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Cyclosporine Induced Biochemical Remission in Childhood Autoimmune Hepatitis

Orjena Žaja Franulović[1], Nada Rajačić[1], Tatjana Lesar[1], Andrea Tešija Kuna[2] and Bernardica Valent Morić[1]

[1] University of Zagreb, »Sestre milosrdnice« University Hospital Centre, Department of Pediatric Gastroenterology and Hepatology, Zagreb, Croatia
[2] University of Zagreb, »Sestre milosrdnice« University Hospital Centre, Clinical Institute of Chemistry, Zagreb, Croatia

A B S T R A C T

The conventional treatment of autoimmune hepatitis (AIH) in children, which includes prednisone alone or in combination with azathioprine, induces remission in most cases but is often associated with poorly tolerated side effects. To avoid the adverse effects, Alvarez et al. introduced an alternative treatment regimen, using cyclosporine A (CyA) as primary immunosuppression. We carried out a retrospective study to evaluate the efficacy and tolerance of CyA treatment in children and adolescents with AIH treated in our center. During 2000–2010 period, nine children (6 female) aged 5–17.5 years, were diagnosed with AIH according to established international criteria. Following the suggested protocol, CyA was administered orally and when the transaminases tended to normalise, dose was adjusted to lover serum levels. Conversion to low dose of prednisone and azathioprine was started after 6 months, with gradual tapering and discontinuation of CyA. All nine patient had elevated transaminases and gammaglobulin levels, with proven histological changes typical for AIH in 8 patients that underwent liver biopsy (in one patient biopsy was contraindicated due to the prolonged prothrombin time). Serum ANA/SMA autoantibodies were positive in all but one patient, who had positive anti-LKM1. Complete or near complete and persistent normalisation of transaminase activity was observed in 8/9 patients within first 6 to 12 months. In one patient with partial response, an overlap syndrome was established. After ursodeoxycholic acid was added complete remission was observed. All patients had excellent clinical course and histological improvement. During the long-term follow-up (1.5–9 yrs; median 4.5 yrs), biochemical relapse occured in one patient after discontinuation of maintenance corticosteroid dose. Despite registered improvement, none of the patients fulfilled the criteria for therapy discontinuation, so all of them are still receiving maintenance doses of prednisone or azathioprine. The applied protocol allowed for the control of the liver inflammatory disease in all of our patients and protected them from the side effects related to steroid treatment. Side effects of CyA were minimal and were well tolerated.

***Key words**: autoimmune hepatitis, cyclosporine, remission, steroid side effects, childhood, prednisone, azathioprine*

Introduction

Autoimmune hepatitis (AIH) is a rare disease of unknown cause that is characterized by a progressive, self-perpetuating inflammation of the liver. It is diagnosed most frequently in the first two decades of life, mainly in females (75%). The prevalence in children and adolescents is estimated at 3–4/100,000, and incidence on 1/100,000[1–3]. Biochemically it is characterized by increased serum alanine (ALT) and aspartate (AST) aminotransferase levels, increased levels of serum globulins (immunoglobulin G) and by the presence of autoantibodies – antinuclear antibodies (ANA), smooth muscle antibodies (SMA), liver kidney microsomal antibodies (LKM1), soluble liver antigen antibodies (SLA), liver and pancreas antigen antibodies (LP) and antibodies to asialoglycoprotein receptor (ASGPR). Two types of AIH have been recognized according to seropositivity for SMA and/or ANA (AIH type 1) or LKM1 (AIH type 2). SLA antibodies and ASGPR can be positive in both AIH type 1 and type 2, and they have prognostic value[4,5]. The clinical spectrum of this disease is very wide, ranging from asymptomatic individuals with abnormal liver function to those with fulminant liver failure which is more common in

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TABLE 1
DIAGNOSTIC CRITERIA FOR AUTOIMMUNE HEPATITIS IN CHILDREN[2,11]

Elevated transaminases	>2x of upper normal limit
Elevated serum immunoglobulin G	
Positive autoantibodies	ANA and/or SMA (titer ≥1:20) – AIH type 1 anti-LKM-1 (titer ≥1:10) – AIH type 2 anti-LC-1 – AIH type 2 anti-SLA – AIH type 1 or type 2 or independently anti-ASGPR – AIH type 1 or type 2
Liver biopsy	Interface hepatitis Multilobular collapse
Viral hepatitis exclusion	
Wilson's disease exclusion	
Normal cholangiogram	

