E.V. Kostyrko, P.V. Shumilov
Pirogov Russian National Medical Research University, Moscow, Russian Federation

Contemporary Methods of Treating Children with Autoimmune Nephric Diseases

Author affiliation:
Elena Vladimirovna Kostyrko, PhD candidate at the department of hospital pediatrics No. 1 of the Pirogov Russian National Medical Research University (RNMRU)
Address: 1 Ostrovityanova Str., Moscow, 117997; **tel.:** +7 (495) 936-93-74; **e-mail:** ks.lenchik@mail.ru

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The review is dedicated to the analysis of contemporary therapies and efficacy thereof for treating children autoimmune nephric diseases. The authors describe peculiarities of using the conventional therapy in children and discuss alternative treatments using cyclosporine, tacrolimus, budesonide and ursodeoxycholic acid, as well as the need in using the second-line drugs for treating patients with resistant autoimmune nephric diseases. The review touches upon the promising approaches to the treatment of this category of patients.
Keywords: *children, autoimmune nephric diseases, autoimmune hepatitis, autoimmune sclerosing cholangitis, treatment.*

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Introduction

Autoimmune nephric diseases is a group of diseases characterized by inflammatory nephric changes of unknown etiology and involving such pediatric conditions as type 1 and 2 autoimmune hepatitis (AIH) and overlap syndrome of AIH and sclerosing cholangitis – autoimmune sclerosing cholangitis (ASC) [1-3]. Diseases are characterized by increased aminotransferase activity in blood serum, formation of autoantibodies and increased concentration of immunoglobulins G (IgG). Histologic examination reveals signs of the so called interface hepatitis[1] [4]. As the listed peculiarities are observed at different types of autoimmune nephric diseases and activity of alkaline phosphatase or γ-glutamyl transpeptidase often remains normal in the onset of the disease, diagnosis of ASC is established on the basis of cholangiography.
The cause of autoimmune attack remains undetermined. However, it is speculated that autoimmune nephric disorders occur as a result of immune system deregulation by environmental triggers in genetically predisposed persons [6].
AIH incidence in Europe and North America is 0.1-1.9 cases per 100,000 people per year, prevalence – 15-25 cases per 100,000 people per year [3, 6, 7]. According to G. Mieli-Vergani et al., the number of juvenile autoimmune nephric diseases has been significantly increasing throughout the last 2 decades [4]. It should be mentioned that diseases of this group in children are characterize by aggressive course and rapidly progress in the absence of immediate immunosuppressive treatment. By the time the diagnosis is established, 36-78% of children already suffer from liver cirrhosis [8-10]. Mild forms of autoimmune nephric diseases described in adults are only rarely observed in young patients [11].

[1] Interface hepatitis (piecemeal necrosis or periportal hepatitis) is characterized by penetration of liver parenchyma by inflammatory lymphoplasmacytic infiltrates, release ("budding") and breakdown of isolated hepatocytes or small groups thereof [5].

Autoimmune hepatitis

Treatment should start immediately after the diagnosis has been established in order to avoid progression of the process. Before immunosuppressive therapy gained wide recognition, up to 40% patients died within 6 months of diagnosis establishment [12, 13]. Speed and completeness degree of response to the therapy depend on severity of the disease at manifestation. Excluding cases of fulminant liver failure with encephalopathy, which usually requires liver transplantation, effectiveness (achievement of remission) of conservative immunosuppressive AIH therapy (i.e. prednisolone and azathioprine) in children is ca. 80% [14].

Criteria of remission in children include complete termination of clinical symptoms, normalization of aminotransferase and serum IgG activity, negative or very low autoantibody titer ($\leq$ 1:20 for antinuclear antibodies [ANA] and anti-smooth muscle antibodies [ASMA]; $\leq$ 1:10 for liver-kidney microsomal type 1 antibodies [anti-LKM-1]) and histologic resolution of inflammation [14, 15]. It should be remembered that histologic response falls behind biochemical response, while clinical-biochemical remission does not always reflect histologic resolution of the disease. However, considerable decrease in portal inflammation intensity and pronouncement of fibrotic changes is observed in 95% of patients after 4 years (on the average) of effective treatment [16].

Signs of effectiveness of the conducted treatment, as demonstrated by ultrasonic data, are observed with a significant lag in the form of higher echostructure homogeneity and decrease in the size of liver. Diagnosis of the disease on the stage of cirrhosis is characterized by decrease in the size of both liver and spleen and signs of blood flow normalization in the system of nephric veins [17].

