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ORIGINAL ARTICLE

The evolving phenotype of autoimmune hepatitis across the millennium: The 40-year experience of a referral centre in Italy

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Abstract

Background and Aims: During recent years, there have been major insight into the pathogenesis, diagnosis and treatment of autoimmune hepatitis (AIH). We aim to evaluate modifications of the clinical-epidemiological phenotype of AIH patients from 1980 to our days.

Methods: Single-centre, tertiary care retrospective study on 507 consecutive Italian patients with AIH. Patients were divided into four subgroups according to the decade of diagnosis: 1981–1990, 1991–2000, 2001–2010 and 2011–2020. We assessed clinical, laboratory and histological features at diagnosis, response to treatment and clinical outcomes. Acute presentation is defined as transaminase levels >10-fold the upper limit and/or bilirubin >5 mg/dL. Complete response is defined as the normalization of transaminases and IgG after 12 months. Clinical progression is defined as the development of cirrhosis in non-cirrhotic patients and hepatic decompensation/hepatocellular carcinoma development in compensated cirrhosis.

Results: Median age at diagnosis increased across decades (24, 31, 39, 52 years, $p < .001$). Acute onset became more common (39.6%, 44.4%, 47.7%, 59.5%, $p = .019$), while cirrhosis at diagnosis became less frequent (36.5%, 16.3%, 10.8%, 8.7%, $p < .001$). Complete response rates rose (11.1%, 49.4%, 72.7% 76.2%, $p < .001$) and clinical progression during follow-up decreased (54.3%, 29.9%, 16.9%, 11.2%, $p < .001$). Antinuclear antibodies positivity increased (40.7%, 52.0%, 73.7%, 79.3%, $p < .001$), while IgG levels/upper limit progressively decreased (1.546, 1.515, 1.252, 1.120, $p < .001$). Liver-related death and liver transplantation reduced from 17.1% to 2.1% ($p < .001$).

Conclusions: In the new millennium, the typical AIH patient in Italy is older at diagnosis, more often presents with acute hepatitis, cirrhosis is less frequent and response to treatment is more favourable.

KEYWORDS
acute onset, autoimmune hepatitis, elderly, epidemiology, treatment response, update

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANAs, antinuclear antibodies; ANOVA, analysis of variance; anti- SMA, smooth muscle autoantibody; anti-LC1, liver cytosol antibody type 1; anti-SLA/LP, anti-soluble liver antigen/liver-pancreas; DILI, Drug-induced liver injury; HLA, human leucocyte antigen; IAIHG, international autoimmune hepatitis group; IgG, immunoglobulin G; LKM1, liver/kidney microsomal antibody type 1; LR-D, liver-related death; LT, liver transplantation; UNL, upper normal limit.

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is an immune-mediated inflammation of the liver, characterized by the presence of hypergammaglobulinaemia, autoantibodies and interface hepatitis on liver biopsy. AIH has a wide spectrum of clinical manifestations ranging from asymptomatic forms with non-liver-specific symptoms to acute hepatitis, often icteric, rarely leading to acute liver failure, or with features of an advanced liver disease with clinically relevant portal hypertension and its complications, such as ascites, jaundice and oesophageal varices.[1,2]

Since its first formal description in the fifties, there have been several insights into pathogenesis and major advances in the diagnostic assessment and treatment options.[3,4] AIH is considered relatively rare, as its prevalence ranges from 16 to 18 cases per 100000 inhabitants in Europe, although its incidence and global burden are rising.[5,6] As the general population is experiencing relevant changes in its composition and distribution, the phenotype of the disease is also expected to encounter significant mutations in terms of demographic and clinical manifestations. For example, many studies nowadays emphasize the relevant increase of elderly with AIH,[7] and recent clinical and epidemiological studies highlight acute hepatitis as a common manifestation of the disease at onset.[8–11]

Studies addressing the modifications of the clinical phenotype over a large period of time are still lacking. The present study aims to evaluate how the clinical-epidemiological features of patients with AIH have changed across the millennium from the standpoint of a single centre which has been collecting over the last 40 years a large cohort of consecutive AIH cases from all over Italy.