AIH – autoimmune hepatitis, ANA – antinuclear antibodies, SMA – smooth muscle antibodies, anti-LKM-1 – liver-kidney microsomal antibodies, anti-LC1 – liver cytosolic antigen 1 antibodies, anti-SLA – soluble liver antigen antibodies, anti-ASGPR- autoantibodies to asialoglycoprotein receptor

AIH type 2[5–8]. Even though rarely, if it is not recognized on time the disease can be diagnosed in the stage of cirrhosis and with signs of chronic liver failure[4,6,9,10]. The diagnosis is based on a combination of biochemical, immunological and histological parameters on the one hand, and on the other by means of exclusion of other liver diseases according to criteria developed by the International Autoimmune Hepatitis Group (IAIHG) (Table 1)[11–13]. Liver biopsy is necessary to establish the diagnosis. The typical histological picture (»interface hepatitis«) includes a dense mononuclear and plasma cell infiltration of the portal areas which expands into the liver lobule and destruction of the hepatocytes at the periphery of the lobule with erosion of the limiting plate[4,9,14,15]. Laboratory and histological features of AIH are at times associated with bile duct disease typical of primary sclerosing cholangitis. This overlap syndrome is refereed to as autoimmune sclerosing cholangitis[16–18].

The conventional treatment of AIH in children consists of initial high daily doses of prednisone with or without azathioprine. Although this treatment induces clinical and biochemical remission in most cases, progression to liver cirrhosis or to liver failure may occur[1–3,8,19,20]. Often, AIH tends to relapse when the dose of steroids is reduced and serious complications related to high prednisone doses are often reported (reduced growth, overweight, osteoporosis with pathological bone fractures, cataract, diabetes, hypertension, psychiatric disorders)[10,15,19,21–24]. Considering the age of peak incidence of the AIH, the significance of these adverse effects is even greater. In order to avoid harmful consequences of corticosteroid therapy and to obtain the remission, alternative treatment regimens have been increasingly explored[25–29]. In 1999. Alvarez and associates published a pilot, multinational, multicenter clinical trial involving 32 children with AIH in which they treated patients with oral cyclosporine (CyA) for 6 months with the aim to obtain the remission of the inflammatory process. After the remission was achieved they continued the therapy with combined low doses of prednisone and azathioprine with few and well-tolerated adverse effects[25–27,29]. In 2006, a follow-up study on 84 children has confirmed the efficiency of the CyA therapy equaling the conventional treatment regimen[26]. Consequently, we used the same CyA treatment regimen for children with AIH at the Pediatric Gastroenterology and Hepatology Department.

In this article we report the results of the study that we carried out to evaluate the efficacy and tolerance of CyA in childhood AIH in our center.

Patients and Methods

The study was conducted retrospectively by chart review. From 2000 to 2010, nine children (6 girls) with diagnosis of AIH according to the scoring system of the IAIHG[2,11] were treated with CyA (Sandimmune or Neoral). None of the patients had received immunosuppressive medication previously. Patients presenting with fulminant liver failure or with other causes of chronic hepatitis, such as hepatitis B or C, Wilson disease, alpha1 -antitrypsin deficiency and non-alcocholic steatohepatitis (NASH) were excluded, as were those with any history of exposure to potentially hepatotoxic agents. One patient has presented later in the follow up period radiological features on magnetic cholangiopancreatography (MRCP) associated with bile duct disease typical of primary sclerosing cholangitis, and he was reffered as having overlap syndrome. Since he was initially treated using the same protocol as the other eight patients, he was included in this study.

Clinical and laboratory evaluation

We collected the data for all nine patients regarding their clinical, laboratory and histological features as well as the efficiency and tolerance of CyA as the primary immunosuppresant, from the moment of the diagnosis through the follow up period of 12 months and for the prolonged period lasting 1.5–9 years overall.

