

*Case report*

## **Cholestatic Viral Hepatitis A with Refractory Pruritus Successfully Treated with a Combination of Molecular Adsorbent Recirculating System and Corticosteroids: A Case Report**

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### **SUMMARY**

**Introduction.** Hepatitis A virus is a major cause of acute viral hepatitis worldwide, with approximately 1.5 million cases annually. Clinical manifestations of the hepatitis A virus infection range from asymptomatic to acute liver failure. Cholestatic viral hepatitis A is a rare clinical manifestation characterized by a prolonged course, refractory pruritus, imminent acute liver failure and generally good prognosis. The treatment of pruritus in cholestatic viral hepatitis A can be challenging because a response to conventional therapy is limited.

**Case report.** We present the effects of a combination of pulse doses of prednisolone and two cycles of MARS (Molecular Adsorbent Recirculating System) in the treatment of a young female patient with cholestatic viral hepatitis A. This treatment option significantly reduced the duration of the disease and the intensity of pruritus and led to full recovery of the patient and normalization of laboratory parameters of cholestasis.

**Conclusion.** This treatment combination has proven to have significant and lasting effects with no relapse of pruritus. Low doses of corticosteroids administered for a short time reduce the risk of side effects. The importance of vaccination of international travellers should be also pointed out here.

**Keywords:** acute viral hepatitis A, cholestasis, intractable pruritus, MARS, corticosteroids

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## INTRODUCTION

Hepatitis A virus (HAV) is the most common acute viral hepatitis worldwide. In general, it has a self-limited course (1). The spectrum of clinical manifestations is wide, from asymptomatic and sub-clinical forms, occurring mainly in children, to symptomatic hepatitis seen in adults. Typical symptoms include fever, malaise, fatigue, nausea, vomiting, weight loss, abdominal discomfort, dark urine, pale stool and jaundice (2).

Cholestatic viral hepatitis A (CVH-A) is a rare clinical manifestation of the HAV infection with a frequency of about 0.8%. It is characterized by elevated liver enzymes and increases in blood bilirubin levels. It often has a prolonged course (12 weeks to 8 months), accompanied by imminent acute liver failure (ALF), pronounced jaundice and intractable pruritus (3). Elevated levels of cholesterol and triglycerides are also common. However, the prognosis is generally good (2). Several treatments (discussed later) have been successful in relieving the accompanying pruritus. Corticosteroids have shown considerable efficacy in achieving pruritus reduction (3). Extracorporeal albumin dialysis (ECAD)

procedures, such as the Molecular Adsorbents Recirculating System (MARS), are generally safe and effective to treat drug-resistant pruritus, yielding significant improvement in pruritus and having minor side effects (4).

Here, we present a case of a young female patient with CVH-A, intractable pruritus and imminent ALF successfully treated with a combination of MARS and corticosteroids. The aim of this paper was to demonstrate the effectiveness of the given treatment and to emphasize the importance of vaccination in high-risk adults.

## CASE REPORT

A 36-year-old Caucasian female patient came for an examination at the outpatient clinic of the Infectious Diseases Clinic one month after returning from a trip to Zanzibar. For the previous week, her temperature had been up to 38.5 °C and she had experienced loss of appetite, nausea, vomiting, yellow skin and sclera discoloration, dark urine and pale stools. She was not vaccinated against hepatitis A virus (HAV). Physical examination showed no

**Table 1.** Laboratory and serological blood test results at outpatient examinations before hospital treatment and after discharge

Parameters*	Day from the onset of illness							Normal range/units
	7 <sup>th</sup>	11 <sup>th</sup>	18 <sup>th</sup>	25 <sup>th</sup>	32 <sup>nd</sup>	68 <sup>th</sup>	123 <sup>rd</sup>	
Hb	116 ↓	116 ↓	118 ↓	121	113 ↓	102 ↓	122	119 - 155 g/L
PLT	165	280	380	333	328	335	217	150 - 400 x 10 <sup>9</sup> L
Total bilirubin	114 ↑	198 ↑	209 ↑	281 ↑↑	378 ↑↑	48.3 ↑	6.1	< 21 μmol/L
Direct bilirubin	112 ↑↑	181 ↑↑	190 ↑↑	245 ↑↑	275 ↑↑	2.2 ↑	3.7	< 5 μmol/L
AST	2083 ↑↑	947 ↑↑	292 ↑	1055 ↑↑	1975 ↑↑	101 ↑	36	< 40 U/L
ALT	2175 ↑↑	1190 ↑↑	284 ↑	597 ↑↑	1142 ↑↑	152 ↑	38	< 40 U/L
GGT	175 ↑	304 ↑	126 ↑	62 ↑	103 ↑	134 ↑	52	< 60 U/L
ALP	376 ↑	826 ↑	466 ↑	387 ↑	461 ↑	351 ↑	110	40 - 130 U/L
Albumin	30.9 ↓	31 ↓	30 ↓	33 ↓	32 ↓	40	42	35 - 52 g/L
CRP	8.77 ↑	17.22 ↑	10.89 ↑	12.03 ↑	14.3 ↑	0.4	0.1	< 5 mg/L
Anti-HAV antibodies IgM class	Positive							
PCR HAV RNA	Positive							
HBsAg	Negative							
Anti-HCV antibodies	Negative							