Key points

The analysis of the Bologna cohort of 507 consecutive AIH Italian patients recruited across four decades (from 1980 to 2020) shows that in the new millennium, the typical AIH patient at diagnosis is a 50-year or older non-cirrhotic woman with acute hepatitis, is responsive to conventional treatment and maintaining remission without disease progression. The ameliorated knowledge of the presenting clinical features of AIH is expected to permit earlier diagnosis, higher response rate to patient-tailored treatment regimens, and a significant improvement in the quality of life.

2 | MATERIALS AND METHODS

2.1 | Patients

This is a single-centre observational retrospective study of 507 patients diagnosed with AIH, recruited between 1981 and 2020 in a third-level centre in Bologna, Italy. More than half of these patients lived in Northern Italy (56%), 21% in Central Italy, 18% in Southern Italy and 6% in major Islands (Sicily and Sardinia). Viral and other notable causes of liver disease (HCV, HBV, HEV, Cytomegalovirus and Epstein Barr viruses, abuse of alcohol, deficit of ceruloplasmin and alpha-1 antitrypsin, possible iron overload) were excluded in all patients. AIH diagnosis fulfilled the criteria issued by the International Autoimmune Hepatitis Group (IAIHG) in 2008.[12] All the AIH diagnosis made before 2008 were retrospectively validated using the simplified 2008 criteria. Patients with concomitant features of primary biliary cholangitis, primary sclerosing cholangitis, autoimmune sclerosing cholangitis or other forms of liver disease have been excluded. Drug use has been consistently and repeatedly assessed in each patient before the AIH diagnosis be formulated, and drug-induced liver injury (DILI) was excluded as conventionally required.

We defined AIH presentation as "acute" when there was clinical evidence of jaundice and/or an increase in transaminase levels of at least 10-fold the upper normal limit (UNL) and/or bilirubin greater than 5 mg/dL, while the remaining patients were asymptomatic or had an insidious onset.[1,13]

2.2 | Biochemistry and immunological features

Biochemical parameters analysed included alanine aminotransferase (ALT), total bilirubin, gamma-globulin and immunoglobulin G (IgG) levels.

Autoantibodies has been assessed using in-house indirect immunofluorescence and immunoblotting until 2000, as previously described in detail[14] and with commercially available tissue sections, cell lines and immunoassays with recombinant proteins thereafter.[15,16] A large number of pre-2000 samples from AIH patients, stored at −80°, were available for autoantibody determination with newly available assays. The following reactivities have been assessed by indirect immunofluorescence: anti-nuclear antibodies (ANAs), anti-smooth muscle antibodies (SMA), liver/kidney microsomal antibody type 1 (anti-LKM1) and liver cytosol antibody type 1 (anti-LC1). Confirmatory tests for anti-LKM1 and anti-LC1 and detection of anti-SLA/LP has been performed with commercially available second-level immunoblotting technique (Liver Profile, Euroimmun, Lübeck, Germany).

The genetic typing at the human leucocyte antigen (HLA) DR3/DR4 loci was performed in 249 patients with standard polymerase chain reaction/sequence-specific oligonucleotide probe hybridization.

2.3 | Histology

Liver biopsy was available for 431 patients (85%) at diagnosis. Even if no morphological features are pathognomonic of AIH,[3,4] all patients had the characteristic histological picture of interface (periportal

or periseptal) hepatitis with a predominantly lymphoplasmacytic necroinflammatory infiltrate, with or without lobular (intra-acinar) involvement and portal–portal or central–portal bridging necrosis. We collected data regarding histological grading and staging according to Ishak's score.[17] A histological diagnosis of cirrhosis required the presence of F5–F6 Ishak's stage. For patients in whom liver biopsy was not performed at diagnosis, the presence of cirrhosis was assessed through biochemical and/or ultrasonographic/elastographic evaluation.[18] Therefore, the diagnosis of cirrhosis was histologically-based in 47 and clinically and instrumentally established in 19 patients.