The detailed personal history with complete clinical examination, abdominal ultrasonography and laboratory evaluation were undertaken, including liver function tests, prothrombin time (PT), blood urea nitrogen and creatinine level, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urinalysis, blood count and serum protein electrophoresis. Indirect immunofluorescence (IIF) with combined substrates of rat stomach/rat kidney/monkey liver/Hep-2 cells (BIOCHIP-Mosaics, Euroimmun, Germany) was used for detection of relevant autoantibodies in serum: smooth muscle antibodies (SMA), liver-kidney microsomes antibodies type 1 (LKM1) and antinuclear antibodies (ANA). Specificity of IIF-positive LKM1 antibodies was further tested with the line immunoassay (EUROLINE test strips, Autoimmune Liver Diseases Profile, Euroimmun, Germany) for reactivity toward CYP2D6 (LKM-1), AMA-M2 and M2-3E(BPO), respectively, The same line immunoassay was used for detection of antibodies to cytosolic liver antigen type 1 (LC-1) and antibodies against soluble liver antigen (SLA). During 2010, all nine patients were tested for the presence of autoantibodies to asialoglycoprotein receptor (anti-ASGPR) in serum with the commercial enzyme linked immunosorbent assay (ELISA, Generic Assays GmbH, Germany).

Other causes of liver disease including viral hepatitis, Wilson disease, alpha1-antitrypsin deficiency and NASH were excluded in all patients. Viral serologies tested included hepatitis B surface antigen, anti-hepatitis B core antibody, anti-hepatitis C virus, anti hepatitis A virus (IgM), anti-Citomegalovirus (IgM) and Epstein-Barr virus anti-viral capsid antigen (IgG and IgM). Serum concentrations of alpha1-antitrypsin and ceruloplasmin and urinary copper content were within normal limits in all children. NASH was excluded according to the insulin resistance calculated by HOMA-IR and ultrasonographic and histologic appearance of the liver tissue. The diagnosis of portal hypertension was considered by the presence of splenomegaly and ultrasonographic findings of the widening of the free border of the lesser omentum to a diameter of more than 1.7 times that of the aorta and confirmed by endoscopy. Percutaneous liver biopsy was performed in 8 patients, while in one girl it was contraindicated due to the prolonged PT. Histopathological examination of the liver biopsy specimens were done in the Clinical Institute for Pathology of the University Hospital Centre Sestre milosrdnice. No histological picture compatible with bile duct obstruction was observed in the 8 liver biopsies obtained before starting CyA treatment. Fibrosis on biopsy was staged according to previously published histological criteria[1,14,30]. The presence of cirrhosis was investigated by histologic examination of percutaneous liver biopsy specimens obtained from 8 children at diagnosis of AIH in combination with examination of the liver surface by ultrasonography, before the CyA therapy.

Patients received the therapy according to the protocol of Alvarez et al.[25]. The CyA was started at a dosage of 3–5 mg/kg/day, divided into 2 equal daily oral doses. The doses were adjusted to achieve the therapeutic whole blood concentration of 200–300 ng/mL. After 3 months, along with tendency of aminotransferases levels normalization, CyA doses were adjusted to concentration of 100–200 ng/mL. The maintenance therapy with low doses of prednisone (0.3–0.5 mg/kg/day) and azathioprine (1–2 mg/kg/day) was introduced after 6 months with gradual reduction of CyA dose for a period of 15 days. Upon discontinuation of CyA at the seventh month, prednisone was then reduced slowly, and azathioprine was kept at the same dosage. If the combination therapy with prednisone and azathioprine led to stabile remission, a monotherapy with either of the drugs was applied as a maintenance therapy.

Subjects were controlled by clinical, laboratory and ultrasonographic evaluation weekly during the first month, every 2 weeks during the second month, once a month during the first 6 months of CyA therapy, every other month during the following 6 months, and every 3 to 6 months thereafter. Autoantibody titers were assayed at diagnosis, after 6 months and at least once a year thereafter. Remission is differently defined in the literature. For the purpose of this study, the 2010. Recommendations of the American Association for Study of Liver Disease (AASLD) were taken into account[1]. Remission was defined as the absence of clinical symptoms in the presence of normal serum aminotransferase levels[1,7,26].

Data were summarized using descriptive statistics. All the averages are given as mean±standard deviation of the means ($\bar{X}$±SD).