Approximately 40% of patients suffer from relapses in the setting of the therapy; they are characterized by higher aminotransferase activity in blood serum, which requires a temporary increase in the glucocorticoid (GC) dosage. Low compliance (adherence to medical recommendations) is a significant predictor of recurrence, especially in adolescents [18].

It is known that correct prescription of immunosuppressive therapy is a key to success; however, AIH treatment regimens for children still feature controversial points, as they reflect experience of separate centers in the absence of randomized controlled studies of pediatric patients [3]. Standard initial AIH treatment regimens involve prednisolone monotherapy or a combination thereof with azathioprine. According to the data obtained by the gastroenterology unit of the Scientific Center of Children's Health (Moscow), prescription of multimodal immunosuppressive therapy in the onset of the disease helps to significantly decrease the AIH recurrence rate. Indeed, the AIH recurrence rate in the children receiving prednisolone only therapy was 60%, in the children receiving multimodal prednisolone/azathioprine therapy – 19%. Thus, prescription of multimodal immunosuppressive therapy to children with AIH is better justified [5].

Children are prescribed higher GC doses than adults in order to rapidly suppress tissue inflammation. Conservative AIH therapy of children involves prednisolone (or prednisone) in the dose of 2 mg/kg per day (up to 60 mg per day) with gradual (4-8 weeks) dose reduction proportionately with aminotransferase activity decrease down to the maintenance dose of 2.5-5 mg per day (depending on the age and weight). In the event of maintenance therapy, daily intake of prednisolone is particularly effective, as the recurrence rate is higher at alternating therapy [4].

There are different points of view on the time of azathioprine prescription: at some centers azathioprine is prescribed only if aminotransferase activity ceases to decrease as a result of prednisolone monotherapy, or if severe steroid side effects occur [1, 19]; at other centers azathioprine is prescribed after several weeks of GC treatment, when serum aminotransferase activity starts to decrease [20]; at some centers azathioprine is used from the beginning as an addition to GC [5, 15]. Regardless of the chosen protocol, in the end, 85% of the patients receive multimodal therapy [21]. Azathioprine is used in the initial dose of 0.5 mg/kg per day; if no toxicity signs are observed, the dose is increased to the maximum level – 2.0-2.5 mg/kg per day.

Care is recommended in the event of azathioprine prescription to patients with autoimmune nephric diseases, especially to children with severe jaundice, due to the drug's hepatotoxic qualities. One other possible side effect of azathioprine (dose-dependent) is a usually reversible bone marrow function suppression, which most commonly manifests itself with leukopenia, sometimes – with anemia and thrombocytopenia, rarely – with agranulocytosis, pancytopenia and aplastic anemia. Most commonly, these complications occur in patients predisposed to myelotoxicity, e.g. with thiopurine methyltransferase (TPMT) deficiency, renal or nephric failure [4]. TPMT activity measurement helps to predict azathioprine metabolism and toxicity thereof before initiating treatment [22], although only patients with virtually zero red blood cell TPMT concentration are at risk of myelosuppression in the setting of azathioprine therapy [22, 23]. Thus, determination of activity of the enzyme is justified only in case of cytopenia, which occurred before or during therapy, or if prescription of very high doses of azathioprine is required [23].

Aminotransferase activity decrease within the first 2 months of treatment is observed in 80% of patients, while complete normalization of this parameter may require several months [1]. Throughout the first 6-8 weeks of treatment, functional nephric samples should be taken on a daily basis in order to correct dosage and prevent severe adverse effects of steroid therapy.

A prospective study involving 72 14-71-year-old patients conducted by P.J. Johnson et al. demonstrated that GC were withdrawn after induction of remission with a combination of prednisolone and azathioprine and maintenance thereof for at least 1 year; remission in the presence of azathioprine intake was observed in 83% of patients [24]. There have been reports of successful maintenance of long-term remission with azathioprine monotherapy in pediatric practice as well [25]. S. Banerjee et al. described experience of treating 5 patients with AIH, in whom GC were withdrawn 378 (on the average; 125-630) days after initiation of therapy, while azathioprine monotherapy lasted for 28-82 months. Only 1 patient had a relapse 75 months after GC therapy termination. He rapidly responded to prednisolone, which was withdrawn again after as few as 6 weeks; no relapses of the disease in the setting of azathioprine monotherapy were observed in the subsequent 7 months of treatment [26]. C. van de Nadort et al. also confirmed the possibility of maintaining AIH remission in children without GC intake. They described experience of treating 7 patients, 3 of whom suffered from liver cirrhosis. GC were completely withdrawn in children after 70 (on the average; 38-102) months; maintenance therapy with azathioprine and ursodeoxycholic acid (UDCA) was used [27]. However, it remains unknown, whether such maintenance therapy is any better than use of low doses of prednisolone and azathioprine.