2.4 | Treatment and clinical outcomes

After the diagnosis was confirmed, the therapeutic regimen with methylprednisolone or prednisone started at the dosage of 0.5–1 mg/kg/day for the first 4 weeks with subsequent slowly progressive tapering of the steroid dosage and strict monitoring of ALT and IgG serum levels; after the first 4 weeks of therapy azathioprine was usually added. Response to therapy was assessed 12 months after treatment initiation. Complete response was defined as the resolution of symptoms (if present) and normalization of ALT and IgG levels.[3,4] Non-responders or intolerant patients were treated with alternative drugs, such as Mycophenolate Mofetil, 5-Mercaptopurine, Budesonide, and Tacrolimus on a patient-by-patient basis.

Clinical progression was defined as cirrhosis development for non-cirrhotic patients assessed through laboratory and/or elastographic evaluation[18] and clinical decompensation/hepatocarcinoma development for previously compensated cirrhosis. Finally, we assessed the composite outcome of liver-related death (LR-D) and liver transplantation (LT).

2.5 | Statistical analysis

We divided patients into four groups according to the decade in which the diagnosis of AIH was made: first group 1981–1990, second group 1991–2000, third group 2001–2010 and fourth group 2011–2020. The overall median duration of follow-up was 64 months (range 24–432 months); the median duration of follow-up of the most recently diagnosed patients (from 2011 to 2020) was 48 months (range 24–120).

Comparative analysis of categorical variables was performed using the χ^2 test. The analysis of variance (ANOVA) test and Pearson's direct linear correlation were used for the evaluation of continuous variables. A p-value <.05 was considered significant. For the statistical analysis, we used the Wizard 1.9.49 software for MacOS-X.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics.

3 | RESULTS

The clinical features of the 507 consecutive patients with AIH are summarized in Table 1, the biochemical, histological and immunological features are reported in Table 2.

During the 1980–2020 period, the median age at onset progressively and significantly increased from 24 to 52 years, as Pearson's correlation shows in Figure 1 ($r=0.381$, $p<.001$). The paediatric population referred to our centre at the time of transition from paediatric to adult care decreased over the decades and dropped in the last decade, as expected ($p<.001$). Female sex maintained its prevalence around 80% throughout the years.

The acute onset became the most frequent clinical phenotype and in the last decade represents the usual presentation of AIH in more than half the cases. Cirrhosis has become significantly less common at the time of diagnosis (from 36.5% to 8.7%, $p<.001$), whereas histological grading and staging remained stable across the decades analysed (Table 2), probably due to selection bias (fewer liver biopsies were performed in cirrhotic patents).

ANA, isolated or in different associations with other autoantibodies, has become the most frequent serological marker over the years, whereas SMA, anti-SLA, anti-LKM1 and anti-LC1 were detected significantly less frequently (Table 2). Median gammaglobulins and IgG levels consistently and significantly declined over the decades ($p<.001$ for both), albeit always above the normal limits. Across the decades, levels of ALT showed a cumulative increase, without reaching statistical significance ($p=.084$), whereas total bilirubin at the time of diagnosis remained consistently similar (Table 2).

Although genetic analysis was available only in half the patients, no differences was found in the prevalence of HLA DR3 or DR4 ($p=.218$ and .660 respectively).

The rate of complete response to conventional treatment increased significantly, reaching 76.2% in the last decade ($p<.001$). In particular, we observed a clear-cut difference before and after the year 2000: in the 1980–2000 period. Only 46 (40.4%) of 114 AIH patients fulfilled the complete response criteria, whereas after the turn of the millennium, 232 (74.4%) of 312 did so ($p<.001$).

In the last decade, the improved response rate is associated with a significant drop in the progression of the disease, which is reduced to 11.2% ($p<.001$). In addition, there is a steady and well-defined reduction of major outcomes such as the need for LT and LR-D ($p<.001$), as outlined in Table 1.