Results

Table 2 enumerates the basic demographic, clinical and laboratory features of the nine children with AIH at presentation. The diagnosis of AIH was made at a mean age of 14 years (range 5 to 17,5 years). Five of them manifested clinically as acute hepatitis which included abrupt onset of jaundice, complaints of arthralgias and myalgias or nonspecific symptoms (inappetence, exhaustion, all including yellow colored sclerae). Three cases showed laboratory features of chronic hepatitis (persistently elevated transaminases) but without evident clinical symptoms. In one female patient complaints were atypical (headache). Four children had a positive family history for one or more diseases of immune-mediated pathogenesis: insulin dependent diabetes in 1; thyroiditis in 2; and autoimmune thrombocytopenia and vitiligo in 1. Elevated ESR was registered in 3 patients prior to starting treatment with CyA. No one had increased CRP values. In all the cases elevated transaminases (>2x above upper limit of normal-UNL) were noted. GGT was slightly above normal level in 2/9 patients, while clearly elevated values of GGT were observed in all the other cases. Two patients had increased total serum bilirubin, four of them had values slightly above normal, while three patients had normal values. Reduced serum albumin wasn't registered and prolonged prothrombin time was recorded in three cases. All the patients had increased serum im-

TABLE 2
CLINICAL AND LABORATORY CHARACTERISTICS BEFORE CYCLOSPORINE INITIATION IN 9 CHILDREN WITH AIH

Age – years	5–17.5 (median 14)	
AIH type 1/AIH type 2, N (%)	8/1 (88.8%/11.1%)	
Male/female; N (%)	6/3 (6.66%/33.3%)	
Presentation of the disease	Acute hepatitis Elevated transaminases Atypical	
Laboratory characteristics; $\overline{X}$ (SD)	Total serum bilirubin (μmol/L)	45.03 (46.3)
	AST (U/L)	740.8 (574.8)
	ALT (U/L)	733.4 (386.5)
	GGT (U/L)	212 (242)
	ESR (mm/3,6 ks)	39.1 (34.9)
	CRP (mg/L)	3.4 (2.4)
	Gamma globulin (g/L)	35.1 (19.1)
	IgG (g/L)	37.7 (23.9)
	Albumin (g/L)	40.5 (3.42)
	Prothrmobin time (%)	73 (24.6)

AIH – autoimmune hepatitis, SD – standard deviation

munoglobulin G (IgG) values. Ascites or portal hypertension weren't ultrasonographically verified. Eight children diagnosed with AIH type 1 had positive SMA titer (>1:80). One patient had positive LKM-1 antibodies titer (>1:40) and was diagnosed with autoimmune hepatitis type 2. In 5/8 cases with AIHA type 1, ANA titer were positive as well. During the year 2010, given the new possibility in our laboratory, anti-ASPGR titer was determined negative in all the cases except one in whom anti-ASGPR was defined early after diagnosis was made prior to starting CyA therapy. In all the other cases the titer was determined in the remission phase. Percutaneous liver biopsy was done in 8 children. Chronic active hepatitis with portal mononuclear infiltrates and piecemeal necrosis was found in 4 of them. In 3 patients bridging necrosis were observed. In one child, periportal proliferation of fibrous tissue with lymphocytes and without lobular penetration was verified. In one female CyA therapy was initiated without prior liver biopsy due to significantly prolonged PT. During the long-term follow-up in 3 children extrahepatic autoimmune disorders were present (ulcerative colitis, thyroiditis in one and autoimmune hemolytic anemia).

As mentioned earlier, remission was defined as the lack of clinical symptoms and normal aminotransferase serum levels[1,7,26]. During the CyA treatment and follow-up period we selected ALT, GGT, PT and serum IgG levels as the most important laboratory monitoring parameters. The comparison of initial values with values after 3, 6 and 12 months of therapy is presented in Table 3. Three months after therapy initiation a clear decline of transaminases was observed. Similar trend continued after 12 months, with still slightly elevated ALT values in two patients, albeit with clear decline in regard to initial values (increase of <2x UNL). In one of them the overlap syndrome was diagnosed in the follow-up period. In the other case complete ALT normalization was achieved in prolonged time, after 15 months of therapy. Noteworthy is the fact that the female patient with AIHA type 2 achieved ALT normalization 3 months after CyA introduction. Similar trend was observed in GGT values, except in previously described case of overlap syndrome in which significant increase after 3 months of CyA therapy was noticed. After ursodeoxycholic acid (UDCA) introduction into therapeutic protocol, GGT values were normalized. Within 3 months of CyA therapy, PT values were ameliorated or completely normalized in all the patients. IgG values during follow-up gradually decreased. After 12 months of therapy values within the reference range were registered in 5/9 patients. In others, these values were of upper normal limit, but notably lower compared with the initial values. In later course (more than 18 months), gradual normalization was observed in all the patients. In the period of 12 to 24 months, following the normalization of serum IgG levels, negativization of autoantibodies ensued in all of the patients.