\* Hb– Hemoglobin, PLT – Platelets, AST - Aspartate aminotransferase, ALT - Alanine aminotransferase, GGT - Gamma-glutamyl transferase, ALP – Alkaline phosphatase, CRP – C reactive protein, PCR – polymerase chain reaction, RNA - ribonucleic acid, HCV – hepatitis C virus, ↑ - higher value compared to the reference value, ↑↑ - ten times and more higher compared to the reference value, ↓ - lower than the reference value.

pathological findings apart from icterus and adynamism. Her vital parameters were within the physiological limits. Biochemical and serological blood test results at the first outpatient examination are shown in Table 1. CVH-A was diagnosed based on the clinical symptoms, positive anti-HAV IgM, positive PCR HAV RNA and biochemical parameters of cholestasis. The treatment was started with silymarin, ursodeoxycholic acid (UDCA) 250 mg three times a day, proton pump inhibitor (PPI), rehydration therapy and multivitamins.

On the 10<sup>th</sup> day of the disease, pruritus appeared and became the dominant symptom which gradually worsened. Twenty days after the onset of the illness, the other symptoms gradually regressed until they disappeared, except for malaise and the loss of appetite. During outpatient examinations, some skin excoriation was observed but there were no signs of hepatic encephalopathy (HE) and haemorrhagic syndrome. Changes in biochemical blood test results are given in Table 1. Abdominal ultrasound scan did not show any pathological findings, apart from mild hepatomegaly, which ruled out any kind of mechanical obstruction. Although cholestyramine was administered in doses of 4 g twice a day, the patient developed insomnia with daytime sleepiness and intractable pruritus. On the 34<sup>th</sup> day of the disease, the patient was hospitalized at the Infectious Diseases Clinic due to clinical and laboratory signs of severe cholestasis, presence of a hepatocyte lesion and impaired hepatic synthetic function.

On admission, laboratory tests were performed (Table 2) and serological test were repeated. Negative HbsAg, anti-HCV and anti-HEV tests excluded the presence of co-infections. Positive anti-EBV-EBNA and anti-CMV IgG indicated the old infection. UDCA was discontinued and the treatment with vitamins A, D and E administrated orally was initiated together with parenteral rehydration, correction of electrolyte disturbances and albumin deficit. The patient was given Rifaximin tablets 200 mg twice a day and probiotic for 7 days as a supportive treatment because of the imminent liver failure. In addition, vitamin K ampoules (10 mg/day) and nadroparin-calcium (2850 IU/day) were ad-

ministered due to the coagulation disorder of the liver. The serum immunological findings (AMA, ANA, ASLA, ASMA) were within the physiological values which ruled out autoimmune hepatitis. Although the patient's hemoglobin values were lower than normal (Table 2), hemolytic anemia was not diagnosed due to negative direct and indirect Coombs tests and haptoglobin serum levels within normal ranges in two samples taken on different days. Wilson's disease was also ruled out because the serum levels of copper and ceruloplasmin were within the normal reference range, as were the copper values in a 24-hour urine sample. The urine culture was sterile and pathogenic bacteria, amoeba and lamblia, were not found in the stool. Microbiological tests for the presence of parasites in stool and urine were also found to be negative. There were no extrahepatic manifestations either.

Due to drug-resistant pruritus, on the 5<sup>th</sup> day of hospital treatment, the first MARS treatment was started. The vascular access was obtained by insertion of a double lumen dialysis catheter into the right internal jugular vein. It was conducted using a conventional hemodialysis machine (PrismaflexR System, Gambro Lundia AB, Lund, Sweden) with a standard buffered dialysis solution for continuous venovenous hemodiafiltration (CVVHD).