Alternative treatment

Standard AIH therapy regimens in children, especially in girls, have more severe and prolonged side effects than in adults. Moreover, long-term prednisolone treatment even in low doses (< 0.5 mg/kg per day) has been demonstrated to lead to the risk of severe sequelae [28-30], which is why the development of alternative AIH treatment schedules using different immunosuppressive drugs remains a topical issue.

CYCLOSPORINE

A pilot multicenter study of 32 patients with AIH, who have not previously undergone any treatment, was conducted in order to determine the possibility of using cyclosporine for inducing remission and effectiveness of such a protocol [31]. Cyclosporine was prescribed as monotherapy for the period of 6 months (in the first 3 months the drug concentration in blood was 250 ± 50 ng/ml on the average, in the subsequent 3 months – 200 ± 50 ng/ml). Later, the therapy would be supplemented with prednisolone in low doses (0.3-0.5 mg/kg per day) and azathioprine (1.5 mg/kg per day); cyclosporine would be withdrawn 1 month after, and the

children would remain on maintenance therapy with prednisolone and azathioprine. Use of this regimen resulted in persistence of high aminotransferase activity in 17% of patients and high γ-globulin concentration in 47%. Full biochemical remission was observed in all patients after 12 months of treatment. The obtained data indicate that high GC doses used for standard treatment are better in terms of rapid suppression of immunoglobulin production [31].
Later, the developed protocol was used to treat a larger group of patients. That time, the study involved 84 children: 80 children with type 1 AIH and 4 children with type 2 AIH; all of these patients had never before undergone immunosuppressive therapy. Normalization of aminotransferase activity was observed in 94% of patients; 72% of patients featured such a normalization within the first 6 months of treatment. Absence of differences in response to treatment of patients with type 1 or 2 AIH reconfirmed the data obtained by D. Debray et al. on the possibility of using cyclosporine for treating patients with type 2 AIH [32]. A considerably delayed remission was observed in patients with the total bilirubin level > 1.2 mg/dl and portal hypertension at the time of diagnosis establishment. Researchers emphasized the absence of relapses during treatment; however, the follow-up period was short (the average follow-up duration was 29 months) [33]. Only a study by O.Z. Franulović et al. demonstrated a good long-term prognosis after cyclosporine therapy. Indeed, recurrence was observed only in 1 patient out of 9 children with AIH, who achieved remission and avoided steroid side effects, during the long-term follow-up (1.5-9 years) due to withdrawal of the maintenance prednisolone dose [34]. However, it is necessary to conduct controlled studies in order to confirm advantages of this protocol in terms of side effects and long-term prognosis.

TACROLIMUS

An open-label pilot prospective study of 20 patients with type 1 AIH was conducted in order to study effectiveness of tacrolimus-including treatment protocol [35]. 17 patients would receive treatment for the first time; in 3 patients, standard therapy schedules used before involvement into the study were ineffective. Liver cirrhosis was diagnosed in 6 children. Patients would be followed up for a year; the target tacrolimus concentration in blood was 2.5-5 ng/ml. In 3 cases tacrolimus monotherapy resulted in full remission; in 14 cases low doses of prednisolone or azathioprine were added in order to achieve remission (11 patients received prednisolone, 4 – azathioprine; 1 patient would receive both prednisolone and azathioprine at different periods of time); in 2 cases treatment was terminated. The obtained results demonstrate the possibility of using tacrolimus as an alternative method of treatment, but monotherapy therewith is rarely sufficient for full biochemical remission. On the other hand, the use thereof helped to significantly reduce doses of prednisolone and azathioprine and, thus, reduce intensity of side effects of these drugs [35]. Further studies should be aimed at specifying whether tacrolimus is suitable for long-term maintenance therapy.