Regarding the control histopathological examination, only in one girl complete resolution of histological changes was noticed but she developed relapse after the therapy discontinuation. Control histology has improved significantly in 7/9 patients, however the signs of mild necroinflammatory activity was still present necessitating immunosuppressive therapy continuation (low doses of azathioprine or prednisone). Finally the comparison of histological findings wasn't possible in one female that did not undergo initial liver biopsy due to the prolonged PT.

As side-effect of CyA, 2/9 patients developed hypertrichosis, while one female developed transient gingival hypertrophy. No one has developed renal function disorder or arterial hypertension. All children included in the study live a normal and fulfilled life of their peers, with-

TABLE 3
SELECTED LABORATORY PARAMETERS BEFORE CYCLOSPORINE AND VALUES AT 3, 6 AND 12 MONTHS AFTER TREATMENT INITIATION

	Before therapy ($\overline{X}$, SD)	3 months ($\overline{X}$, SD)	6 months ($\overline{X}$, SD)	12 months ($\overline{X}$, SD)
ALT (U/L)	733.4 (386.5)	84.25 (77.25)	55.75 (45.3)	31 (19.8)
GGT (U/L)	212 (242)	133.8 (205.7)	85.4 (130.3)	58.13 (54.9)
IgG (g/L)	37.7 (23.9)	25.9 (11.3)	20.7 (6.5)	17.2 (4.13)
PT (%)	73 (24.6)	86.4 (17.1)	96.5 (19.9)	93.43 (17.6)

PT – prothrombin time, $\overline{X}$ – mean, SD – standard deviation

out severe infections or any occurrence of malignant disease in the prolonged follow-up period (up to 9 years). With low doses of prednisone and azathioprine significant side-effects was not present as well. Growth and pubertal development are normal in all children. During long-term follow-up (1.5 to 9 years span) relapse with the regular use of prednisone and/or azathioprine hasn't occurred in 8/9 patients. A single female patient diagnosed with AIH type 2 has fulfilled the criteria required for complete cessation of immunosuppressive therapy (normalization of clinical and laboratory results as well as histological findings). After therapy discontinuation she developed biochemical relapse necessitating reintroduction of prednisone and azathioprine followed by gradual dose tapering and complete cessation of prednisone. Stable remission has been achieved with described therapeutic protocol. Similar cases considering AIH type 2 are described in the literature which raises the question of life-long immunosuppressive therapy[19,20]. In all the other patients further immunosuppressive therapy is conducted with low doses of prednisone or azathioprine, except in one male in short term follow-up (1.5 year) in whom combined therapy with prednisone and azathioprine is still conducted with gradual reduction of corticosteroid dosage.

Discussion and Conclusion

The results of our retrospective study presented in this paper indicate that cyclosporine is able to induce complete clinical and biochemical remission in children with AIH when given as first-line therapy during a 6 months period, with no significant adverse effects during the earlier and later follow-up.

It is well known that AIH responds satisfactory to immunosuppressive treatment. If left untreated, it generally progresses rapidly to cirrhosis and liver failure so the treatment should be initiated promptly. The goal of the treatment is to reduce or eliminate liver inflammation, induce remission, improve symptoms, and prolong survival[1,3,4,7,13]. Because AIH is a rare disease, there are only a small number of papers discussing different types of available treatment regimens. Data on the comparing results of different types of the immunosuppressive therapy are limited in both adults and children. Considering the significance of adverse effects of corticosteroid therapy, therapeutic alternatives have been investigated extensively in recent years[10,25–29]. After the first reports about remission induction with short-term CyA monotherapy in children with AIH were published[25], we decided to use the same protocol in our centre. The aim of this approach was to protect children and adolescents from adverse effects of high doses of corticosteroids that are used to obtain the remission of autoimmune inflammatory process.