The MARS device (MARS flux, Gambro Lundia AB, Lund, Sweden) consisted of an albumin-impregnated, highly permeable dialyzer with 500 mL of 20% serum albumin. Unfractionated heparin (bolus: 1000 IU, then 500 IU/h) was used for extracorporeal anticoagulation. The target APTT was 60 – 90 s (the arterial line segment before the blood pump). The blood flow rate (Q<sub>b</sub>) was 150 ml/min, while the albumin dialysate flow rate (Q<sub>alb</sub>) was equal to the blood flow rate (Q<sub>alb</sub> = Q<sub>b</sub> = 150 ml/min). The net ultrafiltration flow rate (Q<sub>nuf</sub>) was 0 ml/h, and the non-albumin dialysate flow rate (Q<sub>d</sub>) was 1000 ml/h. The total duration of the first cycle was 8 hours. The second cycle of the MARS dialysis was performed on the 11<sup>th</sup> day of hospitalization and it also lasted 8 hours. Laboratory blood tests and arterial blood gas tests were done on the same day, right before and after the ECAD procedure (Table 2).

**Table 2.** Laboratory blood tests and arterial blood gas analysis results during hospital treatment

Parameters *	Values on admission	MARS 1st cycle		MARS 2nd cycle		Values on discharge	Normal range/units
		Before	After	Before	After		
Hb	99 ↓	102 ↓	98 ↓	95 ↓	92 ↓	101 ↓	110 - 157 g/L
PLT	350	301	264	261	210	317	135 - 450 10 <sup>9</sup> /L
INR	0.960	1.010	1.040	1.010	1.060	0.890 ↓	0.9 - 1.1
ACT	33	34.7	39.7 ↑	31.8	58.2 ↑	28.9	25.0 - 35.0 sec
Fibrinogen	3.86	2.19	2.61	3.14	2.68	3.22	2 - 5 g/L
DDimer	0.68 ↑	0.79 ↑	2.16 ↑	0.7 ↑	2.97 ↑	0.41	< 0.50 ug/ml FEU
Total bilirubin	391.3 ↑↑	355.5 ↑↑	322.9 ↑↑	303.8 ↑↑	211.1 ↑↑	98.5 ↑	5- 21 μmol/L
Direct bilirubin	287.8 ↑↑	262.5 ↑↑	159.2 ↑	152.1 ↑↑	149.2 ↑↑	66.1 ↑↑	0.1 - 3.4 μmol/L
AST	1794 ↑↑	1136 ↑↑	1177 ↑↑	552 ↑↑	309 ↑	152 ↑	0 - 40 IU/L
ALT	1093 ↑↑	688 ↑↑	696 ↑↑	542 ↑↑	373 ↑	220 ↑	0 - 40 IU/L
GGT	116 ↑	122 ↑	119 ↑	226 ↑	274 ↑	321 ↑	7 - 50 IU/L
ALP	502 ↑	476 ↑	493 ↑	606 ↑	463 ↑	467 ↑	34 - 104 U/L
BUN	3	2.1 ↓	1.9 ↓	1.9 ↓	1.9 ↓	2.1 ↓	3 - 8 mmol/L
Creatinine	56	49	42 ↓	38 ↓	38 ↓	55	49 - 106 μmol/L
TC	6.55 ↑	6.63 ↑	6.45	6.21	8.15 ↑	8.94 ↑	5.21 - 6.50 mmol/L
TG	4.23 ↑	4.21 ↑	3.53 ↑	3.95 ↑	4.22 ↑	3.76 ↑	0.10 - 1.70 mmol/L
HDL	0.42 ↓	0.48 ↓	0.48 ↓	0.44 ↓	0.61 ↓	0.80 ↓	1.10 - 2.50 mmol/L
LDL	4.30 ↑	4.24 ↑	4.37 ↑	3.97 ↑	4.32 ↑	4.50 ↑	0.10 - 3.50 mmol/L
Albumin	25 ↓	32 ↓	34 ↓	29 ↓	31 ↓	35	35 - 52 g/L
CRP	15.2 ↑	14.2 ↑	12.0 ↑	10.1 ↑	3.6	1.7	0 - 5 mg/L
IL-6	27.2 ↑	22.1 ↑	24.2 ↑	14.8 ↑	20 ↑	10.2 ↑	< 7.0 pg/mL
AFP	1.65	1.82	2.23	2.91	3.37	4.32	0 - 7.40 IU/ml
Sodium	134 ↓	137	138	136 ↓	138	139	137 - 147 mmol/L
Potassium	3.6	3.6	3.7	3.9	3.8	4.5	3.5 - 5.3 mmol/L
ph, AB	7.42	7.43	7.45	7.47 ↑	7.43	7.40	7.35 - 7.45
Lactate, AB	1.0	1.2	0.8	1.1	0.7	0.6	0.5 - 1.5 mmol/l