4 | DISCUSSION

This study analyses the modifications of the clinical, biochemical, immunological, histological and genetic features of 507 AIH patients consecutively referred to a tertiary centre in Bologna, Italy, from 1980 to 2020. To our knowledge, this is one of the largest studies on AIH assessing at presentation clinical phenotype, biochemical, histological and immunological features, treatment response and disease

TABLE 1 Clinical features and progression of the disease in 507 patients with autoimmune hepatitis, aggregated according to the decade of onset.

	1981–1990 (*N* = 54)	1991–2000 (*N* = 107)	2001–2010 (*N* = 176)	2011–2020 (*N* = 170)	*p*-value
Median age at onset, years (range)	24 (2–80)	31 (3–74)	39 (5–81)	52 (11–80)	**<.001**
Female sex, *N* (%)	46 (85.2)	81 (75.7)	136 (77.3)	128 (75.3)	.487
Paediatric onset (<15 years) *N* (%)	15 (27.8)	20 (18.7)	22 (12.5)	1 (0.58)	**<.001**
Acute onset[a], *N* (%)	21/53 (39.6) Missing: 1	44/99 (44.4) Missing: 8	83/174 (47.7) Missing: 2	100/168 (59.5) Missing: 2	**.019**
Cirrhosis at diagnosis[b], *N* (%)	19/52 (36.5) Missing: 2	16/98 (16.3) Missing: 9	17/158 (10.8) Missing: 18	14/161 (8.7) Missing: 9	**<.001**
Complete response[c], *N* (%)	3/27 (11.1) Missing: 27	43/87 (49.4) Missing: 20	117/161 (72.7) Missing: 15	115/151 (76.2) Missing: 19	**<.001**
Disease progression[d], *N* (%)	19/35 (54.3) Missing: 19	26/87 (29.9) Missing: 20	27/160 (16.9) Missing: 16	16/143 (11.2) Missing: 27	**<.001**
Major outcomes[e], *N* (%)	6/35 (17.1) [*5 LT, 1 LR-D*] Missing: 19	8/87 (9.2) [*5 LT, 3 LR-D*] Missing: 20	4/160 (2.3) [*1 LT, 3 LR-D*] Missing: 16	3/143 (2.1) [*1 LT, 2 LR-D*] Missing: 27	**<.001**

Bold was used for statistical significant results.

[a]Acute onset is defined as transaminase levels >10-fold the upper limit and/or bilirubin >5 mg/dL.

[b]The diagnosis of cirrhosis was histologically based among 47 patients (Ishak's stage F5–F6) and clinically and instrumentally established among 19 patients.

[c]Complete response was defined as resolution of symptoms (if present) and normalization of ALT and IgG levels after 12 months treatment initiation.

[d]Disease progression is defined by development of cirrhosis in non-cirrhotic patients and hepatic decompensation/hepatocellular carcinoma development in previously compensated cirrhosis.

[e]Composite outcome of liver-related deaths (LR-D) and liver transplantation (LT).

TABLE 2 Biochemical, immunological, histological and genetic features of 507 patients with autoimmune hepatitis, aggregated according to the decade of diagnosis.