Using the described protocol we achieved normalization of ALT levels in a period of 6 months in 6/9 patients (66.66%) and in 7/9 after 12 months (77.77%). In 2 of our patients, after 12 months of therapy, ALT levels were slightly elevated (<2xUNL), albeit with clear decline in regard to initial values. In one of them the overlap syndrome was diagnosed in the follow-up period and remission was achieved after UDCA introduction. In the other case complete ALT normalization was achieved in prolonged time, after 15 months of therapy. In all of our patients, soon after the CyA therapy initiation and during the follow-up period, there were no any clinical signs of the liver disease. Therefore, if we analyze patients with only signs of AIH, remission was achieved after 12 months in 7/8 patients (87.5%) and in all of them in prolonged period of 15 months. These results are similar to the results of other studies where the same CyA protocol was used. In the study of Alvarez (32 children), the aminotransferase levels were normalized after 6 months in 90% of patients and in all patients after 12 months[25]. In a follow-up study (84 children), normalization of aminotransferase levels was achieved in 72% of patients during a 6 months period and in all of patients during a 12 months period[26]. These results are similar or better than the results achieved with conventional treatment regimen which includes prednisone alone or in combination with azathioprine[1,15,19–21]. Debray et al. also demonstrated the effectiveness of CyA in a larger number of patients with type 2 AIH (15 children) in whom ALT activities normalized within 6 months, confirming that either type of AIH responds equally well to immunosuppressive treatment. In addition, this retrospective study confirmed the importance of considering CyA as initial therapy in very sick patients[27].

The beneficial use of CyA was first reported in 1985 in an adult patient with type 1 AIH and confirmed in 1987 in a 14-year-old boy with type 1 AIH refractory to corti-

costeroid therapy. Since then, only a few case reports have been published[27–29,32–34]. CyA, lipophilic cyclic polypeptide, is a potent immunosuppressive agent used in organ transplantation to prevent allograft rejection. The use of CyA has been extended beyond the transplant setting to include certain disorders that are thought to be immunologically mediated. The main goal of CyA therapy is the inhibition of interleukin-2 production which interferes with primary helper T-cell recruitment and activation[29,31,32]. In our study, the normalization of IgG levels was achieved in only 2/9 patients in a 6 month period. That can be explained with the fact that CyA interferes primarily with cellular immune response. Normalization of IgG levels was achieved in four other patients after the introduction of prednisone and azathioprine, and in remaining two patients normalization was finally achieved after 18 months. In patients who conducted a long term CyA therapy for transplantation, a large number of adverse effects were described, such as increased risk of developing nephrotoxicity, arterial hypertension, hyperlipidemia, hirsutism, lymphoproliferative disorders and infections[31,32]. On the other hand, when used for shorter period, so far there are no reports about significant adverse effects of CyA monotherapy, except for cosmetic changes. There are some very encouraging data on the efficiency of CyA treatment in patients with other autoimmune liver diseases (autoimmune cholangitis and giant cell hepatitis), however on a small number of pediatric patients[26,28,29,33,34]. The adverse effects of the CyA in our patients were mild, mostly transient cosmetic changes. All of our patients had an excellent clinical course and histological improvement on follow-up liver biopsy. We can conclude that CyA leads to a complete and persistent remission of inflammation of the liver in variable periods of time.

Optimal duration of immunosuppressive treatment of AIH is unknown. According to the available data, treatment withdrawal is successful only if there is histological resolution of inflammation. It is advisable not to attempt to withdraw treatment within 3 yrs of diagnosis or during or immediately before puberty. It has been reported that only 20% of patients with type 1 can successfully and permanently stop treatment, whereas this is rarely achieved in AIH type 2. Long- term treatment is required for the majority of patients with most patients surviving long-term with excellent quality of life on low-dose medication. Development of end-stage liver disease requiring liver transplantation despite treatment, however, has been reported 8–14y after diagnosis in 8.5% of children with AIH[1,4,7,16,20,21]. In our patients, during a long term follow-up period (1.5 to 9 years), biochemical relapse occurred in one patient after withdrawal of maintenance low dose prednisone therapy within 4 yrs of diagnosis, despite previously recorded longstanding aminotransferase normalization and histological resolution. In remaining 8/9 patients, despite registered improvement, none of them fulfilled the criteria for therapy discontinuation due to the mild necroinflammatory activity still present necessitating immunosuppressive therapy with low doses of azathioprine or prednisone. This fact raises the question of life-long immunosuppressive therapy.

