPI prescription in patients referred to specialist gastroenterology assessment, we recently started re-evaluating the indication of these drugs in our outpatients clinic, with the aim to provide an updated picture of this phenomenon in the specialist setting in Italy. Preliminary data related to the first 40 patients on chronic PPI treatment referred to our clinic in the last 2 months show that median duration of PPI treatment before referral is 36 months, and that approximately 30% of patients are treated outside the indications contained in the SIGE position paper [1]. Moreover, in two-thirds of these patients, no previous attempt at PPI tapering or withdrawal had previously been carried out before referral, despite the absence of an evidence-based indication to chronic PPI use. Lastly, following the recently proposed strategies of how to reduce or stop PPI treatment, we already managed to discontinue or decrease the intensity of PPI treatment while controlling symptoms in 70% of these patients [10].

In conclusion, we feel that the implementation in everyday clinical practice, at both the gastroenterology specialist and primary care physician setting, of the guidelines put forward in the SIGE position paper may provide health as well as economic benefit, and should be actively pursued in order to improve the quality of care dispensed to our patients.

Conflict of interest
None declared.

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