BUDESONIDE

Topical GC budesonide is one other possible alternative for remission induction and maintenance in the event of autoimmune nephric diseases; it features very few systemic adverse events. 90% of budesonide is subject to metabolism and deactivated during the primary progression through liver; this results in low systemic bioavailability, reduction in the amount and decrease in the degree of adverse side reactions. However, this drug should not be used in patients with liver cirrhosis, i.e. in most patients with AIH.
A randomized multicenter study of 208 10-70-year-old patients was conducted in order to analyze effectiveness and safety of budesonide therapy in comparison with prednisone use in patients with AIH [36]. The study consisted of 2 stages of 6 months each. In the first stage the patients were randomized into the budesonide group (3 mg TID or BID after biochemical remission) and the prednisone group (initial dose – 40 mg/day; gradual reduction down to 10

mg/day). Later, all the patients would be receiving only budesonide (3 mg TID or BID). All the patients were receiving azathioprine throughout the study (1-2 mg/kg per day). Simultaneous analysis of pediatric and adult cohorts after 6 months of treatment demonstrated that full biochemical remission without specific GC side effects was registered in 47% of the budesonide group patients and in only 18% of the prednisone group patients. Full biochemical remission rate in the budesonide group was 60% and 39% in the prednisone group. Taking biochemical response as ALT activity decrease < 2 norms, 89% of the budesonide group patients and 81% of the prednisone group patients responded to the therapy. No significant differences between the patients randomized in the initial stage to the budesonide group and the prednisone group in terms of achievement of full response were observed by the end of stage B. These data allowed the authors to conclude that the combination of budesonide and azathioprine helps to achieve and maintain remission in patients with AIH without histologic signs of liver cirrhosis. In the event of simultaneous azathioprine intake, effectiveness of budesonide treatment and prednisone treatment is comparable. However, budesonide therapy outperforms prednisone treatment in terms of the risk of development of specific GC adverse events (moon face, acne, hirsutism, stretch marks, diabetes, glaucoma) [36].

Later, M. Woynarowski et al. published results of treating 46 children, who took part in the aforementioned study. Full biochemical remission without specific GC side effects was achieved in 16% of the budesonide group patients and in 15% of the prednisone group patients after 6 months of treatment. The full biochemical remission rate in the budesonide group was 32% and 33% in the prednisone group. Full biochemical remission was registered in 50% of the budesonide group patients and in 42% of the prednisone group patients after 12 months of treatment. The registered remission rate was considerably lower than that achieved by means of the standard treatment. Moreover, steroid side effects were only statistically insignificantly different between children of the 2 groups, except for higher weight gain in the prednisone patients (5.1 vs 1.2 in the budesonide group) [37].

According to G. Mieli-Vergani, results of the study conducted by M. Woynarowski et al. do not indicate the possibility of using budesonide as the first line AIH therapy in children. Firstly, the original study was developed for adult patients (not pediatric patients), which is why the initial prednisone dose was too low for optimal response in children. Moreover, all the patients were prescribed azathioprine from the onset of the disease regardless of the presence of jaundice, which is why poor response to treatment might have been caused by its toxicity. Secondly, the analyzed cohort consisted not only of the patients who have never undergone treatment before, but also of the patients after disease relapse, who might have constituted the subgroup with poor response to therapy. As long as the children involved in the study did not undergo cholangiography, some patients were likely to have ASC. Thus, recurrence-prone patients and children with ASC might have been accidentally randomized to the budesonide group affecting the response rate. Thirdly, according to the study design the budesonide dose would be reduced in correlation with the response, whereas the prednisone dose would be reduced in accordance with the protocol; this complicates comparison of results. Thus, budesonide might be offered as an alternative to the patients without cirrhosis included into the group of risk of development of steroid side effects; however, its role as the first line AIH therapy remains to be proven. Also, further studies are required to determine the optimal dose of budesonide, which would allow to achieve rapid normalization of aminotransferase activity comparable with the action of prednisone in the dose of 2 mg/kg per day and gradually diminished in correlation with the response [38].

URSODEOXYCHOLIC ACID

A.R. Reyzis et al. described experience of treating 9 children by means of UDCA monotherapy (in the dose of 15-20 mg/kg per day). The authors concluded that UDCA may be used as an alternative to classical methods of treatment in the event of early AIH detection and presence of

contraindications to treatment with prednisone or other immunosuppressants. However, in the given clinical case activity normalization of aminotransferases required 7 years, of alkaline phosphatase – 8 years, of γ-glutamyl transpeptidase – 10 years; this casts a certain doubt on effectiveness of the treatment [39]. Moreover, now that harmful effect of high UDCA doses on the long-term prognosis in patients with primary sclerosing cholangitis has been revealed, UDCA is used with care even in patients with signs of cholangitis [19, 40]. We were unable to find any reports of UDCA use for AIH monotherapy in children in accessible foreign sources.