In conclusion, CyA is effective in achieving the remission in children with AIH. Adverse effects of this therapy have significantly lower incidences and are of a lesser importance. However, one must consider carefully the side effects of CyA; in this study, they appeared to be limited. Although long-term nephrotoxicity needs to be evaluated, our results suggest that close monitoring of CyA blood levels and maintenance of CyA doses at the lowest dosage are needed to control symptoms and aminotransferase levels while avoiding nephrotoxicity. In the future we need a randomized controlled trial to compare the CyA and the conventional prednisone and azathioprine treatment regimen.

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O. Žaja Franulović

University of Zagreb, »Sestre milosrdnice« University Hospital Centre, Vinogradska 29, 10 000 Zagreb, Croatia
e-mail: orjenazf@yahoo.com

CIKLOSPORIN U TERAPIJI AUTOIMUNOG HEPATITISA DJEČJE DOBI

S A Ž E T A K

Standardni pristup liječenju autoimunog hepatitisa (AIH) u djece podrazumijeva prednizon kao monoterapiju ili u kombinaciji s azatioprinom. Remisija se ovim pristupom postiže u velikog broja djece no pod cijenu učestalog razvoja ozbiljnih nuspojava. Alvarez i suradnici su s ciljem izbjegavanja nuspojava kortikosteroidne terapije započeli s primjenom ciklosporina (CyA) kao primarne imunosupresije u djece s AIH[25]. U Klinici za pedijatriju KBC Sestre milosrdnice proveli smo retrospektivno istraživanje kako bi ocijenili učinkovitost i podnošljivost CyA u djece I adolescenata s AIH koji su liječeni u našem centru. U periodu od 2000–2010. godine, kod 9 djece (6 djevojčica) u dobi 5–17,5 godina, postavljena je dijagnoza AIH u skladu s prihvaćenim međunarodnim kriterijima[2]. Prema protokolu Alvarez, terapija CyA započeta je peroralnim putem uz snižavanje doze nakon postizanja postupne normalizacije transaminaza. Prijelaz na terapiju niskim dozama prednizona i azatioprina započet je nakon 6 mjeseci uz postupno ukidanje CyA kroz 2 tjedna. Svi pacijenti su inicijalno imali povišene vrijednosti transaminaza i serumskih gamaglobulina uz histološke promjene tipične za AIH u 8/9 kod kojih je načinjena biopsija jetre (u jednog djeteta biopsija je bila kontraindicirana zbog značajno produženog protrombinskog vremena). Serumska ANA/SMA antitijela su bila pozitivna kod 8/9 (AIH tip 1), dok je jedna djevojčica imala pozitivan titar anti-LKM1 antitijela (AIH tip 2). Potpuna ili gotovo potpuna normalizacija transaminaza postignuta je u 8/9 pacijenata kroz 6–12 mjeseci. U jednog pacijenta s djelomičnim odgovorom na terapiju kod kojeg je u kasnijem tijeku utvrđen sindrom preklapanja, remisija je postignuta nakon uvođenja ursodeoksikolne kiseline. Kod svih je zabilježen odličan klinički tijek i poboljšanje histološkog nalaza. Tijekom dugotrajnog praćenja (1,5–9 godina: medijan 4,5 g), biokemijski relaps je zabilježen u jedne djevojčice nakon ukidanja održavajuće terapije niskim dozama kortikosteroida. Usprkos zabilježenog poboljšanja, niti jedan od preostalih 8 pacijenata nije ispunio kriterije za potpuno ukidanje imunosupresivne terapije stoga se kod svih i dalje provodi održavajuća terapija prednizonom ili azatioprinom. Tijekom dugotrajnog praćenja naših pacijenata zabilježene su tek rijetke i prolazne nuspojave CyA kozmetskog tipa, bez razvoja ozbiljnijih nuspojava. Primijenjeni protokol omogućio je dobru kontrolu upalnog procesa jetre u svih pacijenata i sačuvao ih od nuspojava kortikosteroidne terapije.