\* Hb- Hemoglobin, PLT - Platelets, INR - International normalized ratio, ACT - activated coagulation time, AST - Aspartate aminotransferase, ALT - Alanine aminotransferase, GGT - Gamma-glutamyl transferase, ALP - Alkaline phosphatase, BUN - Blood urea nitrogen, TC - Total cholesterol, TG - Triglyceride, HDL - High-density lipoprotein, LDL - Low-density lipoprotein, CRP - C reactive protein, IL - 6 - interleukin 6, AFP -  $\alpha$ -fetoprotein, AB- arterial blood gas analysis, ↑ - higher than the reference value, ↑↑ - ten times and more higher than the reference value, ↓ - lower than the reference value.

Throughout the hospital stay, the treatment prescribed on admission remained. In addition, on the 11<sup>th</sup> day of hospitalization, small doses of the corticosteroid prednisone were introduced. For the following nine days, they were administered orally in decreasing doses (30 mg, 20 mg and 10 mg in three days, respectively). UDCA was also reintroduced.

After two ECAD procedures and introduction of corticosteroids, itching gradually disappeared and an improvement both in the general condition of the patient and the laboratory test results was observed

(Table 2). After 21 days of hospital treatment, the patient was discharged. The UDCA treatment was continued with silymarin and vitamins A and E. At outpatient follow-ups, the patient denied pruritus. A complete normalization of the serum values of bilirubin, aminotransferases and cholestasis parameters was observed on the 123<sup>rd</sup> day of the onset of the disease (Table 1).

## DISCUSSION

Most HAV infections in developing countries are asymptomatic because of early childhood expo-

sure. In sub-Saharan Africa and South Asia, HAV is hyperendemic (5). Miller et al. reported that the seroprevalence of antibodies to HAV was 99% among 403 healthy adults in Tanzania, which was our patient's travel destination (6). In developed countries, the infection often occurs in adolescents and adults as an acute hepatitis (5). In Serbia, the prevalence of anti-HAV reaches the maximum in the fourth decade (7). The frequency of CVH-A is about 0.8% (8).

Different causes have been described in literature. Host factors, such as an underlying chronic liver disease or older age, are correlated with disease severity. There are 4 HAV genotypes described in humans. The sub-types Ia and Ib (especially co-infections) are associated with a long-term course of the disease. The exchange of nucleotides in the mid-section of the untranslated sector 5 of the HAV genome may also intervene with the severity of the liver damage (9). Cytokines and other inflammatory promoters like TNF- $\alpha$  and IL1 play a role in causing cholestasis (8).

Histopathological findings of liver biopsy in CVH-A in most cases show marked centrilobular cholestasis, spotty necrosis in the periportal space with interlobular bilirubin accumulation, especially in the zone 3 (3, 10). Our patient refused the proposed liver biopsy.

The most distressing and persistent symptom in patients with CVH-A is pruritus. It may be related to various mediators including bile acids, endogenous opioid peptide, histamine and lysophosphatidic acid. Pruritogens cause itching through the activation of the G-protein-coupled receptors (GPCRs) and the transient receptor potential (TRP) ion channels on the afferent nerve endings in the skin (11).

There are numerous treatments but there is no final treatment to be recommended. UDCA lowers the levels of the transient bile salts and the levels of bilateral sulfide steroids and thus reduces the pruritus.

Rifampicin and phenobarbital, which act to promote liver metabolism by stimulating cytochrome P 450 enzymes, have been suggested as possible treatment options in the literature. Anti-histamines have a limited effect on relieving pruritus (3). Bile acid-binding resins, such as cholestyramine, prevent the reabsorption of bile salts from the intestines and lower cholesterol levels. Other

therapies (naloxone, naltrexone, nalmefene) prevent the binding of endogenous opioid agonists, the levels of which are elevated in cholestasis (12). In this case, the outpatient treatment with UDCA, cholestyramine and silymarin did not reduce pruritus.

The mechanism of action of corticosteroids in CVH-A depends on its anti-inflammatory effects and the improvement of the multidrug resistance-associated protein 2 (mrp2) actions which increase the transport of bilirubin out of the hepatocytes, thus making it more efficient (13). In CVH-A, corticosteroids have generally been used as a prolonged therapy lasting several months with a gradual dose reduction (3). In our patient's case, we applied a pulse treatment regimen with prednisolone for nine days. The onset of the corticosteroid therapy coincides with the date of the second MARS cycle. Nevertheless, a significant drop in the total and direct bilirubin values as well as in aminotransferase activity at the end of corticosteroid pulse therapy (before discharge) is evident compared to the values after the second MARS cycle (Table 2). In addition, a significant reduction in the intensity of pruritus was observed.