Treatment of resistant cases

In most cases, AIH responds to GC treatment, as confirmed in the diagnostic point system developed by the International AIH Group (IAIHG) [41]. However, some patients remain resistant to standard therapy schemes and should be prescribed other immunosuppressive drugs.
After the data on successful use of mycophenolate mofetil (MMF) as the second line therapy in adult patients were obtained, M.M. Aw et al. published results of treatment of 26 children with autoimmune hepatic diseases (18 patients with AIH and 8 patients with ACS). All the patients were initially prescribed the standard multimodal therapy (prednisolone in the dose of 2 mg/kg per day and azathioprine in the maximum dose of 2 mg/kg per day). 1 of the following 2 criteria served as an indication to MMF prescription: infeasibility of remission achievement/maintenance by means of prednisolone azathioprine use or development of severe side effects. The initial MMF dose was 20 mg/kg per day; the MMF dose would reach the maximum level (40 mg/kg per day) within 2 weeks. If MMF was prescribed, azathioprine would be withdrawn. As a result, 18 children responded to MMF; AST activity normalized in 14 patients. Within the subsequent follow-up period of 61.5 months on the average (19.5-96.3) the AST activity remained within the normal range in 12 patients. 8 children (6 of them with ASC) did not respond to the conducted therapy: AST activity remained heightened in 7 patients, whereas 1 patient required liver transplantation due to process decompensation; clinical signs of portal hypertension were detected in 1 child. Thus, the study demonstrated the possibility of using MMF in "difficult-to-treat" children with AIH (although not in children with ASC) [42].
The possible backup drugs for treating patients with resistant cases of autoimmune hepatic diseases are also calcineurin inhibitors cyclosporine and tacrolimus [32, 43].
There have been singular reports of successful treatment of resistant cases in children by means of rituximab – monoclonal antibodies to CD20 antigen found on the surface of B lymphocytes [44] – and infliximab – monoclonal antibodies to tumor necrosis factor α [45].

Autoimmune sclerosing cholangitis

In case of early initiation of treatment, ASC responds to immunosuppressive therapy used for AIH [43]. In most cases, the altered functional liver samples normalize within several months of treatment, although long-term prognosis is worse than in the event of AIH, as cholepathia continues to progress despite the treatment in approximately 50% of the patients [2]. In the event of ASC, the standard AIH treatment regimen is usually supplemented with UDCA in the dose of 15-20 mg/kg per day, although it remains undetermined, whether such therapy delays progression of cholepathia. ASC is often associated with inflammatory intestinal disorders, which have to be ruled out even in the absence of symptoms and properly treated if identified, as progression of cholepathia has been proven to be associated with persistent intestinal inflammation. Indeed, according to the literature data, hepatic disorder outbreaks often follow exacerbations of intestinal manifestations [4].

Treatment duration and prognosis

The optimal duration of immunosuppressive therapy at autoimmune hepatic diseases is unknown; however, treatment should be withdrawn only in the event of histological resolution of the inflammation. Response to treatment may be controlled by assessing IgG concentration and autoantibody titers, the fluctuations whereof correlate with the disease activity [46]. It is important to mention that the absence of serum autoantibodies does not rule out the risk of recurrence; however, the immunosuppressant dose should be reduced with care if the autoantibody titer increases [15]. It has been determined that treatment withdrawal within the first 2 years is usually accompanied by relapses [47]. Thus, treatment withdrawal might be considered only after 1-2 years of having normal functional liver samples, normal IgG levels and negative or low autoantibody titers in the absence of inflammatory activity (determined on the basis of liver biopsy). D. Vergani and G. Mieli-Vergani report that treatment withdrawal is never discussed within 3 years of diagnosis establishment and during / immediately before puberty, when relapses are especially common [21]. It has been reported that ca. 20% of children with type 1 AIH (not type 2 AIH) may successfully and permanently discontinue treatment [1].
W.S. Lee et al. analyzed prognostic parameters at autoimmune hepatic diseases in children and determined that the lag between the first symptoms and initiation of treatment is the main factor associated with an adverse outcome. Their data also demonstrate that the prognosis would become worse in the event of refusal from treatment or low compliance, that is why the awareness of the need in long-term treatment of patients and parents remains an important factor of prognosis improvement. Moreover, the study unambiguously demonstrates that the prognosis in children with ASC is worse than in children with AIH: 5 out of 9 patients with ASC required liver transplantation or died within the thirteen-year-long follow-up period (cf. 3 out of 23 children with AIH) [19, 48]. Several researchers demonstrated the correlation of prognosis with the total bilirubin level at the time of diagnosis [1, 33]. Unlike in adult patients, cirrhosis in the event of primary liver biopsy in children with AIH does not affect the long-term prognosis [8, 49, 50].
Children with AIH responding to immunosuppressive therapy feature a favorable prognosis and high quality of life on low doses of drugs: the ten-year survivability is 80% [43, 49]. However, it is reported that 3-18% of patients feature progression to the terminal stage of disease requiring liver transplantation 8-14 years after diagnosis establishment despite the treatment [1, 8, 51].