	1981–1990 (*N* = 54)	1991–2000 (*N* = 107)	2001–2010 (*N* = 176)	2011–2020 (*N* = 170)	*p*-value
ALT × UNL, median (range)	10 (1.1–60)	14 (1.1–88)	14.7 (1–92)	18 (1.5–90)	.084
Bilirubin mg/dl, median (range)	3.35 (0.16–32.8)	1.7 (0.4–37.8)	1.92 (0.28–62)	1.9 (0.17–25.8)	.307
ɣ-globulins g/L, median (range)	25.5 (10.5–60)	24.5 (9.6–52)	20.6 (9–63)	18.9 (7–50)	**<.001**
IgG × UNL, median (range)	1.55 (0.76–3.86)	1.51 (0.72–5.48)	1.25 (0.5–3.04)	1.12 (05–4.48)	**<.001**
Grading[a], median (range)	12 (7–15) Missing: 10	8 (4–14) Missing: 20	8 (4–18) Missing: 27	8 (4–17) Missing: 19	.299
Staging[b], median (range)	2 (1–4) Missing: 10	2 (1–5) Missing: 20	2 (0–5) Missing: 27	2 (0–6) Missing: 19	.827
ANA, *N* (%)	22/54 (40.7) Missing: 0	53/102 (52) Missing: 5	123/167 (73.7) Missing: 9	134/167 (79.3) Missing: 1	**<.001**
SMA, *N* (%)	31/54 (57.4) Missing: 0	65/102 (63.7) Missing: 5	79/165 (47.9) Missing: 11	72/165 (43.6) Missing: 5	**.008**
Anti-LKM1, *N* (%)	11/53 (20.8) Missing: 1	19/98 (19.4) Missing: 9	24/150 (16) Missing: 26	7/161(4.3) Missing: 9	**<.001**
Anti-LC1, *N* (%)	11/53 (20.8) Missing: 1	12/85 (14.1) Missing: 22	7/101 (6.9) Missing: 75	7/133 (5.3) Missing: 37	**.005**
Anti-SLA/LP, *N* (%)	4/34 (11,8) Missing: 20	7/55 (12.7) Missing: 52	12/56 (21.4) Missing:120	6/109 (5.5) Missing: 61	**.024**
HLA-DR3, *N* (%)	14/29 (48.3) Missing: 25	22/64 (34.4) Missing: 43	34/94 (36.2) Missing: 82	31/63 (49.2) Missing: 107	.218
HLA-DR4, *N* (%)	7/29 (24.1) Missing: 25	17/64 (26.6) Missing: 43	22/93 (23.7) Missing: 82	11/63 (17.5) Missing: 107	.660

Note: All continuous numerical data are reported as median (range). [a]Grading and [b]Staging according to Ishak classification.

Bold was used for statistical significant results.

Abbreviations: ALT, alanine aminotransferase; ANAs, antinuclear antibodies; anti-LC1, liver cytosol antibody type 1; anti-LKM1, liver/kidney microsomal antibody type 1; anti-SLA/LP, anti-soluble liver antigen/liver-pancreas; HLA, human leucocyte antigen; IgG, immunoglobulin G; SMA, smooth muscle autoantibody; UNL, upper normal limit.

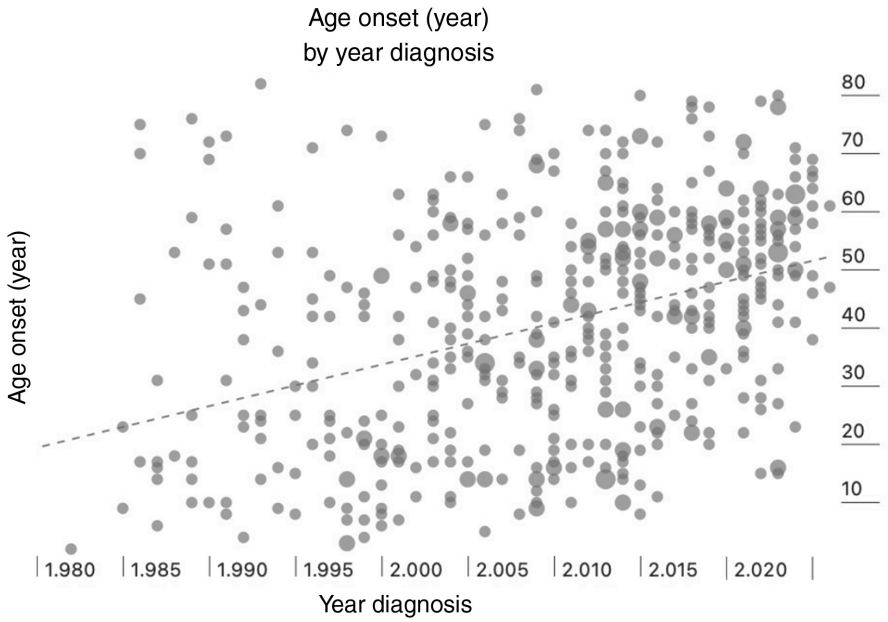

FIGURE 1 Pearson's correlation between age at diagnosis and year of diagnosis ($R = 0.381$).

progression, and comparing the changes occurred across four different decades.