MARS is used for the elimination of albumin-bound toxins which cannot be removed via hemofiltration, hemodiafiltration or plasmapheresis.

Indications for MARS include ALF, acute decompensation of chronic liver disease (AoCLF), acute alcoholic hepatitis, spontaneous peritonitis, type 1 hepatorenal syndrome, liver failure after surgery or liver transplantation (OLT) and intractable pruritus in cholestatic syndromes (14). This is the second time MARS has been used in our institution.

It was successfully used for the first time in the treatment of ALF as part of acute hepatitis B infection (15). A review of the literature has shown that MARS is an effective treatment for intractable pruritus with a significant decrease in the bilirubin and bile acid levels after the procedure. No changes in transaminase, albumin and ammonia or prothrombin time have been observed. This is explained by the fact that MARS replaces only the excretory functions of the liver and not the metabolic. In addition to filtration of pruritogens, systemic changes in cytokine/chemokine levels and changes in the gene expression of blood cells have been described in the literature (12, 16). This is consistent with the laboratory results obtained for our patient

(Table 2). Total cholesterol and triglyceride levels remained almost unchanged. The level of serum IL-6 in our patient was slightly elevated during the hospital treatment. A slight, clinically insignificant increase in the level of this cytokine was observed immediately after the MARS therapy.

After the first MARS procedure, the reduction in the intensity of pruritus was insignificant. In the further course, the intensity of pruritus gradually decreased until it completely disappeared on the 52<sup>nd</sup> day from the onset of the disease, 7 days after the second MARS cycle. There was no relapse, although, in the literature, pruritus improvement has been mainly described as short-term (16). In this case, it may be explained as a result of a combined use of the MARS procedure and low doses of corticosteroids. This procedure is considered safe. Mild thrombocytopenia is the most common side effect

but it did not have any clinical implications. However, MARS units are expensive and operators require special training (16).

## CONCLUSION

The case we report demonstrates the effectiveness of a combination of corticosteroids and the MARS procedure in the treatment of CVH-A and uncontrollable pruritus. This treatment has proven to have significant and lasting effects with no relapse of pruritus. The pulse therapy regime reduces the doses and duration of the steroid intake, thus reducing possible steroid side effects. MARS is effective and safe but it is expensive and requires special training of the personnel. The importance of vaccination of international travellers should also be pointed out.

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# Holestatski virusni hepatitis A praćen upornim svrabom koji je uspešno lečen kombinacijom sistema za recirkulaciju molekularnih adsorbenata i kortikosteroida: prikaz slučaja

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## SAŽETAK

**Uvod.** Virus hepatitisa A je glavni uzrok akutnog virusnog hepatitisa širom sveta, sa oko 1,5 miliona slučajeva godišnje. Kliničke manifestacije virusnog hepatitisa A kreću se od asimptomatskih formi do akutne insuficijencije jetre. Holestatski oblik virusnog hepatitisa A je retka klinička manifestacija koju karakterišu produženi tok, neizdrživ svrab, preteća akutna insuficijencija jetre i, generalno, dobra prognoza. Lečenje svraba kod holestaznog hepatitisa A predstavlja izazov budući da je odgovor na konvencionalnu terapiju ograničen.

**Prikaz slučaja.** U ovom prikazu slučaja predstavljamo efikasnost primene kombinacije pulsniha doza prednizolona i dvaju ciklusa sistema za recirkulaciju molekularnih adsorbenata (engl. *Molecular Adsorbents Recirculating System* – MARS) u lečenju mlade bolesnice sa holestaznim virusnim hepatitisom A. Ovom terapijskom opcijom znatno je skraćeno trajanje bolesti, smanjen je intenzitet svraba i postignut je potpuni oporavak uz normalizaciju laboratorijskih parametara holestaze.

**Zaključak.** Ova terapijska kombinacija je pokazala značajnu delotvornost, i to sa trajnim efektom i bez ponovnog javljanja svraba. Kraća primena malih doza kortikosteroidne terapije smanjuje njihove moguće neželjene efekte. Takođe, želimo istaći značaj vakcinacije, posebno za putnike u međunarodnom saobraćaju.

**Ključne reči:** akutni virusni hepatitis A, holestaza, uporan svrab, sistem za recirkulaciju molekularnih adsorbenata, kortikosteroidi