Liver transplantation

Ca. 10% of children with AIH and 20% of patients with ASC require liver transplantation. It is indicated to patients with a disease manifesting itself as fulminant liver failure (with encephalopathy) and patients developing the terminal stage of a hepatic disease despite the treatment. The five-year posttransplantation survivability of children with AIH is 86% [52]. AIH relapses after transplantation are reported in 12-46% of cases, ASC relapses – in approximately 70% of cases and more (in the presence of active inflammatory intestinal disorder). Recurrence diagnosis is based on changes of biochemical parameters, autoantibody seropositivity, interface hepatitis (histological data), dependence on GC and presence of cholangiopathy at ASC. Relapse may occur even years after transplantation; successful treatment thereof largely depends on early diagnosis [53].
It was observed in the late 1990s that AIH may occur *de novo* after liver transplantation in the children who required transplantation not due to an autoimmune hepatic disease. This condition was characterized by a histological pattern of interface hepatitis in association with high IgG level and detection of autoantibodies, particularly, of ANA, ASMA, classical anti-LKM-1, as well as of atypical anti-LKM-1, which stain renal canaliculi, but not liver [54]. Later, *de novo* AIH after transplantation was confirmed by several studies of adult and pediatric patients; however, it remains undetermined, whether liver damage in this patient is a form of transplant rejection or a consequence of autoimmune damage, which may have been caused by drugs or virus infection. It has been proven that prednisolone as a monotherapy or in combination with

azathioprine or MMF in the framework of the same regimen as for classic AIH is effective for *de novo* AIH. Rapamycin was used as the second line drug in children (n = 6) with *de novo* AIH or AIH relapse after transplantation who did not respond to prednisolone dose increase in combination with the use of azathioprine or MMF. All the patients demonstrated positive response [55].

Prospects

There are several directions of further development of therapy of autoimmune hepatic diseases. Firstly, there is development and use of new immunosuppressive agents. Indeed, there is practice of successful use of everolimus [56] and sirolimus [57] for treating resistant AIH cases; use of belatacept, leflunomide, fingolimod and chemokine receptor inhibitors is expected in the future [58]. Secondly, development of antifibrotic agents is an attractive prospect, as they may supplement immunosuppressive therapy. Simtuzumab – humanized monoclonal antibodies to LOXL2 (lysyl oxidase homolog 2) preventing collagen binding – is analyzed as an antifibrotic agent for primary sclerosing cholangitis and nonalcoholic fatty liver disease in clinical trials at the moment [59-61]. Thirdly, accentuation and use of therapeutic potential of antigen-specific T-regulatory cells considered to be the most promising candidates for inhibiting CD4 and CD8 T cells at the moment. Fourthly, some researchers consider possible immunization of young children with AIH-associated autoantigens in order to prevent autotolerance loss in the future [58].

Conclusion

The first reports of autoimmune hepatic diseases in children are dated from slightly more than 50 years ago. A huge breakthrough has been made in the studies of genetic nature, pathogenesis and diagnosis of autoimmune hepatic diseases in whole and in pediatric practice in particular since then. However, a range of treatment questions remains unsolved due to the lack of randomized controlled studies of effectiveness of different treatment regimens. Protocols used for treating adult patients are often used in pediatric practice as well. It is not always justified due to age peculiarities of course of these diseases, as well as to unfavorable prognosis in the event of early manifestation thereof. Taking the aforementioned into consideration, it is important and relevant to peruse treatment experience of different clinics. This review is an attempt to analyze the state-of-the-art; it also presents the main therapy regimens developed and used at different centers and highlights promising methods of treating children with autoimmune hepatic diseases.

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Conflict of interest

The authors declared they have no competing interests to disclose.

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