Interestingly, we found a significant increase of the age at diagnosis (Figure 1), that steadily rose from 24 years in 1981–1990 to 52 years in 2011–2020. Historical studies describing the epidemiology of AIH report a bimodal age distribution at presentation, with a first peak during the second decade of life and a second peak around 50 years.[2] On the other hand, recent data showed that the disease has been increasingly recognized in all age groups.[3,4] Ngu et al.[7] reported a peak in the sixth decade of life in New Zealand. Similarly, in Finland, the highest incidence and prevalence rate was in the 45–84 age group.[19] In a US population-based study, Tunio NA et al. demonstrated the highest prevalence in elderly (>65 years) and an increase of AIH prevalence rate until the seventh decade of life.[20] The marked reduction of patients with paediatric onset referred to our centre in the last two decades is all but unexpected, since most of the patients born after 2000 at the time of this study are supposed to be on the whole adolescents and young adults still in the clinical care of paediatricians or paediatric hepatologists and most likely not transitioned yet from the child-centred to an adult healthcare system.

A recent systematic review and meta-analysis demonstrated the gradual increase in the incidence and prevalence of AIH with the highest rates observed in adults aged over 65 years and the lowest in children.[5] A similar observation, also reflected by our findings, can be explained by the progressive aging of the general population in Italy, where the number of people who are ≥60 years old in 2020 has doubled compared with 1980 and the mean age of Italian population increased from 41.9 years in 2002 to 45.7 years in 2020.[21] Moreover, immunosenescence might be advocated as an additional mechanism leading to concomitant and parallel loss of "efficiency" of the immune system over time,[22] leading to a reduced ability to discriminate between self and non-self. Finally, the increase of polypharmacotherapy in the elderly population could elicit mechanisms that are supposed to be trigger factors inducing or exacerbating AIH.[23]

In our cohort, the prevalence of female sex was stable over time, with a female–male ratio of approximately 5:1, in line with the most recent epidemiological studies.[24–27]

Form the clinical standpoint, an increase of the acute phenotype is steadily observed over the decades, reaching its peak during the 2011–2020 period, when more than half of the patients had a diagnosis of AIH during an acute/icteric hepatitis. In addition, several reports suggest the rise of acute onset AIH as emerging clinical phenotype from early 2000 to our days not only in adults, but also in the paediatric setting.[7,9,11,28–30] This constant increase of the acute phenotype of AIH over the years requires some tentative explanations. Firstly, we believe that the increased awareness of the disease and the introduction of validated easy-to-use diagnostic criteria allow the prompt identification of this rare liver disorder. Secondly, standardized and commercially available assays for autoantibody detection are today largely available and offer a reliable tool in support of the diagnosis. Finally, the increased exposure to environmental/pharmacological trigger factors could elicit AIH-like liver injury: recent examples are liver injury with autoimmune features after SARS-CoV-2 vaccination[31,32] and autoimmune-like hepatitis following turmeric supplementation.[33,34] Both exposures have been added to the list of potentially hepatotoxic substances.[35] These observations reinforce the need for population-based studies and active pharmacovigilance, not only after vaccine procedure, but also for herbal and dietary supplements.

In this regard, in our cohort, drug use has been consistently and repeatedly assessed in each patient before the AIH diagnosis was formulated as conventionally required, and suspected DILI patients were excluded from the study. In addition, presence of potential

histological clues consistent with DILI, such as eosinophilic infiltration has been systematically ruled out on the available liver biopsies.[36] Finally, only very few patients with an appropriate follow-up did not experience a biochemical relapse with the need to reinstitute immunosuppressive treatment, suggesting that our cohort included only genuine AIH rather than DILI.

In parallel with the rise of the acute phenotype, we identified a sharp reduction of cirrhosis at the time of diagnosis, a figure that in the last decade dropped to 8.7%. A possible explanation for this decrease could be the prompt identification and correct treatment of the disease in its early phase during its acute presentation, thus preventing multiple and possibly overlooked episodes of recurrent acute hepatitis[37,38] and thus its progression towards fibrosis and cirrhosis.[39]

Conversely, recent epidemiological reports show cirrhosis detected at diagnosis among 34%–35% of patients,[20] a finding suggesting not only a role for the different genetic predisposition in disease expression, but also a delayed access to diagnosis and cure in different countries and populations.[40–42]

As far immunologic features are concerned, we identified a progressive decline of gamma-globulin and IgG levels at diagnosis over the four decades. This finding is consistent with the rise of the acute forms, which often presents with gamma-globulin and IgG levels within normal or near-normal limits,[43] and also with the declining number of cirrhotic, typically characterized by hypergammaglobulinaemia, at the time of diagnosis.

Over the years, a significant increase of ANA positivity, and a progressive decrease of anti-LC1 and anti-LKM-1 positivity at diagnosis were observed: this trend is consistent with the increasing median age of our patients, given the fact that anti-LC1 and anti-LKM are typically detected in children, whereas ANA are most commonly detected among adults.[44] On the other hand, the prevalence of SMA and anti-SLA/LP autoantibodies appears to be highly fluctuating over the decades. However, the serological profile of AIH does not appear to affect its clinical expression, the response to treatment and the risk of disease progression.[45]

Prednisone or prednisolone alone or in combination with azathioprine has been and still is the mainstay therapy for AIH. In our centre, all patients received steroids plus azathioprine (if well tolerated) as first line treatment, and clinical, biochemical and immunological response is the main guide to modulate treatment, according to internationally recognized treatment schedules. The complete response definition has been modified only recently. Before 2010, it was considered transaminases below 2-fold the UNL, which has proved to be suboptimal, whereas after 2010, the achievement of complete response required both transaminase and IgG normalization.[3,4]

We observed that the immunosuppressive regimen applied before 2001 lead to a complete response - assessed according to the most recent definition - only in 40.4% of AIH patients, while after 2001 this percentage reached 74.4%. As a consequence, in recent decades, we noticed a significant reduction of the deteriorating progression of the liver disease during follow-up (in 1981–1990 about 1 patient every 2 showed a worsening course, compared with only one patient out of 10 in the last decade) and the major adverse outcomes dropped in last decades to a mere 2.1%. These observations reinforce the clinical relevance of achieving a complete biochemical response, possibly with minimal and reversible side effects during a chronic treatment. Other factors have possibly contributed to the improved prognosis of this disease, such as the availability of second- and third-line treatments such as mofetil mycophenolate, 5-mercaptopurine, budesonide, and tacrolimus, introduced in recent years into current clinical practice, and particularly useful in non-responders or intolerant patients.[46] Moreover, the reduced number of paediatric and cirrhotic AIH patients in the most recent decades could be an additional explanation for the higher rate of complete response, as cirrhosis and paediatric onset are both known to be predictive factors of non-response.[47] On the other hand, advanced age and acute phenotype at onset are both positive predictors of response to immunosuppressive treatment and are likely to account for the overall improvement in treatment efficacy and favourable long-term clinical outcome.[10,47,48]

The significantly reduced LR-D and need for LT observed over the decades in our cohort reflect this positive development in the management of the AIH patient and is in keeping with the Northern America and European trends.[49,50]

There are a number of limitations in our study that need to be acknowledged: it is a single-centre experience with all patients of Caucasian origin and given the retrospective nature of the study, some evaluations are weakened by missing data. In addition, the proportion of patients with paediatric onset dropped, and is underrepresented in the last decade. Finally, the study covered a large period of time during which the management of AIH has been significantly modified, and the study design did not permit to analyse treatment schedule for each patient.

In conclusion, in this study, we evaluated a large cohort of 507 Italian patients with AIH across four decades. We found that in the new millennium, in general, the typical AIH patient is a 50-year or older woman, with acute hepatitis, non-cirrhotic, who responds favourably to immunosuppressive treatment and is very unlikely to experience disease worsening. In addition, as a consequence of early diagnosis, prompt treatment and high rate of complete response, in the last decade dreaded clinical outcomes such as LR-D and need for LT are drastically reduced.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors do not have any disclosures to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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